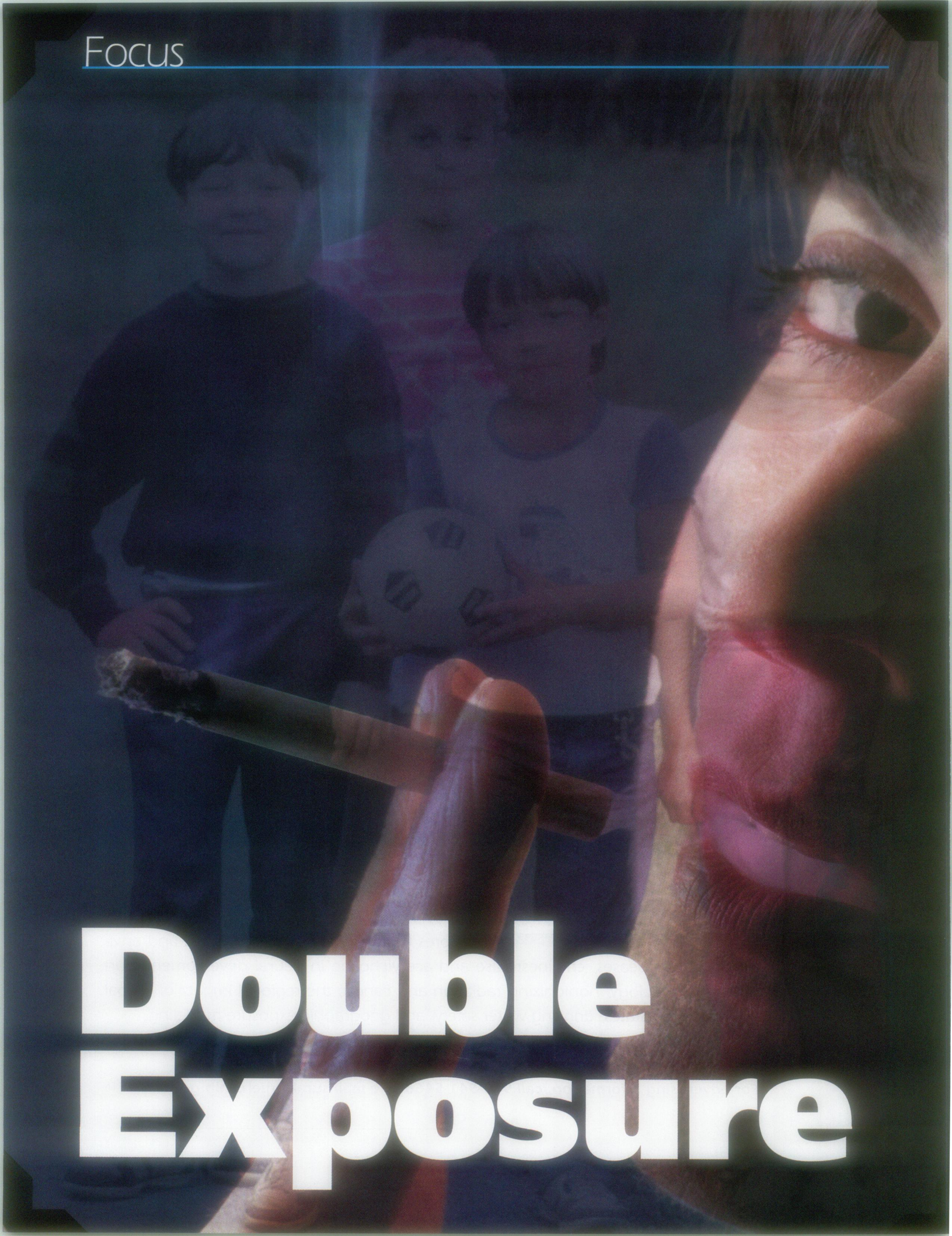

Double Exposure

If a person were to travel back in time 20 years and walk through a restaurant, office building, or airport terminal in the United States, he might notice one difference above all others. Perhaps more than the outmoded communications technologies, hairstyles, and clothing, he might be struck by the prevalence of tobacco smoke in the air. Not only was the percentage of smokers far higher in the United States 20 years ago, smokers were also allowed to indulge in their habit virtually anywhere. While it was known at the time that smokers jeopardized their own health, there was little evidence that nonsmokers could be harmed by inhaling the fumes that floated in the air. Those who complained about being exposed to secondhand smoke were often dismissed as selfish or irrational. That attitude is changing as one scientific study after another finds strong associations between a variety of human illnesses and exposure to what is now called environmental tobacco smoke (ETS). Although some scientists insist that the evidence implicating ETS as a cause of disease is stronger than the evidence implicating most, if not all, other environmental toxins, cigarette manufacturers continue to cast doubt on this contention, and the debate over the link between ETS and human illness continues.

Mounting Evidence

ETS is defined as the sum of sidestream smoke, which is released from the burning tip of a cigarette, and mainstream smoke, which is exhaled by the smoker. Mainstream smoke and sidestream smoke are qualitatively similar in composition, but differ in the concentration of their constituents because of their different combustion characteristics. Sidestream smoke is a result of less complete combustion than mainstream smoke and thus contains considerably higher concentrations of carcinogenic and toxic substances.

Tobacco smoke contains more than 4,500 compounds in particle phase. These compounds include more than 40 known or suspected human carcinogens and many toxic agents such as carbon monoxide, nitrogen oxides, ammonia, acrolein, and nicotine. Tobacco smoke also contains respirable suspended particles, which contain dicyclic and polycyclic aromatic hydrocarbons, some of which are known animal carcinogens.

Researchers cite a series of watershed reports as establishing the link between ETS and human illness. In 1986, the U.S. Surgeon General's report, *The Health Consequences of Involuntary Smoking*, reviewed 13 spousal studies on passive smoking and lung cancer, 11 of which showed a positive association. (Studies of spouses are often used for epidemiology studies on the effects of ETS exposure because of the presumed high level of exposure a nonsmoking spouse gets from a smoking spouse.) The report concluded that ETS is a cause of disease, including lung cancer, in healthy nonsmokers. That same year, the National Academy of Sciences' National Research Council reached much the same conclusions in their report, *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. Also in 1986, the International Agency for Research on Cancer completed a meta-analysis entitled *Evaluation of the Carcinogenic Risk of Chemicals to Humans—Tobacco Smoking*. This study supported a causal relationship between ETS and lung cancer.

The next important publication was the U.S. Environmental Protection Agency's (EPA) 1992 report, *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. This report reviewed 30 epidemiological studies on passive smoking and lung cancer, 24 of which showed positive associations. The EPA classified ETS as a known ("Class A") human carcinogen and calculated that it contributes to approximately 3,000 deaths each year in the United States among nonsmokers. The report also documented causal associations between ETS and lower respiratory tract infections (such as pneumonia and bronchitis), otitis media (middle ear disease), and exacerbation of asthma in children.

In 1997, the California Environmental Protection Agency (CalEPA) released a report entitled *Health Effects of Exposure to Environmental Tobacco Smoke*, which comprehensively covered studies conducted following the EPA's report. The CalEPA report confirmed the EPA's findings on the links between ETS, lung cancer, and respiratory disease, and also found causal association with heart disease, retardation of fetal growth, sudden infant death syndrome (SIDS), and nasal sinus cancer.

In December 1998, the Report on Carcinogens Subcommittee of the Board of Scientific Counselors of the National Toxicology Program met in Research Triangle Park, North Carolina, to discuss possible classification of ETS as a known human carcinogen. This classification is bestowed on compounds for which there is sufficient evidence of carcinogenicity from studies in humans, indicating a causal relationship between exposure to the agent, substance, or mixture and human cancer. The subcommittee voted unanimously in favor of classification of ETS as a known human carcinogen. A meta-analysis on ETS was prepared for this review, but has not yet been published. A final report is expected to be submitted to the secretary of the Department of Health and Human Services in late spring.

Determining Exposure to ETS

Assessing the means by which individuals are exposed to ETS and the rates at which they are exposed is a complex task. By definition, ETS is diluted in air, and in any given environment will likely vary in concentration from barely detectable levels to levels nearly as high as those experienced by active smokers. The amount of smoke one may be exposed to in a microenvironment varies with length of exposure, the number of cigarettes being smoked, the ventilation system in the building, and the adsorptive qualities of structural components, draperies, and furniture.

The most direct method of assessing exposure is through the use of area or personal monitoring equipment. These devices typically sample air for respirable suspended particles and vapor-phase nicotine. Personal monitoring devices worn by study subjects are the most accurate, as they account for the subjects' movement in and out of different microenvironments. However, personal monitoring devices do not measure all of the components of ETS. They are also relatively expensive, and thus not feasible for studies with large sample sizes.

Exposure to ETS can be assessed indirectly through the use of mathematical formulas and mass balance models. These tools take into account the concentrations of tobacco smoke in different microenvironments and the amount of time spent by individuals in each microenvironment. Mass balance models have yielded results reasonably close to actual measured levels of ETS for single rooms.

In epidemiological studies, questionnaires and interviews are the primary tools used to determine and quantify exposure to ETS. Questionnaires can provide detailed information on several factors. They may measure ETS source strength—the level of smoke in the air to which people are exposed, usually measured in micrograms of nicotine per cubic meter of air ($\mu g/m^3$). They may gather retrospective exposure information that is not available through direct measurement or biomarkers (current biomarkers can only measure exposure to ETS over the previous 7–40 hours) or information on long-term exposure, which

A Smoking Gun

1986 The U.S. Surgeon General publishes a report, *The Health Consequences of Involuntary Smoking*, that concludes that ETS is a cause of disease, including lung cancer, in nonsmokers.

The National Academy of Sciences' National Research Council also concludes that ETS causes a variety of diseases in its report *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.*

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The EPA also classifies ETS as a known ("Class A") human carcinogen.

1994–1995 The Occupational Safety and Health Administration conducts hearings on the proposed regulation of indoor air quality, including exposure to ETS.

1997 President Clinton signs an executive order that bans smoking in federal facilities. Forty-three states currently restrict smoking in government workplaces; 23 states have extended these limitations to private-sector workplaces.

The California Environmental Protection Agency publishes *Health Effects of Exposure to Tobacco Smoke*, which finds links between ETS and lung cancer, respiratory disease, heart disease, retardation of fetal growth, SIDS, and nasal sinus cancer.

1998 A federal judge in North Carolina overturns the EPA classification of ETS as a known human carcinogen in a suit brought by tobacco companies.

The Report on Carcinogens Subcommittee of the National Toxicology Program votes unanimously to recommend listing of ETS in the report as a known human carcinogen.

is relevant for many health effects. They can record simultaneous information on time–activity patterns (how long a person is in a smoky room) and modifying environmental factors, including amount of ventilation. They can also gather information on possible confounders, including diet, consumption of alcohol, and exposure to other pollutants at home and in the workplace. Questionnaires are also the least expensive method of gathering information.

Concerns about questionnaires include the lack of a commonly accepted format, lack of a common standard by which to validate questionnaires, and the possibility of misclassification of exposure. Misclassification can occur in a variety of ways, including the respondents' failure to recall exposure precisely, intentional false reporting of exposure, and biased recall of the amount of smoke to which they were exposed. The latter has become a more pertinent issue in recent years as the public awareness of the adverse health effects of ETS has increased.

Various biomarkers can also be used to gauge human exposure to ETS. Biomarkers can serve to validate questionnaire responses by indicating recent exposure to ETS, and they add to the plausibility of associations between involuntary smoking and disease documented in epidemiological studies. However, no biomarker is effective for measuring cumulative past exposure.

The most sensitive and specific markers are nicotine and its metabolite cotinine. Cigarettes contain about 1.0–7.0% nicotine by weight, of which 15–25% is emitted in mainstream smoke and 40% is emitted in sidestream smoke. A number of studies have either assumed or concluded that body fluid nicotine levels can serve as a quantitative indicator of ETS exposure. The circulating half-life of nicotine is generally less than 2 hours. Therefore, it can only be relied upon to detect recent exposures. Cotinine, however, has a half-life in the blood, urine, or plasma of adult nonsmokers of 7–40 hours. Hence, cotinine levels provide information about more chronic exposure to tobacco smoke in both smokers and nonsmokers.

Concerns have been raised about the nonspecificity of both nicotine and cotinine as biomarkers of ETS exposure, as nicotine is found in various common foods including tomatoes, potatoes, eggplant, and certain teas. The amounts of nicotine found in such foods, however, are minuscule relative to the amount found in ETS, and massive amounts of such foods would have to be consumed to equal the exposure gained from ETS. Critics have also pointed to the fact that few studies have assessed cotinine levels in nonsmokers relative to airborne nicotine, and they question the biomarker's accuracy in determining quantitative exposure to ETS.

Other compounds including carbon monoxide, thiothers, thiocyanate, and tobacco-specific *N*-nitrosamines have been studied as possible biomarkers for ETS exposure. However, all but tobacco-specific *N*-nitrosamines have complications that limit their potential as reliable biomarkers.

Recently, the presence of nicotine in human hair has been used as a biomarker of ETS exposure. Human hair has a high affinity for airborne nicotine, and chamber studies have revealed a linear relationship between the extent of airborne nicotine exposure and its adhesion to hair strands. This relationship has been measured as much as 4–6 weeks after exposure.

Degrees of Exposure

Given that the percentage of smokers has declined and regulations increasingly limit the areas where people can smoke, the question arises as to what degree people in the United States are exposed to ETS. Levels of exposure in the numerous published studies have varied tremendously over time and by location. However, most have confirmed that nonsmokers working and living with smokers are exposed to significant levels of ETS. In its 1992 report, the EPA stated that smokers comprise approximately 26% of the U.S. adult population, "causing nearly universal exposure to at least some ETS." An article by James Pirkle and colleagues, published in the 24 April 1996 issue of the *Journal of the American Medical Association*, reviewed the findings of the Third National Health and Nutrition Examination Survey, conducted between 1988 and 1991. This study used cotinine as a biomarker for ETS exposure. Pirkle found that 43% of children aged 2 months to 11 years lived in a home with at least one adult smoker, and 37% of adult nonsmokers either lived in a home with at least one smoker or were exposed to ETS at work. Of all nonsmokers, 87.9% had detectable levels of serum cotinine.

In 1994 and 1995, the Occupational Safety and Health Administration conducted hearings on the proposed regulation of indoor air quality, including exposure to ETS. Some witnesses indicated that exposures to ETS in the home exceeded those in the workplace, while others maintained that workplace exposures were comparable to those in the home. Subsequently, S. Katherine Hammond, an associate professor of environmental health sciences at the University of California at Berkeley, and colleagues reviewed relevant studies on

ETS concentrations in the workplace [see *Environmental Health Perspectives* 107(suppl 2)]. She found that significant numbers of U.S. workers are exposed to hazardous levels of ETS, but that policies that ban smoking in the workplace are effective in lowering exposure to pollutants.

Hammond measured mean concentrations of nicotine in workplaces where smoking was allowed at 2–6 μg/m^3 in offices, 3–8 μg/m^3 in restaurants, and 1–6 μg/m^3 in blue-collar workplaces. In all workplaces in which smoking was banned, nicotine concentrations measured less than 1 μg/m^3. Mean concentrations of nicotine in the homes of smokers have been measured at 1–3 μg/m^3.

Most recently, the sampling and analysis group at Tennessee's Oak Ridge National Laboratory, led by Roger Jenkins, conducted studies of workers in a variety of occupations [see *Environmental Health Perspectives* 107(suppl 2)]. Using measurements from personal monitoring devices, Jenkins found that general workplace exposures were much lower than those estimated in earlier studies. For example, the daily uptake of nicotine was 20% of earlier published estimates of 15 μg/m^3 for the most highly exposed workers, versus the Occupational Safety and Health Administration's 1994 estimates of 50–100 μg/m^3. "It is clear that while a small majority of workers are exposed to higher levels of ETS, the vast majority just are not exposed to a lot of ETS," Jenkins says. Questions have been raised about Jenkins's study concerning its accuracy, the quality control of the study, and the potential for bias—the study was funded by the Center for Indoor Air Research, which is heavily funded by the tobacco companies. However, Jenkins says that the Oak Ridge laboratory had full authority over all aspects of the study, and he stands by it as the most comprehensive and representative exposure study to date.

Risk Assessments

Assessing risks associated with exposure to ETS is a daunting task. As with active smoking, a wide variety of ailments ranging from otitis media to lung cancer are associated with exposure to ETS. Many of these diseases have a complex etiology and all have multiple causes, often making causal relationships difficult to determine.

Epidemiological studies form the basis of most risk assessments associating ETS exposure with various disease end points. Both cohort and case–control studies have been used. In cohort studies, the occurrence of an illness over time in nonsmokers is assessed in relation to ETS exposure. In the more common case–control studies, nonsmoking individuals who have been exposed to ETS and who have an illness suspected of being caused by ETS are compared to an appropriate control group.

Determining the degree of exposure to ETS and separating its effects from numerous other potential causes is central to accurately assessing risk. Findings of epidemiological studies have been challenged due to such factors as the suitability of questionnaires for accurately determining past exposure, small sample size, and selection bias. In many cases, epidemiological studies provide varying and imprecise degrees of risk, and exposures have not been characterized for large and representative population samples. However, these factors have been considered by various governmental and nongovernmental agencies in analyzing and weighing the evidence from numerous epidemiological studies on the health effects of ETS exposure. Such agencies have been confident in assigning causal relationships where the studies showed consistent results and where there was a biologically plausible association with ETS and a particular end point.

ETS and Cancer

Based on the clear connections between active smoking and development of lung cancer, numerous studies have examined the relationship between ETS exposure and lung cancer. By 1986, accumulated evidence led the International Agency for Research on Cancer, the National Research Council, and the U.S. Surgeon General each to conclude that exposure to ETS increases the risk of lung cancer in nonsmoking adults. In 1992, the EPA released a meta-analysis of the 31 published studies at that time on ETS and lung cancer, and concluded that nonsmokers living with smokers have a 19% greater risk of contracting lung cancer than nonsmokers who don't live with smokers.

The EPA's report was criticized for a host of reasons, including possible misclassification of smokers as nonsmokers (which would result in an understatement of the effect), possible publication bias in favor of studies showing a positive association, and difficulty in obtaining risk estimates adjusted for underreporting of exposure to ETS. A series of population-based studies designed to address some of these weaknesses was in progress at the time of the release of the EPA's meta-analysis. These studies subsequently found results similar to those of the EPA. Based on these more recent findings, CalEPA concluded in its 1997 report that exposure to ETS causes about a 20% greater risk of lung cancer among nonsmokers.

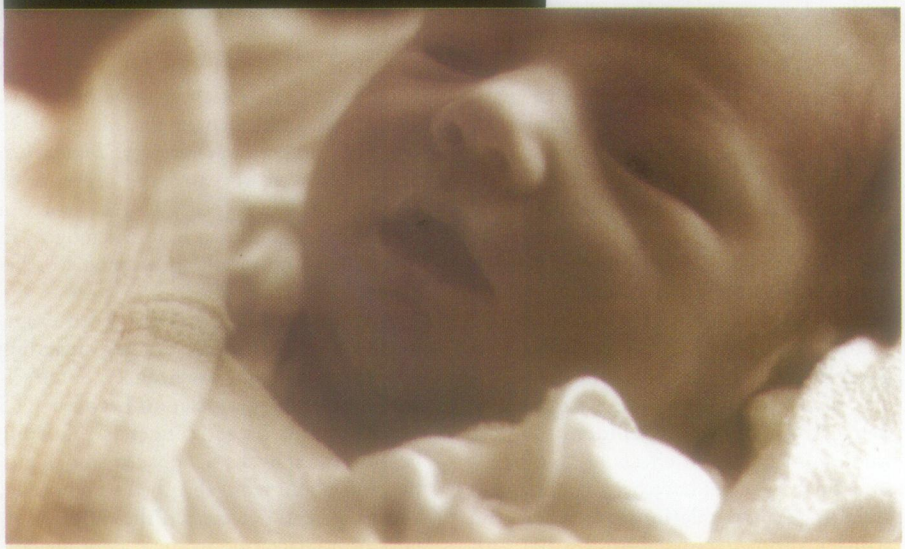
The biological plausibility of ETS exposure leading to lung cancer was enhanced in a recent study by William Parsons, a physician at Sainte Anne's Hospital in Sainte-Anne-de-Bellevue, Québec, working in cooperation with Stephen Hecht of the University of Minnesota Cancer Center in Minneapolis. The study, published in the March 1998 issue of *Cancer Epidemiology, Biomarkers and Prevention*, revealed the presence of significant levels of NNAL-Gluc, a metabolite of a known lung carcinogen, in the urine of nonsmoking hospital workers exposed to ETS.

Exposure to ETS has also been examined as a cause of other cancers, including breast, cervical, and nasal cancer. Some scientists believe an association between ETS exposure and breast cancer is plausible because carcinogens in tobacco smoke and their metabolites are absorbed systemically, and have been detected in the nipple aspirates of nonlactating women. Four analytical epidemiological studies were reviewed by CalEPA for an association between ETS exposure and breast cancer. The agency concluded that, while all four studies suggested an increased risk of breast cancer from exposure to ETS, the results cannot be considered conclusive because three of the studies showed either no association between active smoking and breast cancer or a weaker association for active smoking than for passive smoking—findings that have yet to be reconciled.

It appears that some people may be genetically more susceptible than others to breast cancer as a result of exposure to tobacco smoke. Aromatic amines are detoxified or bioactivated by xenobiotic metabolizing enzymes, including *N*-acetyltransferase. In a study published in the 13 November 1996 issue of the *Journal of the American Medical Association*, Christine Ambrosone, a research epidemiologist with the National Center for Toxicological Research in Jefferson, Arizona, and colleagues found that postmenopausal women who exhibit a certain *N*-acetyltransferase polymorphism (slow acetylators) have a decreased capacity to detoxify carcinogenic aromatic amines in cigarette smoke. This may make such women who smoke or who are exposed to tobacco smoke more susceptible to breast cancer.

The CalEPA report reviewed one cohort and three case–control studies investigating the relationship between ETS and cervical cancer. A positive but nonsignificant association was reported in the cohort study and a significant, positive

Environmental Tobacco Smoke (ETS) and Children



- At least six studies have reported lower birth weights for infants of nonsmoking mothers exposed to ETS during pregnancy.
- Several studies have linked ETS exposure in pregnant women with growth retardation and congenital malformations in their babies.
- Studies have shown a significant association—up to 40% increased risk—of suddent infant death syndrome (SIDS) in infants exposed to ETS.
- Extensive epidemiological evidence links ETS to an increased risk of lower respiratory tract illnesses such as bronchitis and pneumonia in children of parents who smoke.
- Reports of the U.S. Surgeon General have concluded that exposure to ETS can reduce lung function in children. Increasing evidence shows that ETS may contribute significantly to childhood asthma.
- The U.S. Surgeon General, the Environmental Protection Agency, and the National Research Council have all concluded that there is an association between exposure to ETS and middle ear disease in children.

association was found in two of the case–control studies. In the third, exposure of spouses of smokers to ETS was associated with an increased risk of cervical cancer and intraepithelial neoplasia in nonsmokers, but the result was of borderline statistical significance.

Based on data from the one cohort and two case–control studies, CalEPA concluded that there is strong evidence that exposure to ETS increases the risk of nasal cancer in nonsmoking adults. The studies showed an increased risk ranging from 1.7 to 3.0.

Not only does ETS by itself appear to be a carcinogen, but in combination with other agents it may magnify the risk of certain cancers exponentially. Many smokers drink alcohol, and studies have shown that alcohol and tobacco smoke taken together combine in a multiplicative rather than additive fashion to increase the risk of oral and pharyngeal cancer. In a study published in the 1 June 1988 issue of *Cancer Research*, William Blot, then chief of the Biostatistics Branch at the National Cancer Institute in Bethesda, Maryland, and colleagues found that the risk of such cancers increased 35-fold among those who smoked two or more packs of cigarettes per day and drank more than four alcoholic drinks per day. Although these studies examined the relationship between alcohol and active smoking, the potential exists for similar risks associated specifically with ETS exposure.

While research on ETS and adult health has focused primarily on cancer risk, nearly two dozen studies have examined the association between ETS and cardiovascular disease. In its 1997 meta-analysis of these studies, CalEPA concluded that there is a 30% risk of coronary heart disease due to exposure to ETS. The American Heart Association's Council on Cardiopulmonary and Critical Care has also concluded that ETS both increases the risk of heart disease and is a major preventable cause of cardiovascular disease and death.

ETS and Children's Health

The effect of ETS on infants and children, who are frequently unable to avoid exposure and who are generally more susceptible to environmentally related disease than adults, is of particular concern. Numerous studies have demonstrated associations between exposure to ETS and a variety of childhood illnesses, and the damaging effects appear to begin prior to birth. At least six studies have reported lower birth weights for infants of nonsmoking mothers exposed to ETS during pregnancy. Other studies have suggested an association between ETS exposure in pregnant women and growth retardation and congenital malformations in their offspring.

Postnatal exposure to ETS also appears to have deleterious effects on the health of young children, according to a chapter on ETS in *Environmental Toxicants* (in press) by Jonathan Samet and Sophia Wang, researchers at the School of Hygiene and Public Health at Johns Hopkins University in Baltimore, Maryland. To date, 10 studies have addressed the association between SIDS and ETS exposure. Most of these studies have shown a significant association—as much as a 40% greater risk of SIDS—although in some cases it was impossible to separate the effects of exposure to ETS from those of maternal smoking during pregnancy. According to the CalEPA report, there is "compelling evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS."

Extensive epidemiological evidence from throughout the developing world links ETS exposure to increased risk of severe lower respiratory tract illness in children. These studies indicate that the risk of developing lower respiratory illnesses including bronchitis and pneumonia is 1.5–2.0 times higher during the first year of life for young children whose mothers smoke than for those whose mothers do

not smoke. ETS is presumed to increase the risk of infection by respiratory pathogens, primarily through lowering defenses against respiratory viruses rather than through a direct toxic effect, although the mechanism by which infection occurs is not known.

Data from numerous surveys demonstrate a greater frequency of common respiratory symptoms, including coughing, phlegm, and wheezing, among children of smokers. One of the most common chronic diseases of childhood is asthma. While the underlying mechanisms remain to be identified, the epidemiological evidence linking ETS exposure and childhood asthma is mounting. "Exposure to ETS could plausibly contribute to the onset of asthma or exacerbate the status of children having that disease," says Samet. "Inflammation of the airways is a hallmark of asthma, and inhalation and deposition of ETS could sustain or increase the degree of inflammation."

Several reports, including the 1984 and 1986 reports of the U.S. Surgeon General, have concluded that exposure to ETS can reduce the lung function of children. A 1983 longitudinal study by Ira Tager, a professor of epidemiology at the School of Public Health at the University of California at Berkeley, and colleagues has shown that lifelong exposure of a child to a mother who smokes reduces growth of the FEV_1, a measure of lung capacity, by as much as 10.7%.

One of the most frequent diseases diagnosed in children at outpatient facilities is otitis media, an illness that can lead to varying degrees of hearing loss. The U.S. Surgeon General's Office, the National Research Council, and the EPA have reviewed the literature on ETS and otitis media, and all have concluded that there is an association between ETS exposure and this disease. A 1997 meta-analysis by Derek Cook and David Strachan, professors of epidemiology at the Department of Public Health Sciences at St. George's Hospital in London, concluded that a child has a 48% greater risk of otitis media if either parent smokes. The study appeared in the January 1998 issue of *Thorax*.

Public Action and Reaction

Numerous individual studies and meta-analyses from around the world have come to the conclusion that exposure to ETS is a health hazard. As a result of these findings, the EPA has classified ETS as a Class A carcinogen (although the classification was overturned in a lawsuit filed by members of the tobacco industry), and the National Toxicology Program has recommended such an action. Smoking has been banned from many public facilities, workplaces, and modes of transportation including all domestic and international flights offered by U.S. carriers. In many other facilities, smokers have been confined to designated areas. While these actions are popular with the nonsmoking public, they remain controversial, and the science on which they are based continues in part to be scrutinized and debated.

A number of scientists, particularly those in the employ of tobacco companies, remain skeptical about the association between levels of ETS actually encountered by the nonsmoking public and serious illness. They have criticized scientific journals for failing to publish negative findings and meta-analyses or for disregarding those that are published. They criticize many of the epidemiological studies for declaring causal associations based on marginal odds ratios, or ratios that, if adjusted for relevant biases such as diet and misclassification, would be rendered insignificant.

"The problem with epidemiological studies is that they compare people with different lifestyles, and that makes it almost impossible to tease out the factors that lead to disease," says Chris Coggins, senior vice president of science and technology for Lorillard Tobacco Company. "For example, we know that smokers also tend to have poorer diet, exercise less, and drink more alcohol than nonsmokers. You can generate a hypothesis from [epidemiological] studies . . . but you can't prove anything. The studies related to ETS exposure and lung cancer are particularly weak. The results are all over the map."

Jennifer Jinot, an environmental scientist with the EPA and coauthor of the agency's 1992 report, counters that the various studies do prove a connection between ETS and cancer, among other illnesses. "We did a meta-analysis, but we looked at the data in a number of different ways," she says. "We were particularly influenced by the dose–response relationship. We saw a consistently increasing risk [of disease] with increasing [ETS] exposure, regardless of the confounding factors."

The limitations of epidemiological studies have placed increased importance on animal, genotoxicity, and mechanistic studies in which conditions can be tightly controlled and results observed in a relatively short period of time. In its deliberations on classifying ETS as a known human carcinogen, the National Toxicology Program has shown considerable interest in recent studies by Hanspeter Witschi and colleagues at the Institute for Toxicology and Environmental Health at the University of California at Davis that exposed male mice to sidestream smoke. These animals showed a significant increase in lung tumor multiplicity under some circumstances, but not under others. Critics, including Coggins, contend that Witschi's studies did not use a reasonable surrogate of ETS, exposed test animals to unrealistically high levels of respiratory particles, and relied on only one strain of mouse, a strain known for its propensity to develop spontaneous lung neoplasms. Coggins contends there are other well-designed studies exposing rats to ETS that have found no increase in lung carcinogenesis, including one by Hans-Jurgen Haussman of the INBIFO research center in Köln, Germany, published in the July 1998 issue of *Inhalation Toxicology*.

While neither epidemiological nor animal studies have revealed unequivocal proof of the link between ETS and disease, the issue remains very much alive in the nation's boardrooms, legislatures, and courts. In 1997, flight attendants from U.S. airlines wrested a $300 million settlement from five major tobacco companies in a class action suit alleging illness from exposure to ETS on airline flights. No doubt other suits will follow. Such actions, coupled with public demands for a healthful environment, will continue to generate the need for more definitive answers on the connection between ETS and human health.

John Manuel