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Annotated Bibliography of Recent Studies on the Health Effects of Air Pollution

In the last year, hundreds of scientific papers on the health effects of air pollution have been published reporting on effects ranging from respiratory symptoms to premature mortality. The studies extend our understanding of the short- and long-term effects of exposure to common air pollutants, provide new information on potential cardiovascular mechanisms, and identify especially susceptible populations, including children.

This bibliography represents a small sampling of studies published from mid-2001 to mid-2002 in peer-reviewed journals. The new studies link air pollution with lung cancer, heart attacks, strokes, high blood pressure, congenital heart defects, asthma, and even brain damage. They identify diabetics, asthma patients, those with congestive heart failure, and children who play outdoors as being at increased risk. The recent research elucidates several pathways to explain the effects of air pollution on the cardiovascular system.

This bibliography does not attempt to be comprehensive: exclusion does not imply that a study is unimportant; inclusion does not imply endorsement.

LONG-TERM MORTALITY STUDIES

European Long Term Cohort Study Confirms PM-Mortality Link

A study published by The Lancet concludes that *"long-term exposure to traffic-related air pollution may shorten life expectancy."*

Dutch researchers studied 5,000 people in the Netherlands from 1986 to 1994 that were participants in a prospective cohort study on diet and cancer. They found that people living near major roads with higher concentrations of black smoke were at increased risk of premature death from cardiopulmonary causes.

The researchers note that traffic emissions contain many pollutants that might be responsible for the mortality association, including ultrafine particles, diesel soot and nitrogen oxides, though they added that nitrogen dioxide is unlikely to cause death.

"The specificity of the association and the consistency with chronic morbidity studies, adds to the plausibility of traffic-related air pollution effects," conclude the researchers.

The study is significant because it confirms the Harvard Six Cities Study and the American Cancer Society study which linked long-term exposure to particulate air pollution to premature death in the U.S.

Hoek, G., Brunekreef, B., Goldbohm, S., Fischer, P., van den Brandt, P. A. Association Between Mortality and Indicators of Traffic-Related Air Pollution in the Netherlands: A Cohort Study, The Lancet, Vol. 19, pp. 1203-1209, 2002.

Research Links Air Pollution to Lung Cancer

Prolonged exposure to fine particulate air pollution significantly increases the risk of dying from lung cancer and cardiopulmonary causes, according to a new study of 500,000 adults in over 100 American cities.

The new study extended the follow-up period for participants in the study of the American Cancer Society cohort from seven to 16 years, and looked at recent fine particle monitoring information for the years 1999-2000. Importantly, investigators reported that prevailing levels of $PM_{2.5}$ in the U.S. are associated with significant health risks.

Authors concluded that: *"the findings of this study provide the strongest evidence to date that long term exposure to fine particulate air pollution common to many U.S. cities is an important risk factor for cardiopulmonary disease mortality. In addition, the large cohort and extended follow-up have provided an unprecedented opportunity to evaluate associations between air pollution and lung cancer mortality. Elevated fine particulate air pollution exposures were associated with significant increases in lung cancer mortality. Although potential effects of other unaccounted for factors cannot be excluded with certainty, the associations between fine particulate air pollution and lung cancer mortality as well as cardiopulmonary mortality are observed even after controlling for cigarette smoking, body mass, diet, occupational exposure, numerous other individual risk factors, and after using recent advances in statistical modeling to control for regional and other spatial differences."*

Pope, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., and Thurston, G.D. Lung Cancer, Cardiopulmonary Mortality, and Long-term Exposure to Fine Particulate Air Pollution, Journal of the American Medical Association, Vol. 287, No. 9, March 6, 2002.

Mortality Risk Analyses Should be Based on Long-Term Studies

A debate has raged in the public policy arena about whether to use the short-term or the long-term epidemiological studies to estimate the risks of premature mortality attributable to particulate air pollution. A study by K✧nzli et al. presents a conceptual model for the interpretation of these studies, which shows that short-term time-series and long-term cohort studies address different aspects of the association between air pollution and death. Time-series studies capture only cases in which death has been triggered by air pollution exposures that occur shortly before death, while cohort studies capture all air pollution-related categories of death, including deaths of persons whose underlying health condition leads to premature death, without being related to the level of pollution shortly before death.

For these reasons, the authors conclude *"that time-series analyses underestimate cases of death attributable to air pollution and that assessment of the impact of air pollution on mortality should be based on cohort studies."*

The National Academy of Sciences recently issued a report on "Estimating the Public Health Benefits of Proposed Air Pollution Regulations." Importantly, the report concluded that EPA has appropriately based their estimates of morality on long-term cohort studies, which give "a more complete assessment because they include long-term, cumulative effects of air pollution." In particular, the report concluded that EPA's use of the American Cancer Society (ACS) study for the evaluation of PM-related premature mortality was reasonable, given the size and precision of the study.

K✧nzli, N., Medina, S., Kaiser, R., Qu■nel, P., Horak, F., Jr., and Studnicka, M. Assessment of Deaths Attributable to Air Pollution: Should We Use Risk Estimates Based on Time Series or on Cohort Studies? Am. J. Epidemiol. 2001;153:1050-5.

National Research Council, Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution Regulations, "Estimating the Public Health Benefits of Proposed Air Pollution Regulations," National Academies Press, 2002.

SHORT-TERM MORTALITY STUDIES

Strong Evidence for PM-Mortality Relationship Persists in Updated Study

In May 2002, researchers reported an error in the default assumptions in the software used to analyze the National Morbidity, Mortality and Air Pollution Study (NMMAPS). The researchers concluded that a refined analysis changes the quantitative estimates of risk, but the major conclusions remain the same. The three important conclusions of the study remain unchanged by the re-analysis: strong evidence of an association between acute exposure to particulate air pollution (PM_{10}) and daily mortality; the association is strongest for respiratory and cardiovascular causes of death; the association can not be attributed to other pollutants including NO_2, CO, SO_2 or O_3, nor to weather.

The software error does affect all time series studies of air pollution, but only certain recent studies with two or more smooth curves in the generalized additive model (GAM).

Further, the reported error has no affect on the results of the landmark long-term studies of particles, the Harvard Six Cities Study and the American Cancer Society study both of which were reanalyzed in depth and upheld in 2000. These studies found that prolonged exposure to particulate air pollution significantly increases the risk of dying from cardiopulmonary causes.

Importantly, the long-term studies provide the basis for the large risk estimates associated with particulate air pollution, so these estimates remain unchanged by recent developments.

Researchers conclude that *"... there was strong evidence for a positive association between acute exposure to PM_{10} and death, even with very conservative adjustments for trend, seasonality, and weather."*

Dominici, F., McDermott, A., Zeger, S.L. and Samet, J.M. On the Use of Generalized Additive Models in Time-Series Studies of Air Pollution and Health, Am. J. Epidemiol., Vol. 156, No. 3, pp 193-203, August 1, 2002.

"Harvesting" Theory Disproven

Some have argued that the short-term increases in mortality associated with air pollution represent a "harvesting" effect, that is, the advancement of death by a few days in very frail people. This theory of mortality displacement has been dispelled by analyses of single-city mortality studies. Two recent studies have strengthened this conclusion by re-examining multi-city data sets in the U.S. and in Europe.

Researchers from Johns Hopkins University conducted an analysis of daily mortality, particulate air pollution, and weather in **Pittsburgh, PA, Minneapolis, MN, Seattle, WA, and Chicago, IL**.

Researchers found larger relative risks of mortality associated with particulate air pollution for periods of 1 to 2 months, compared to shorter periods of 1 to 4 days.

They conclude: *"These analyses provide additional evidence that associations of particle indexes and mortality do not imply only an advance in the timing of death by a few days for frail individuals."*

Another study examined this issue in the context of the multi-city "Air Pollution and Health: A European Approach" (APHEA-2) study. The study showed that the effect size estimate for airborne particles more than doubled when long-term effects, up to 40 days, were considered.

Researchers reported, *" our study confirms that the effects observed in daily time-series studies are not due primarily to short-term mortality displacement."* They also report that, *"risk assessment based on short-term associations likely underestimate the number of early deaths that are advanced by a significant amount, and that estimates based on the cohort studies, or studies such as this one, would more accurately assess the public health impact."*

Dominici, F., McDermott, A., Zeger S.L., and Samet, J. Airborne Particulate Matter and Mortality: Time-Scale Effects in Four U.S. Cities. American Journal of Epidemiology, In press.

Zanobetti, A., Schwarz, J., Samoli, E., Gryparis, A., Touloumi, G., Atkinson, R., Le Tertre, A., Bobros, J., Celko, M., Goren, A., Forsberg, B., Michelozzi, P., Rabczenko, D., Aranguez Ruiz, E., and Katsouyanni, K. The Temporal Pattern of Mortality Responses to Air Pollution: A Multicity Assessment of Mortality Displacement. Epidemiology, Vol. 13, pp. 87-93, 2002.

Air-Conditioning May Account for Regional Differences in Risk Estimates

Studies of acute effects of particulate matter air pollution show variability in the exposure-response relationships between cities. This study explored whether differences in the prevalence of air conditioning and different sources of PM could partially explain the regional heterogeneity.

The study examined data from a study of hospital admissions for cardiovascular and respiratory causes in 14 U.S. cities, data on air conditioning from a 1993 American Housing Survey, and data on PM_{10} emissions source categories, vehicle miles traveled, and population density from U.S. EPA.

Investigators concluded: "*the results suggest that air conditioning and proportion of especially traffic-related particles significantly modify the effect of PM_{10} on hospital admissions, especially for cardiovascular disease."*

Janssen, N.A.H., Schwartz, J., Zanobetti, A., and Suh, H.H. Air Conditioning and Source-Specific Particles as Modifiers of the Effect of PM_{10} on Hospital Admissions for Heart and Lung Disease. Environ. Health Perspect. Vol. 110, pp. 43-49, 2002.

SUSCEPTIBLE POPULATIONS

Airborne Particles Increase the Risk of Heart Disease in Diabetics

Particulate air pollution has been associated with decreased heart rate variability, increased clotting risk factors, and increases in systemic markers of inflammation. Diabetes is a disease characterized by disturbances in all of these cardiovascular risk factors. Researchers hypothesized that since particles and diabetes may affect some of the same pathways, they may interact to increase the risk of cardiovascular disease.

The study examined Medicare data for hospital admissions for heart disease among the elderly in **Cook, County (Chicago), IL.** Investigators found that people with diabetes had twice the PM_{10}-associated risk for heart disease as nondiabetics, and concluded that diabetics are a susceptible population. A follow-up study in **Chicago, IL, Detroit, MI, Pittsburgh, PA, and Seattle, WA** came to similar conclusions.

These findings have important public health implications because more than 5 percent of the U.S. population has been diagnosed with diabetes, and an additional 2.7 percent have undiagnosed diabetes.

Zanobetti, A., and Schwartz, J. Are Diabetics More Susceptible to the Health Effects of Airborne Particles? Am. J. Respir. Crit. Care Med. Vol. 164. pp. 831-833, 2001.

Zanobetti, A., Schwartz, J. Cardiovascular Damage by Airborne Particles: Are Diabetics More Susceptible? Epidemiology, Vol. 13, No. 5, pp. 588-592, Sept. 2002.

PM_{10} and Ozone Have Strong, Immediate Link with Stroke Deaths

Air pollution may play a part in the causation of strokes, one of the leading causes of death and long-term disability, according to a team of researchers from four research centers in Korea and the Harvard School of Public Health. The findings are based on data from **Seoul, Korea**, a city with relatively high PM concentrations and high numbers of fatal strokes.

Researchers reported that rises in PM_{10} and ozone concentrations had a strong, nearly immediate link with stroke deaths. Stroke mortality also increased in association with NO_2, SO_2 and carbon monoxide concentrations. The effects persisted after controlling for potential confounding factors such as weather and season. Researchers conclude *"that PM_{10} and gaseous pollutants are significant risk factors for acute stroke death and that the elderly and women are more susceptible to the effect of particulate pollutants."*

A seven-year follow-up study in **Seoul** examined daily stroke deaths in relation to air pollution. After controlling for influences such as temperature, relative humidity, and atmospheric pressure, researchers observed a statistically significant relationship between same day concentrations of total suspended particulates and sulfur dioxide, and death from ischemic strokes. Ischemic strokes, the most common type of strokes, occur when a blood clot or narrowed artery cuts off blood supply to the brain.

Hong, Y.-C., Lee J.-T., Kim, H., Ha, E.-H., Schwartz, J., and Christiani, D.C. Effects of Air Pollutants on Acute Stroke Mortality. Environ. Health Perspec. Vol. 110, pp. 187-191, 2002.

Hong, Y.-C., Lee, J.-T., Kim, H., Kwon, H.-J., Air Pollution: A New Risk Factor in Ischemic Stroke Mortality, Stroke, Vol. 33, No. 9, pp. 2165.

PM_{10} and Ozone Air Pollution Worsens the Health of Adults with Severe Asthma

Very few panel studies of adults with severe or moderately severe asthma have been conducted. Most previous studies have been of children. Desquoroux and colleagues designed a study with stringent criteria for inclusion, rigorous medical surveillance, and a long period of observation.

Sixty adult patients with severe asthma and receiving medical treatment were followed by their physicians in **Paris, France** for a period of 13 months. Daily levels of SO_2, PM_{10}, NO_2, and ozone were provided by the air quality monitoring network.

Increases in PM_{10} were associated with an increase in the incidence of asthma attacks 3-5 days later. The delayed effect of PM is consistent with impacts on inflammatory mechanisms.

Increases in the maximum 1-hour ozone level were associated with increased asthma attacks among allergic patients, after 2 days. The results suggest that weak concentrations of ozone may increase bronchial reactivity with allergens in allergic asthma patients.

"The results of our study suggest that ambient Paris levels of PM_{10} and O_3 affected health of severe asthmatics, despite their treatment," report the study authors.

Desqueroux, H., Pujet, J.-C., Prosper, M., Squinazi, F., Momas, I. Short-Term Effects of Low-Level Air Pollution on Respiratory Health of Adults Suffering from Moderate to Severe Asthma. Environmental Research Section A, Vol. 89, pp. 29-37, 2002.

Nitrogen Dioxide and Ozone Increase the Risk of Death in Patients with Severe Asthma

A study of 1,000 patients over 14 years old in **Barcelona, Spain** was conducted to assess the relationship between acute exposure to air pollution, pollen, and mold spores in a cohort of patients that had previously been admitted to an emergency room for an asthma exacerbation. Records were evaluated to determine which of these patients died during the period from 1985-1995. Air pollution, pollen, and spore levels were measured a city monitoring station.

Researchers found that asthmatic patients with a history of more than one emergency room admission for asthma had an increased risk of dying on days with high nitrogen dioxide concentrations. High ozone days during the spring and summer also increased the risk of death in patients with severe asthma. The association with particles, pollen and spores was not significant.

"Nitrogen dioxide and ozone may exacerbate severe asthma and even cause death among asthmatic subjects," reported the researchers.

Sunyer, J., Basagana, X., Belmonte, J., and Anto, J.M. Effect of Nitrogen Dioxide and Ozone on the Risk of Dying in Patients with Severe Asthma. Thorax, Vol. 57, No. 8, pp. 687-693, August, 2002.

Air Pollution Exerts Greater Mortality Impact in Patients with Congestive Heart Failure

This study examined the short-term association between a variety of air pollutants and mortality among patients with congestive heart failure in Seoul, Korea.

"... It seems clear that air pollution in Seoul was related to an increased daily mortality and that congestive heart failure patients were particularly susceptible," conclude the researchers, strengthening the case that an important mechanism of air pollution effect involves the cardiovascular system.

Kwon, H.-J., Cho, S.-H., Nyberg, F., and Pershagen, G. Effects of Ambient Air Pollution on Daily Mortality in a Cohort of Patients with Congestive Heart Failure. Epidemiology, Vol. 12, pp. 413-419, 2001.

Sensitive Individuals are Highly Susceptible to Airborne Particles

"Part of the explanation for the persistent epidemiological findings of associations between mortality and morbidity with relatively modest ambient exposures to airborne particles may be that some people are much more susceptible to particle-induced responses than others," write Professor Dale Hattis of Clark University, and coauthors.

This study relied on an analysis of studies of human systemic responses to dust and other agents that induce acute changes in lung function to quantitatively explore variability among individuals in breathing rates and deposition to the deep lung.

The study found that 99.9th percentile individuals respond to doses of particles 150 to 450 times smaller than are needed to affect average people.

Hattis D, Russ A, Goble R, Banati P, Chu M., Human Interindividual Variability in Susceptibility to Airborne Particles. Risk Analysis, Vol. 4, pp. 585-599, August, 2001.

EFFECTS ON CHILDREN

Ozone and Carbon Monoxide Linked to Cardiac Birth Defects

Women in Southern California who are exposed to high concentrations of ozone and carbon monoxide may be at increased risk of giving birth to babies with serious heart defects, including holes in the heart, arterial defects, or pervasively malformed hearts, according to a study by UCLA researchers.

California maintains a registry of birth defects. The study correlated motor vehicle related air quality data with information on more than 9,000 babies born between 1990

and 1993 in **Los Angeles, Riverside, San Bernardino, and Orange counties**. Researchers calculated average monthly pollution exposure estimates for each pregnancy in the study.

Risk of holes in the heart increased in a dose-response fashion with increasing second-month carbon monoxide exposure. The second month of pregnancy is a critical period for fetal heart development. In addition, second-month ozone exposure increased the risk of aortic artery and valve defects.

Researchers concluded, *"…our results substantially extend the epidemiologic data on the potential relation between increases in ambient air pollutants during vulnerable pregnancy periods and congenital malformations."*

Ritz, B., Yu, F., Fruin, S., Chapa, G., Shaw, G.M. and Harris, J.A. Ambient Air Pollution and Risk of Birth Defects in Southern California. Am. J. Epidemiol. Vol.155, No. 1, pp. 17-25, 2002.

Particle Pollution Retards Lung Function Growth In Teenagers, Akin to Smoking

A study of California teenagers has found that PM_{10} air pollution retards lung function growth as much as smoking.

Researchers studied 110 children who had moved from communities that are part of the California Children's Health Study to determine whether changes in air quality caused by relocation were associated with changes in annual lung function growth rates. Researchers found that changes in PM_{10} exposure during adolescent growth years have a *"measurable and potentially important effect on lung function growth and performance."*

Reductions in annual respiratory growth rates during adolescence may be a significant predictor of respiratory health in later life.

The reductions observed *"suggest that ambient air pollution exposure has a similar magnitude of effect on lung function development to that previously observed for children who are active smokers,"* reports the study.

"The results of this study, together with those of the numerous previously reported investigations of PM_{10} and its association with increased morbidity and mortality, underscore the national concern about particulate exposure and its relation to public health," researchers conclude.

Another study followed 1,600 Southern California children enrolled as fourth graders in 1996 for four years. Significant deficits in lung function growth rate were associated with exposure to acid vapor, NO_2, $PM_{2.5}$, and elemental carbon. Exposure to ozone was correlated with reduced growth in peak flow rate. Larger deficits in lung function growth rate were observed in children who spent more time playing outdoors, confirming findings from an earlier study of another similar cohort. The results *"provide further*

evidence that ambient levels of air pollution in southern California have a detrimental effect on lung function growth in children" conclude the authors.

Avol, E.L., Gauderman, W.J., Tan, S.M., London, S.J., and Peters, J.M. Respiratory Effects of Relocating to Areas of Differing Air Pollution Levels. Am. J. Respir. Crit. Care Med. Vol 164, pp. 2067-2072, 2001.

Gauderman, W.J., Gilliland, G.F., Vora,H., Avol, E., Stram, D., McConnell, R., Thomas, D., Lurmann, F., Margolis, H.G., Rappaport, E.B., Berhane, K., and Peters, J.M. Association between Air Pollution and Lung Function Growth in Southern California Children: Results from a Second Cohort. Am. J. Respir. Crit.Care Med. Vol. 166, pp. 76-84, 2002.

Air Pollution Stunts Lung Function Growth in School Children

Researchers in Austria have followed almost a thousand school children from 8 communities for 3 years, with lung function measurements taken in the winter and summer. Higher summertime PM_{10} concentrations were associated with a slower increase in FEV_1 (forced expiratory volume in one second), a proxy for large airways' growth, and with another lung function measure intended to reflect the growth of small airways.

Exposure to NO_2 and ozone also reduced lung-function growth, confirming earlier work.

The authors conclude, *"...the present study provided further evidence for a long-term effect of particulate matter <10 μm in diameter on the development of pulmonary function in elementary schoolchildren. Early impairment of lung-function growth could lead to lower lung-function parameters in adulthood, predisposing to chronic pulmonary diseases."*

Horak, F., Jr., Studnicka, M., Gartner, C., Spengler, J.D., Tauber, E., Urbanek, R., Veiter, A., Frischer, T. Particulate Matter and Lung Function Growth in Children: A 3-yr Follow-up Study in Austrian Schoolchildren. Eur. Respir. J., Vol. 19, pp. 838-845, 2002.

Inner City Children with Asthma Experience Respiratory Symptoms and Decreased Lung Function in Relation to Air Pollution

The effect of daily ambient air pollution was studied in a cohort of 850 asthmatic children ages 4-9 living in eight inner city urban areas in the U.S. The urban areas studied were **Bronx** and **East Harlem, NY, Baltimore, MD, Washington, DC, Detroit, MI, Cleveland, OH, Chicago, IL** and **St. Louis, MO.**

The impact of pollution developed over several days, with the largest effects seen in morning measurements of lung function. NO_2, SO_2, and PM_{10} were associated with an increase in morning asthma symptoms, with NO_2 exhibiting the strongest influence. Ozone exhibited the greatest effect on peak expiratory flow rate. Adverse respiratory effects were reported in all the cities studied.

Researchers conclude: *"this longitudinal analysis supports previous time-series findings that at levels below current USA air-quality standards, summer-air pollution is significantly related to symptoms and decreased pulmonary function among children with asthma."*

Mortimer, K.M., Neas, L.M., Dockery, D.W., Redline, S., Tager, I.B. The Effect of Air Pollution on Inner-City Children with Asthma, Eur. Respir. J. Vol. 19, pp. 699-705, 2002.

Truck Traffic Contributes to Childhood Asthma Hospitalizations

A study in **Erie County, New York** (excluding the city of Buffalo) has shown that children living in neighborhoods with heavy truck or trailer traffic within 200 meters of their homes had increased risks of asthma hospitalization. The study examined hospital admission for asthma amongst children ages 0-14, and residential proximity to roads with heavy traffic.

Lin, S., Munsie, J.P., Hwang, S.-A., Fitzgerald, E., and Cayo, M.R. Childhood Asthma Hospitalization and Residential Exposure to State Route Traffic. Environmental Research, Section A, Vol. 88, pp. 73-81, 2002.

Coarse Particles ($PM_{10-2.5}$) Associated with Asthma Hospitalization Among Children

This study used two analytical techniques to assess associations between different size fractions of particulate matter and asthma hospitalization among children ages 6-12 living in **Toronto, Canada** between 1981 and 1993.

The researchers found a stronger effect of coarse particles ($PM_{10-2.5}$) on asthma hospitalization compared with both $PM_{2.5}$ and PM_{10}, using both analytical techniques. The stronger effect of $PM_{10-2.5}$ persisted, even after adjusting for the effects of gaseous air pollutants.

There are few studies of the coarse particle fraction, and they are of particular interest because U.S. EPA will likely establish a new standard for coarse particles.

Lin, M., Chen, Y, Burnett, R.T., Villeneuve, P.J., and Krewski, D. The Influence of Ambient Coarse Particulate Matter on Asthma Hospitalization in Children: Case-Crossover and Time-Series Analyses. Environ. Health Perspect. Vol. 110, pp. 575-581, 2002.

Decreases in Air Pollution Shown to Improve Children's Health

The reduction in SO_2 and total suspended particulate levels in eastern Germany following reunification provides a natural experiment to assess associated improvements in human health. This study sought to examine the effect of the decline in air pollution due to a reduction in coal combustion on elementary school children's symptoms of bronchitis.

Researchers conclude, *"the prevalence of nonasthmatic respiratory disorders may be reduced within a short time period by improving air quality. Our data on long-term exposures to air pollution indicate the reversibility of adverse health effects in children and add further evidence of a causal association with combustion-related air pollutants."*

Heinrich, J., Hoelscher, B., Frye, C., Meyer, I., Pitz, M., Cyrys, J., Wjst, M., Neas, L., and Wichmann, H.-E. Improved Air Quality in Reunified Germany and Decreases in Respiratory Symptoms. Epidemiology, Vol. 13, pp. 394-401, 2002.

BIOLOGIC MECHANISMS AND CARDIAC EFFECTS

Breathing Smog Causes Blood Vessels to Constrict

A chamber study on healthy human volunteers has demonstrated that breathing ozone and particulate matter for only two hours, at levels typical of a polluted day in Los Angeles, causes a major artery in the arm to constrict significantly.

Scientists observed that breathing air pollutants caused an immediate constriction of 2 to 4 percent in the blood vessel in the arm. Although this is unlikely to harm a healthy person in the short term, it could impact those with existing heart disease or circulatory problems, and could possibly trigger a heart attack, according to researchers.

The authors concluded, *"This finding is important because ... it provides evidence that the observations shown by large epidemiological studies are biologically plausible."*

Brook, R.D., Brook, J.R., Urch, B., Vincent, R., Rajagopalan, S., and Silverman, F. Inhalation of Fine Particulate Air Pollution and Ozone Causes Acute Arterial Vasoconstriction in Healthy Adults. Circulation, Vol. 105, pp. 1534-1536, 2002.

PM_{10} Provokes Inflammatory Response in Laboratory Animals, in Human Lung Cells In Vitro, and in Humans

Scientists have found that inhalation of urban particles will increase the blood levels of endothelins, potent vasoconstrictors which can increase blood pressure and contribute to congestive heart failure. A study in laboratory rats found that exposure to urban particulate matter (PM) increased endothelin levels, and also caused an increase in blood pressure. The researchers found that particles can cause rapid (2 hours) and sustained (24 hours) systemic cardiovascular changes, without a requirement for acute lung injury.

In another study, researchers hypothesized that following PM_{10} exposure, cytokines, proteins produced in the lung, are released into the blood, inducing a systemic inflammatory response, which plays a role in cardiopulmonary effects. This study exposed cultured human bronchial epithelial cells to ambient particulate matter obtained from air filters in **Ottawa, Canada**. Researchers found that concentrations of various proteins produced increased in a dose-dependent manner. They concluded that *"primary human bronchial epithelial cells exposed to ambient PM_{10} produce proinflammatory*

mediators that contribute to the local and systemic inflammatory response, and we speculate that these mediators may have a role in the pathogenesis of cardiopulmonary disease associated with particulate air pollution."

A third study measured cytokines in the circulation of healthy young army cadets in Singapore exposed to air pollution during the 1997 Southeast Asian forest fires.

Vincent, R., Kumarathasan, P., Goegan, P., Bjarnason, S.G., Gu■nette, J., B■rub■, D., Adamson, I.Y., Desjardins, S., Burnett, R.T., Miller, F.J., and Battistini, B. Inhalation Toxicology of Urban Ambient Particulate Matter, Acute Cardiovascular Effects in Rats. Health Effects Institute, Research Report 104, 2001.

Fujii, T., Hayashi, S., Hogg, J.C., Vincent, R., and Van Eeden, S.F. Particulate Matter Induces Cytokine Expression In Human Bronchial Epithelial Cells. Am. J. Respir. Cell Mol. Biol. Vol. 25, pp. 265-271, 2001.

Van Eeden, S.F., Tan, W.C., Suwa, T., Mukae, H., Terashima, T., Fujii, T., Qui, D., Vincent, R., and Hogg, J.C. Cytokines involved in the Systemic Inflammatory Response Induced by Exposure to Particulate Matter Air Pollutants (PM_{10}), Am. J. Respir. Crit. Care Med. Vol. 164. pp. 826-830, 2001.

Inhaled Ultrafine Particles Pass into the Bloodstream

With the aid of a radioisotope enhanced imaging technique, researchers in Belgium have shown that ultrafine particles can enter a person's bloodstream from the lungs. This study of human volunteers was intended to investigate whether the smallest particles can move from the lungs into the circulation, where they might have a direct effect on cardiovascular endpoints.

Alternative hypotheses hold that particles produce pulmonary inflammation with a systemic release of cytokines, which may influence cardiovascular endpoints. Alternately, it has also been proposed that pollutants may cause alterations in cardiac autonomic function thus causing changes in heart rate variability and increasing the risk of sudden cardiac death.

The investigators conclude that *"...we are confident that our findings provide plausible evidence for particle translocation from the lung into the blood and then its distribution to the organs,"* and that this process could account for cardiovascular illness and death related to ambient particle pollution.

Nenmar, A., Hoet, P.H.M., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M.F., Vanbillioen, H., Mortelmans, L., Nemery, B., Passage of Inhaled Particles in to the Blood Circulation in Humans. Circulation, Vol. 105, pp. 411-414, 2002.

PM Accelerates and Aggravates Artery Disease

A study of laboratory rabbits found that atherosclerosis, a disease marked by cholesterol-lipid-calcium deposits in the walls of the arteries, was accelerated by exposure to PM_{10},

compared to rabbits exposed to clean air. Athererosclerosis is the leading cause of disease and death in Western societies. The study also found that pollution exposure increased susceptibility to plaque rupture, which can trigger heart attacks.

"Progression of atherosclerosis and increased vulnerability to plaque rupture may underlie the relationship between particulate air pollution and excess cardiovascular death," concluded the investigators.

Suwa, T., Hogg, J.C., Quinlan K.B., Ohgami, A., Vincent, R., van Eeden, S.F. Particulate Air Pollution Induces Progression of Atherosclerosis. J. Am Coll. Cardiol. Vol. 39, pp. 943-945, March 20, 2002.

Healthy Workers Exposed to $PM_{2.5}$ Experience Reduction in Heart Rate Variability

Decreased heart rate variability is an indicator of the diminished ability of the heart to respond to stress, and is a risk factor for mortality from cardiovascular disease. This is the first study to examine the effects of $PM_{2.5}$ on a younger population, by incorporating continuous personal monitoring in an occupational setting.

The study population was relatively young boilermaker construction workers occupationally exposed to residual oil fly ash and metal fumes. Continuous monitoring of $PM_{2.5}$ exposure took place during and away from work. Statistically significant decreased heart rate variability was observed in association with 1-hour average $PM_{2.5}$ concentrations. The effect on heart rate variability was smaller than has been reported in elderly populations.

The findings suggest *"a relatively rapid-acting component in the mechanism of action of $PM_{2.5}$ on heart rate variability changes,"* according to the researchers.

A follow-up study by the same group of researchers at the Harvard School of Public Health explored the effect of specific metallic components of $PM_{2.5}$ on the cardiac function of boilermakers. The effect of six metals – vanadium, nickel, chromium, lead, copper and manganese – on heart rate and heart rate variability were examined. Measurements were collected by a portable electrocardiogram monitor and a personal monitor of airborne concentrations. After adjusting for age, baseline heart rate, and smoking status, small changes in heart rate were seen for all the metals, suggesting an association between airborne metals and significant alteration in heart function.

Magari, S.R., Hauser, R., Schwartz, J., Williams P.L., Smith, T.J., and Christiani, D.C. Association of Heart Rate Variability with Occupational and Environmental Exposure to Particulate Air Pollution. Circulation, Vol. 104, pp. 986-991, 2001.

Magari, S.R., Schwartz, J., Williams, P.L., Hauser, R., Smith, T.J., and Christiani, D.C. The Association of Particulate Air Metal Concentrations with Heart Rate Variability. Environ. Health Perspect. Vol. 110, No. 9, pp. 875-880, September 2002.

Diesel Exhaust-Like Particles Lodge in the Lung

Autopsies of lungs from non-smoking female residents of Mexico City reveal that fine particle air pollutants overwhelm the lungs' clearance mechanisms and are retained in lung tissue.

The study compared residents of highly polluted Mexico City with residents of the far cleaner Vancouver, British Columbia, and found significantly higher numbers of particles imbedded in the lungs of in long-term residents of Mexico City. Some of the particles retained in the lungs of Mexico City residents resembled diesel exhaust samples. The study design excluded smokers and those with occupational exposures.

This study provides the first direct evidence that increased lifetime exposure to air pollution results in higher particle retention in the lung. The findings provide biological plausibility to epidemiologic studies showing adverse effects of particles from chronic exposures.

"Our observations indicate that long-term residence in an area of high ambient particle concentrations is associated with greater numbers of retained particles in the lung; this shows for the first time that the aggregated ultrafine particles in ambient air can also be found in lung tissue," the study concludes.

Brauer, M., Avila-Casado, C., Fortoul, T.I., Vedal, S., Stevens, B., and Chung, A. Air Pollution and Retained Particles in the Lung, Environ. Health Perspec. Vol. 109, pp. 1039-1043, 2001.

Blood Pressure Rises During Air Pollution Episode

Blood pressure is a well-established risk factor for cardiovascular disease and deaths.

This study used data from a January 1985 air pollution episode in Central Europe, and a World Health Organization project to monitor measures related to cardiovascular disease in over 2,000 adults in **Augsburg, Germany**.

During the air pollution episode, 24-hour concentrations of total suspended particulates and SO_2 were associated with an increase in blood pressure, after adjusting for other risk factors and weather.

"The observed increase in systolic blood pressure associated with ambient air pollution could be related to a change in cardiovascular autonomic control," report the researchers.

Ibald-Mulli, A., Stieber, J., Wichmann, H.-E., Koenig, W., and Peters, A., Effects of Air Pollution on Blood Pressure: A Population-Based Approach. Am. J. Public Health, Vol. 91, pp. 571-577, 2001.

Particle Exposure Causes Lung Inflammation in Laboratory Animals

Researchers used a concentrating device to test whether short-term exposures to ambient air particles from **Boston, MA** caused pulmonary inflammation in normal rats and in rats with chronic bronchitis. Inflammation was assessed by washing the lungs and measuring concentrations of white blood cells, a marker for inflammation. Concentrated particles were associated with an increase in inflammation in both the normal and the bronchitic animals.

The concentrations used in this study were comparable to cumulative 24-hour concentrations of $PM_{2.5}$ found in developing countries.

The researchers conclude, "*this work demonstrated that short-term exposures to $PM_{2.5}$ concentrated from Boston's atmosphere induce an inflammatory reaction in the lungs of rats. . . .The magnitude of pulmonary inflammation was associated with elements originating from combustion sources."*

Saldiva, P.H.N., Clarke, R.W., Coull, B.A., Stearns, R.C., Lawrence, J., Murthy, G.G.K, Diaz, E., Koutrakis, P., Suh, H., Tsuda, A., and Godleski, J.J. Lung Inflammation Induced by Concentrated Ambient Air Particles is Related to Particle Composition. Am. J. Respir. Crit. Care Med. Vol. 165, pp. 1610-1617, 2002.

Toxicology Study in Human Volunteers Helps Explain Utah Valley Epidemiology Studies

The temporary closure of a steel mill in the Utah Valley during a labor dispute in the late 1980's provided a unique opportunity to study the health of residents during period the mill was closed, compared to before and after the closure. A series of epidemiological studies published in the 1990s reported associations between elevated PM concentrations and increased elementary school absences, bronchitis and asthma hospital admissions for pre-school aged children, total respiratory hospital admissions, pulmonary function abnormalities, and mortality.

In what commentators call "a strikingly innovative study", researchers obtained the archived air pollution filters from the late 1980s, extracted the particles, and instilled them in the lungs of healthy human volunteers. The following day, they washed the lungs to check for signs of inflammation. They found more inflammation in those exposed to particles from the monitoring site nearest to the steel mill during the years when the steel mill was operating, compared to when it was closed.

"This is the first demonstration that pulmonary effects after experimental exposure of humans to PM can correlate with health outcomes observed in epidemiologic studies of the same material under normal exposure conditions," the study concluded. Researchers suggest that the metals contained on the particles may contribute to the toxic effect.

Ghio, A.J. and Devlin, R.B. Inflammatory Lung Injury after Bronchial Instillation of Air Pollution Particles. Am. J. Crit. Care Med. Vol. 164, pp. 704-708, 2001.

Beckett, W.S. The Air Pollution Detectives. Am. J. Respir. Crit. Care Med., Vol. 164, No. 4, pp. 515-516, August 2001.

AIR POLLUTION AND BRAIN DAMAGE

Air Pollution May Play a Role in Alzheimer's Disease

The nasal cavity is a common route of entry for inhaled air pollutants. A study has shown that the nasal mucus membrane defenses are severely compromised in children in Mexico City, diminishing protection from inhaled pollutants. Researchers hypothesized that inflammatory processes in the respiratory tract could trigger a chain of events involving the brain.

This study found that **Mexico City** dogs chronically exposed to high concentrations of ozone, PM, and other air pollutants had extensive brain damage compared to dogs from a less polluted city. Researchers observed alterations of the blood-brain barrier, degenerating, shrunken nerve cells surrounded by dying white matter cells, plaques, and neurofibrillary tangles.

Researchers concluded that *"the histopathology we observed in these urban dogs is of sufficient magnitude to warrant concern that similar histopathology may be occurring in humans residing in large polluted metropolitan areas,"* and that *"persistent pulmonary inflammation and deteriorating olfactory and respiratory barriers may play a role in the neuropathology observed in the brains of these highly exposed canines. Neurodegeneratiave disorders such as Alzheimer's may begin early in life with air pollutants playing a crucial role."*

Calder✱n-Garcidue✶as, L., Valencia-Salazar, G., Rodr×guez-Alcaraz, A., Gambling, T.M., Garc×a, R., Osnaya, N., Villarreal-Calder✱n, A., Devlin, R.B., and Carson, J.L. Ultrastructural Nasal Pathology in Children Chronically and Sequentially Exposed to Air Pollutants. Am. J. Respir. Cell Mol. Biol. Vol. 24, pp. 132-138, 2001.

Calder✱n-Garcidue✶as, L., Azzarelli, B., Acuna, H., Garcia, R., Gambling, T.M., Oznaya, N., Monroy, S., Del Rosario Tizapantzi, M., Carson, J.L., Villarreal-Calderon, A., and Rewcastle, B. Air Pollution and Brain Damage. Toxicologic Pathology, Vol. 30, No. 3, pp. 373-389, 2002.