Preface

Thirteen years ago, in 1986, my predecessor, Surgeon General C. Everett Koop, released a comprehensive analysis of the health dangers of environmental tobacco smoke (ETS)*. This landmark Surgeon General's Report, entitled *The Health Consequences of Involuntary Smoking* (U.S. DHHS, 1986), concluded that ETS causes lung cancer in adults and respiratory problems in children, and that simply separating smokers and nonsmokers within the same airspace reduced, but did not eliminate, ETS exposure. Around the same time, the National Academy of Sciences released an independent report that drew similar conclusions (NRC, 1986). Six years later, in 1992, the U.S. Environmental Protection Agency (EPA) released its own risk assessment of the health effects of ETS with respect to lung cancer and respiratory function (U.S. EPA, 1992); the EPA report reaffirmed the conclusions of both earlier reports. In addition, the EPA identified ETS as a Group A carcinogen, estimating that it causes 3,000 lung cancer deaths a year among American nonsmokers. The EPA also estimated that every year, ETS is responsible for up to 26,000 new asthma cases in children; up to 1,000,000 asthma exacerbations; and up to 300,000 cases of bronchitis and pneumonia in toddlers—15,000 of which require hospitalization.

In the 7 years since the EPA report was published, the evidence that ETS causes lung cancer and other serious diseases has continued to accumulate. Lung cancer was the first fatal disease linked to ETS, but in recent years, evidence that ETS exposure causes other major diseases—particularly heart disease—has emerged. In response to rapidly accumulating evidence that ETS causes disease beyond lung cancer and respiratory effects in children, the California Environmental Protection Agency (Cal/EPA) undertook a comprehensive assessment of the total range of health effects correlated with exposure to ETS.

Using the most up-to-date evidence available, Cal/EPA concluded that ETS causes not only lung cancer in adults and respiratory problems in children, but also low birth weight, sudden infant death syndrome, middle ear infections, nasal sinus cancer, and heart disease morbidity and mortality (Cal/EPA, 1997). Significantly, ETS was estimated to account for up to 62,000 heart disease deaths annually—20 times the number of ETS-related lung cancer deaths.

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* Various terms have been used in the scientific literature to describe a nonsmoker's exposure to ambient tobacco smoke. Passive smoking, involuntary smoking, secondhand smoke, and environmental tobacco smoke are the most prevalent and are often used interchangeably by researchers and the public.

Cal/EPA also found evidence that suggests a link between ETS exposure and spontaneous abortion, adverse effects on cognition and behavior, exacerbation of cystic fibrosis, decreased pulmonary function in adults (as well as that previously described for children), and cervical cancer.

The above-mentioned major public health burden caused by ETS more than justifies public policies creating smoke-free workplaces and public areas. They have also motivated many individuals and families to make their homes smoke-free in order to protect children and other loved ones from the toxic chemicals in ETS.

Since the Cal/EPA report was completed, evidence that ETS causes disease has continued to accumulate. Additional studies have been published, including several major reviews confirming the association between ETS exposure and increased risk for both lung cancer and heart disease in nonsmokers. The International Agency for Research on Cancer (IARC) published a large study (Boffetta *et al*., 1998) demonstrating that nonsmokers exposed to ETS experience a 16 percent elevation in the risk of developing lung cancer—a level consistent with other estimates. While the results in this individual study did not reach statistical significance, the consistency of their estimates with those of other studies increases the confidence we can have in the results of earlier studies. Taken together, all the existing published studies demonstrate a significant and important elevation in lung cancer risk associated with ETS exposure.

British investigators (Law *et al*., 1997) conducted an analysis of 19 epidemiological studies on ETS and heart disease that convincingly demonstrated that the elevation in heart disease risk seen in ETS-exposed nonsmokers is unlikely to be due to the effects of other risk factors. Their finding of a 23 percent increased risk for heart disease is almost identical to that recently published in the *New England Journal of Medicine* by a team of U.S. investigators (He *et al*., 1999). Furthermore, a study from San Francisco showed that respiratory symptoms in bartenders improved significantly just 6 weeks after their ETS exposure was eliminated by a new California law requiring smoke-free bars (Eisner *et al*., 1998). California restaurants became smoke-free on January 1, 1995, followed by bars on January 1, 1998 (Macdonald *et al*., 1997; Glantz and Balbach, 1999 in press). The rapid resolution of the effects of the ETS exposure after the smoke-free law went into effect both demonstrates that ETS causes respiratory problems and illustrates that simple control measures can protect nonsmokers. The California legislation was made possible by community action in support of smoke-free environments (Glantz, 1997). Hundreds of communities across America are now following California's lead.

The California Environmental Protection Agency spent 5 years preparing this document, and it solicited input from all interested parties—including the tobacco industry and its consultants. Cal/EPA held several public workshops to solicit input and made drafts available for public comment and criticisms. The final draft was peer reviewed by California's Scientific Review Panel, a body created under California law to provide independent peer review of many scientific aspects of the state's toxic air contaminants and air pollution programs.

The National Cancer Institute (NCI), acting on behalf of the U.S. Public Health Service, recognized the importance of the Cal/EPA report and saw the need to disseminate it broadly as part of their Smoking and Tobacco Control Monograph series. I hope that this broad dissemination will accelerate public recognition that ETS causes lung cancer, heart disease, sudden infant death, and a wide variety of other serious diseases. I also hope that awareness of this evidence will continue to stimulate public policies to protect nonsmokers from ETS exposure.

In a speech to the American Lung Association in 1984, Dr. C. Everett Koop called for a smoke-free society by the year 2000. While we will not accomplish Dr. Koop's goal, we have made major progress. Just 3 percent of the American workforce was employed in a smoke-free environment in 1986 (Gerlach *et al*, 1997). By 1996, nearly two-thirds (64 percent) of the American indoor workforce was covered by a smoke-free workplace policy (NCI, 1999 in press). Additionally, fully 75 percent of all homes have adopted rules that restrict smoking, with more than half completely banning smoking in the home (NCI, 1999 in press). Even among smokers this trend is evident, with 50 percent of current smokers restricting smoking in their home to some degree and nearly one in five reporting that they do not permit smoking anywhere in the home. I can only hope that the information contained in this report will renew the effort to meet the goal of a smoke-free society in which no one would be involuntarily exposed to ETS.

I call on everyone committed to public health to join with me in a renewed effort to complete the creation of a smoke-free society by:

- Encouraging communities to enact clean indoor air ordinances requiring 100 percent smoke-free environments in all public areas and workplaces, including all restaurants and bars.
- Encourage smokers as well as nonsmokers to make their homes smoke-free to protect their children and families from ETS exposure.

With these simple steps, we can all breathe a little easier.

David Satcher, M.D., Ph.D.
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The body of the original Cal/EPA report is presented in this monograph in its entirety, with only minor editorial revision. Due to space considerations, Appendices A and B, which were published alongside the original report, have not been reproduced in this volume. For those readers interested in obtaining copies of the appendices as they appeared in the Cal/EPA report, single copies are available, upon written request, from the California Environmental Protection Agency. Or they may be downloaded as PDF files through the OEHHA web site at http://www.oehha.ca.gov.

Unlike the original Cal/EPA report, this monograph contains a preface by **David Satcher**, M.D., Ph.D., U.S. Surgeon General and Assistant Secretary for Health, Department of Health and Human Services.

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Executive Summary

Exposure to environmental tobacco smoke (ETS) has been linked to a variety of adverse health outcomes. Many Californians are exposed at home, at work, and in public places. In the comprehensive reviews published as *Reports of the Surgeon General* and by the U.S. Environmental Protection Agency (U.S. EPA) and the National Research Council (NRC), ETS exposure has been found to be causally associated with respiratory illnesses—including lung cancer, childhood asthma, and lower respiratory tract infections. Scientific knowledge about ETS-related effects has expanded considerably since the release of the above-mentioned reviews. The state of California has therefore undertaken a broad review of ETS covering the major health endpoints potentially associated with ETS exposure: perinatal and postnatal manifestations of developmental toxicity, adverse impacts on male and female reproduction, respiratory disease, cancer, and cardiovascular disease. A "weight of evidence" approach has been used, in which the body of evidence is examined to determine whether or not it can be concluded that ETS exposure is causally associated with a particular effect. Because the epidemiological data are extensive, they serve as the primary basis for assessment of ETS-related effects in humans. The report also presents an overview on measurements of ETS exposure (particularly as they relate to characterizations of exposure in epidemiological investigations) and on the prevalence of ETS exposure in California and nationally.

ETS, or "secondhand smoke," is the complex mixture formed from the escaping smoke of a burning tobacco product and smoke exhaled by the smoker. The characteristics of ETS change as it ages and combines with other constituents in the ambient air. Exposure to ETS is also frequently referred to as "passive smoking," or "involuntary tobacco smoke" exposure. Although all exposures of the fetus are "passive" and "involuntary," for the purposes of this review, *in utero* exposure resulting from maternal smoking during pregnancy is not considered to be ETS exposure.

GENERAL FINDINGS

ETS is an important source of exposure to toxic air contaminants indoors. There is also some exposure outdoors in the vicinity of smokers. Despite an increasing number of restrictions on smoking and increased awareness of health impacts, exposures in the home, especially of infants and children, continue to be a public health concern. ETS exposure is causally associated with a number of health effects. Listed in Table ES.1 are the developmental, respiratory, carcinogenic, and cardiovascular effects for which there is sufficient evidence of a causal relationship—including fatal outcomes such as sudden infant death syndrome and heart disease

Table ES.1
Health Effects Associated with Exposure to Environmental Tobacco Smoke

Effects Causally Associated with ETS Exposure
Developmental Effects
Fetal Growth: Low birthweight or small for gestational age
Sudden Infant Death Syndrome (SIDS)
Respiratory Effects
Acute lower respiratory tract infections in children (*e.g.*, bronchitis and pneumonia)
Asthma induction and exacerbation in children
Chronic respiratory symptoms in children
Eye and nasal irritation in adults
Middle ear infections in children
Carcinogenic Effects
Lung Cancer
Nasal Sinus Cancer
Cardiovascular Effects
Heart disease mortality
Acute and chronic coronary heart disease morbidity
Effects with Suggestive Evidence of a Causal Association with ETS Exposure
Developmental Effects
Spontaneous abortion
Adverse impact on cognition and behavior
Respiratory Effects
Exacerbation of cystic fibrosis
Decreased pulmonary function
Carcinogenic Effects
Cervical cancer

mortality, as well as serious chronic diseases such as childhood asthma. There are, in addition, effects for which evidence is suggestive of an association, but further research is needed for confirmation. These include spontaneous abortion, cervical cancer, and exacerbation of asthma in adults (Table ES.1). Finally, it is not possible to judge on the basis of the current evidence the impact of ETS on a number of endpoints including congenital malformations, changes in female fertility and fecundability, male reproductive effects, rare childhood cancers, and cancers of the bladder, breast, stomach, brain, hematopoietic system, and lymphatic system.

Many Californians are exposed to ETS, and the number of people adversely affected may be correspondingly large. Table ES.2 presents morbidity and mortality estimates for health effects causally associated with ETS exposure. For cancer, cardiovascular, and some respiratory endpoints, estimates are derived from figures published for the U.S. population, assuming that the number affected in California would be 12 percent of the total. The estimates for middle ear infection, sudden infant death syndrome, and low birthweight were derived using information on prevalence of ETS exposure in California and the U.S.

Relative risk estimates (RR) associated with some of these endpoints are small, but because the diseases are common, the overall impact can be quite large. A relative risk estimate of 1.3 for heart disease mortality in nonsmokers is supported by the collective evidence; this estimate corresponds to a lifetime risk of death of roughly 1 to 3 percent for exposed nonsmokers and approximately 4,000 deaths annually in California. The relative risk estimate of 1.2 to 1.4 associated with low birthweight implies that ETS may impact fetal growth of 1,200 to 2,200 newborns in California, roughly 1 to 2 percent of newborns of nonsmokers exposed at home or at work. ETS may exacerbate asthma (RR ≈ 1.6 to 2) in 48,000 to 120,000 children in California. Large impacts are associated with relative risks for respiratory effects in children such as middle ear infection (RR ≈ 1.62) and lower respiratory disease in young children (RR ≈ 1.5 to 2). Asthma induction (RR ≈ 1.75 to 2.25) may occur in as many as 0.5 to 2 percent of ETS-exposed children. ETS exposure may be implicated in 120 SIDS deaths per year in California (RR ≈ 3.5), with a risk of death approaching 0.1 percent for infants exposed to ETS in their homes. Lifetime risk of lung cancer death related to ETS-exposed nonsmokers may be about 0.7 percent (RR ≈ 1.2). For nasal sinus cancers, observed relative risks have ranged from 1.7 to 3.0, but future studies are needed to confirm the magnitude of ETS-related risks.

SPECIFIC FINDINGS AND CONCLUSIONS

Exposure Measurement and Prevalence

ETS is a complex mixture of chemicals generated during the burning and smoking of tobacco products. Chemicals present in ETS include irritants and systemic toxicants such as hydrogen cyanide and sulfur dioxide; mutagens and carcinogens such as benzo[a]pyrene, formaldehyde, and 4-aminobiphenyl; and the reproductive toxicants nicotine, cadmium, and carbon monoxide. Many ETS constituents have been identified as hazardous by state, federal, and international agencies. To date, over 50 compounds in tobacco smoke have been identified as carcinogens and six identified as developmental or reproductive toxicants under California's Proposition 65 (California Health and Safety Code 25249.5 *et seq*.).

Exposure assessment is critical in epidemiological investigations of the health impacts of ETS, and in evaluating the effectiveness of strategies to reduce exposure. Exposure can be assessed through the measurement of indoor air concentrations of ETS constituents, through surveys and ques-

Table ES.2
Estimated Annual Morbidity and Mortality in Nonsmokers Associated with ETS Exposure

Condition	Number of People or Cases[a]	
	in the U.S.	in California
Developmental Effects		
Low birthweight	9,700 - 18,600 cases[b]	1,200 - 2,200 cases[b]
Sudden Infant Death Syndrome (SIDS)	1,900 - 2,700 deaths[b]	120 deaths[b]
Respiratory Effects in Children		
Middle ear infection	0.7 to 1.6 million physician office visits[b]	78,600 to 188,700 physician office visits[b]
Asthma induction	8,000 to 26,000 new cases[c]	960 to 3,120 new cases[c]
Asthma exacerbation	400,000 to 1,000,000 children[c]	48,000 to 120,000 children[c]
Bronchitis or pneumonia in infants and toddlers (18 months and under)	150,000 to 300,000 cases[c]	18,000 to 36,000 cases[c]
	7,500 to 15,000 hospitalizations[c]	900 to 1,800 hospitalizations[c]
	136 - 212 deaths[c]	16 - 25 deaths[c]
Cancer		
Lung	3,000 deaths[c]	360 deaths[c]
Nasal sinus	N/A[d]	N/A[d]
Cardiovascular Effects		
Ischemic heart disease	35,000 - 62,000 deaths[c]	4,200 - 7,440 deaths[c]

[a] *The numbers in the table are based on maximum likelihood estimates of the relative risk. As discussed in the body of the report, there are uncertainties in these estimates, so actual impacts could be somewhat higher or lower than indicated in the table. The endpoints listed are those for which there is a causal association with ETS exposure based on observations of effects in exposed human populations.*

[b] *California estimates for low birthweight, SIDS, and middle ear infection (otitis media) are provided in Chapters 3, 4, and 6, respectively. U.S. estimates are obtained by dividing by 12 percent, the fraction of the U.S. population residing in California.*

[c] *Estimates of mortality in the U.S. for lung cancer and respiratory effects, with the exception of middle ear infection (otitis media), come from U.S. EPA (1992). U.S. range for heart disease mortality reflects estimates reported in Wells (1988 and 1994), Glantz and Parmley (1991), Steenland (1992). California predictions are made by multiplying the U.S. estimate by 12 percent, the fraction of the U.S. population residing in the State. Because of decreases in smoking prevalence in California in recent years, the number of cases for some endpoints may be somewhat overestimated, depending on the relative impacts of current versus past ETS exposures on the health endpoint.*

[d] *Estimates of the impact of ETS exposure on the occurrence of nasal sinus cancers are not available at this time.*

tionnaires, or more directly through the use of personal monitors and the measurement of biomarkers in saliva, urine, and blood. There are advantages and disadvantages associated with the various techniques, which must be weighed in interpreting study results. One important consideration in epidemiologic studies is misclassification of exposure. Studies on the reliability of questionnaire responses indicate that qualitative information obtained is generally reliable, but that quantitative information may not be. Also, individuals are often unaware of their ETS exposure, particularly outside the home. In studies using both self-reporting and biological markers, the exposure prevalence was higher when determined using biological markers.

Available data suggest that the prevalence of ETS exposure in California is lower than elsewhere in the U.S. Among adults in California, the workplace, home, and other indoor locations all contribute significantly to ETS exposure. For children, the most important single location is the home. Over the past decade, ETS exposures in California have decreased significantly in the home, workplace, and in public places. Over the same period, restrictions on smoking in enclosed worksites and public places have increased (*e.g.*, Gov. Code, Section 19994.30 and California Labor Code, Section 6404.5), and the percentage of the adults who smoke has declined. Decreases in tobacco smoke exposure may not be experienced for some population subgroups, as patterns of smoking shift with age, race, sex, and socioeconomic status. For example, from 1975 to 1988, the overall smoking prevalence among 16 to 18 year olds declined, but after 1988 the trend reversed.

Perinatal Manifestations of Developmental Toxicity

ETS exposure adversely affects fetal growth, with elevated risks of low birth weight or "small for gestational age" observed in numerous epidemiological studies. The primary effect observed, reduction in mean birthweight, is small in magnitude. But if the distribution of birthweight is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants and is strongly associated with perinatal mortality.

The impact of ETS on perinatal manifestations of development other than fetal growth is less clear. The few studies examining the association between ETS and perinatal death are relatively non-informative, with only two early studies showing increased risk associated with parental smoking, and with the sparse data on stillbirth not indicative of an effect. Studies on spontaneous abortion are suggestive of a role for ETS, but further work is needed, particularly as a recent report did not confirm the findings of four earlier studies. Although epidemiological studies suggest a moderate association of severe congenital malformations with paternal smoking, the findings are complicated by the use of paternal smoking status as a surrogate for ETS exposure, since a direct effect of active smoking on sperm cannot be ruled out. In general, the defects implicated differed across the stud-

ies, with the most consistent association seen for neural tube defects. At this time, it is not possible to determine whether there is a causal association between ETS exposure and this or other birth defects.

Postnatal Manifestations of Developmental Toxicity Numerous studies have demonstrated an increased risk of sudden infant death syndrome, or "SIDS," in infants of mothers who smoke. Until recently it has not been possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent epidemiological studies now have demonstrated that postnatal ETS exposure is an independent risk factor for SIDS.

Although definitive conclusions regarding causality cannot yet be made on the basis of available epidemiological studies of cognition and behavior, there is suggestive evidence that ETS exposure may pose a hazard for neuropsychological development. With respect to physical development, while small but consistent effects of active maternal smoking during pregnancy have been observed on height growth, there is no evidence that postnatal ETS exposure has a significant impact in otherwise healthy children. As discussed in greater detail below, developmental effects of ETS exposure on the respiratory system include lung growth and development, childhood asthma exacerbation, and, in children, acute lower respiratory tract illness, middle ear infection, and chronic respiratory symptoms.

Female and Male Reproductive Toxicity Though active smoking by women has been found to be associated with decreased fertility in a number of studies, and tobacco smoke appears to be anti-estrogenic, the epidemiological data on ETS exposure and fertility are not extensive and show mixed results, and it is not possible to determine whether ETS affects fecundability or fertility. Regarding other female reproductive effects, while studies indicate a possible association of ETS exposure with early menopause, the analytic methods of these studies could not be thoroughly evaluated, and therefore at present, there is not firm evidence that ETS exposure affects age at menopause. Although associations have been seen epidemiologically between active smoking and sperm parameters, conclusions cannot be made regarding ETS exposure and male reproduction, as there is very limited information available on this topic.

Respiratory Effects ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. In children, ETS exposure can exacerbate asthma, and increases the risk of lower respiratory tract illness and acute and chronic middle ear infection. Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS. Odor annoyance has been demonstrated in several studies.

Regarding chronic health effects, there is compelling evidence that ETS is a risk factor for induction of new cases of asthma as well as for increasing the severity of disease among children with established asthma. In addition, chronic respiratory symptoms in children—such as cough,

phlegm, and wheezing—are associated with parental smoking. While the results from all studies are not wholly consistent, there is evidence that childhood exposure to ETS affects lung growth and development, as measured by small but statistically significant decrements in pulmonary function tests; associated reductions may persist into adulthood. The effect of chronic ETS exposure on pulmonary function in otherwise healthy adults is likely to be small and is unlikely by itself to result in clinically significant chronic disease. However, in combination with other insults (*e.g.*, prior smoking history, exposure to occupational irritants or ambient air pollutants), ETS exposure could contribute to chronic respiratory impairment in adults. In addition, regular ETS exposure in adults has been reported to increase the risk of occurrence of a variety of lower respiratory symptoms.

Children are especially sensitive to the respiratory effects of ETS exposure. Children with cystic fibrosis are likely to be more sensitive than healthy individuals. Several studies of patients with cystic fibrosis, a disease characterized by recurrent and chronic pulmonary infections, suggest that ETS can exacerbate the condition. Several studies have shown an increased risk of atopy (a predisposition to develop IgE antibodies against common allergens, which can then be manifested as a variety of allergic conditions) in children of smoking mothers, though the evidence regarding this issue is mixed.

Carcinogenic Effects The role of ETS in the etiology of cancers in nonsmokers was explored, as smoking is an established cause of a number of cancers (lung, larynx, oral cavity, esophagus, and bladder), and a probable cause of several others (cervical, kidney, pancreas, and stomach). Also, ETS contains a number of constituents which have been identified as carcinogens.

Reviews published in the 1986 *Report of the Surgeon General,* by the National Research Council in 1986, and by the U.S. EPA in 1992 concluded that ETS exposure causes lung cancer. Three large U.S. population-based studies and a smaller hospital-based, case-control study have been published since the completion of the U.S. EPA review. The population-based studies were designed to, and have successfully, addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized. Results from these studies are compatible with the causal association between ETS exposure and lung cancer already reported by the U.S. EPA, Surgeon General, and National Research Council. Of the studies examining the effect of ETS exposure on nasal sinus cancers, all three show consistent associations, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. Further study is needed to characterize the magnitude of the risk of nasal sinus cancer from ETS exposure.

The epidemiological and biochemical evidence suggests that exposure to ETS may increase the risk of cervical cancer. Positive associations were observed in two of three case-control studies, and a statistically non-significant positive association was observed in the only cohort study con-

ducted. Findings of DNA adducts in the cervical epithelium as well as nicotine and cotinine in the cervical mucus of ETS-exposed nonsmokers provides biological plausibility.

For other cancer sites in adults, there has been limited ETS-related epidemiological research in general; there is currently insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and the risk of occurrence. A review of the available literature clearly indicates the need for more research. For example, although compounds established as important in the etiology of stomach cancer are present in tobacco smoke, only a single cohort study has been performed for this site. Precursors of endogenously formed N-nitroso compounds suspected of causing brain tumors are present in high concentrations in ETS, and the one cohort and two case-control studies available suggest a positive association, but the results are based on small numbers and may be confounded by active smoking. In biochemical studies of nonsmokers, higher levels of hemoglobin adducts of the established bladder carcinogen, 4-aminobiphenyl, have been found in those exposed to ETS. However, no significant increases in bladder cancer were seen in the two epidemiological studies (case-control) conducted to date, although both studies were limited in their ability to detect an effect. Several compounds in tobacco smoke are associated with increased risk of leukemia, but only one small case-control study in adults, reporting an increased risk with ETS exposure during childhood, has been performed. Finally, all four studies on ETS exposure and breast cancer suggest an association, but in two of the studies the associations were present only in select groups, and in three studies there is either no association between active smoking and the risk of breast cancer, or the association for active smoking is weaker than for passive smoking. Moreover, there is no indication of increasing risk with increasing intensity of ETS exposure. Still, results from a recent study suggest that tobacco smoke may influence the risk of breast cancer in certain susceptible groups of women, an association which requires further investigation.

Regarding childhood cancers, it is unclear whether parental smoking increases risk, either overall or for specific cancers such as acute lymphoblastic leukemia or brain tumors, the two most common cancers in children. The lack of clarity is due to the conflicting results reported and the limitations of studies finding no association. The epidemiological data on ETS exposure and rare childhood cancers also provide an inadequate foundation for making conclusions regarding causality. Some studies in children found small increased risks in relation to parental smoking for neuroblastoma, Wilm's tumor, bone and soft-tissue sarcomas, but not for germ cell tumors. Studies to date on these rare cancers have been limited in their power to detect effects. The impact of ETS exposure on childhood cancer would benefit from far greater attention than it has received to date.

Cardiovascular Effects The epidemiological data from prospective and case-control studies conducted in diverse populations, in males and females and in western and eastern countries, are supportive of a causal association

between ETS exposure from spousal smoking and coronary heart disease (CHD) mortality in nonsmokers. To the extent possible, estimates of risk were determined with adjustment for demographic factors and often for other factors related to heart disease—factors such as blood pressure, serum cholesterol level, and obesity index. Risks associated with ETS exposure were almost always strengthened by adjustment for other cofactors. For nonsmokers exposed to spousal ETS compared to nonsmokers not exposed, the risk of CHD mortality is increased by a factor of 1.3. The association between CHD and risk is stronger for mortality than for non-fatal outcomes, including angina.

Data from clinical studies suggest various mechanisms by which ETS causes heart disease. In a number of studies wherein nonsmokers were exposed to ETS, carotid wall thickening and compromise of endothelial function were similar to, but less extensive than those experienced by active smokers. Other effects observed include impaired exercise performance, altered lipoprotein profiles, enhanced platelet aggregation, and increased endothelial cell counts. These findings may account for both the short- and long-term effects of ETS exposure on the heart.

ATTACHMENT I

Review of the OEHHA Assessment of Environmental Tobacco Smoke by the Scientific Review Panel (SRP)

Interest in the health effects of second-hand tobacco smoke on the part of members of the Scientific Review Panel (SRP) on Toxic Air Contaminants led to a request by the SRP for a health assessment of environmental tobacco smoke and a collaborative agreement between the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board (ARB) to initiate such an assessment. SRP members reviewed the drafts as they were developed and participated in each of the workshops held as the document underwent public review. The final draft reflected the input of SRP members, as well as that of other reviewers.

Specific changes made at the request of the SRP following its review of the final draft include the addition of new studies (*e.g.*, the results of Kawachi *et al.*'s analysis of cardiovascular disease risk in the Nurse's Health study, published after the release of the final draft, in which it was reported as an abstract), a discussion of issues related to misclassification of smoking status and cancer risk, and clarifying language in the presentation of attributable risk estimates; minor editorial changes were also requested and made. The SRP discussed the assessment and made findings on the health effects of exposure to environmental tobacco smoke as a result of its review; these findings are included in this attachment.

UNIVERSITY OF CALIFORNIA, IRVINE

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DEPARTMENT OF CHEMISTRY IRVINE, CALIFORNIA 92717-2025

July 18, 1997

Richard Becker, Ph.D.
Director
Office of Environmental
Health Hazard Assessment
301 Capitol Mall, Second Floor
Sacramento, California 95814

Dear Dr. Becker:

On behalf of the Scientific Review Panel (SRP/Panel) I am pleased to transmit to you our Findings as a result of our review of the Office of Environmental Health Hazard Assessment (OEHHA) final report "Health Effects of Exposure to Environmental Tobacco Smoke" (ETS).

As you will see in a review of the SRP meeting transcript, the Panel is very impressed with the quality of the report and view it as the most current and definitive statement of the science applicable to ETS. As we noted OEHHA staff scientists are to be highly commended for this successful completion.

We are also pleased that the Air Resources Board (ARB) is considering holding an "informational hearing" on the report. As you will see in the enclosed Findings, the Panel views ETS as a toxic air contaminant, and it has a major impact on public health.

If the Panel may be of further help as this health risk is addressed in California, we would be pleased to do so.

We trust our Findings and this transmittal letter will be made a part of the final report

Sincerely,

James N. Pitts, Jr. Ph.D.
Chairman
Scientific Review Panel

Enclosure

cc: John D. Dunlap, Chairman, ARB
Scientific Review Panel Members
Bill Lockett, ARB

Findings of the Scientific Review Panel on
HEALTH EFFECTS OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE
as Adopted at the Panel's June 19, 1997 Meeting

The Scientific Review Panel (SRP/Panel) has reviewed the report "Health Effects of Exposure to Environmental Tobacco Smoke" prepared by the Office of Environmental Health Hazard Assessment (OEHHA). The Panel members also reviewed the public comments received on this report. Based on this review, the SRP makes the following findings:

1. Environmental Tobacco Smoke (ETS) is an important source of exposure to toxic air contaminants. Thus, despite an increasing number of restrictions on smoking and increased awareness of health impacts, exposures continue to be a major public health concern.

2. A causal association exists between ETS exposure from spousal smoking and coronary heart disease (CHD) mortality in nonsmokers. Risks associated with ETS exposure were almost always strengthened by adjustment for other cofactors. For nonsmokers exposed to spousal ETS compared to nonsmokers not exposed, the risk of CHD mortality is increased by a factor of 1.3. The association between CHD and risk is stronger for mortality than for non-fatal outcomes, including angina. Heart disease is the primary fatal endpoint from ETS exposure.

3. ETS is a complex mixture of chemicals generated during the burning and smoking of tobacco products. Chemicals present in ETS include irritants and systemic toxicants, mutagens and carcinogens, and reproductive and developmental toxicants. To date, over 50 compounds in tobacco smoke have been identified as carcinogens and six as developmental or reproductive toxicants under California's Proposition 65 (California Health and Safety Code 25249.5 *et seq.*) and twelve have been identified as a toxic air contaminant under AB 1807.

4. The 1986 *Report of the Surgeon General,* the 1986 National Research Council report *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*, and the 1992 U.S. EPA report *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* have established that ETS exposure causes lung cancer. Results from recent epidemiological studies are compatible with the causal association already established.

5. Available data suggest that the prevalence of ETS exposure in California is lower than elsewhere in the U.S. Nevertheless, among adults in California, the workplace, home and other indoor locations all contribute significantly to ETS exposure. For children the most important single location is the home.

6. ETS exposure adversely affects fetal growth, with elevated risks of low birth weight or "small for gestational age" observed in numerous epidemiological studies. The primary effect observed, reduction in mean birth weight, is small in magnitude. If the distribution of birth weight is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birth weight is associated with many well-recognized problems for infants and is strongly associated with perinatal mortality.

7. Numerous studies have demonstrated an increased risk of sudden infant death syndrome, or "SIDS," in infants of mothers who smoke. Until recently it has not been possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent epidemiological studies now have demonstrated that postnatal ETS exposure is an independent cause of SIDS.

8. ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. In children, ETS exposure can exacerbate asthma, and increases the risk of lower respiratory tract illness, and acute and chronic middle ear infection. Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS. Odor annoyance has been demonstrated in several studies.

9. Regarding chronic health effects, there is compelling evidence that ETS is a risk factor for induction of new cases of asthma as well as for increasing the severity of disease among children with established asthma. In addition, chronic respiratory symptoms in children, such as cough, phlegm, and wheezing, are associated with parental smoking. While the results from all studies are not wholly consistent, there is evidence that childhood exposure to ETS affects lung growth and development, as measured by small, but statistically significant decrements in pulmonary function tests; associated reductions may persist into adulthood.

10. The effect of chronic ETS exposure on pulmonary function in otherwise healthy adults is likely to be small. However, in combination with other insults (*e.g.*, prior smoking history, exposure to occupational irritants or ambient air pollutants), ETS exposure could contribute to chronic respiratory impairment in adults. In addition, regular ETS exposure in adults has been reported to increase the risk of occurrence of a variety of lower respiratory symptoms (e.g. bronchitis and wheezing apart from colds).

11. Children are especially sensitive to the respiratory effects of ETS exposure. Children with cystic fibrosis are likely to be more sensitive than healthy individuals. Several studies of patients with cystic fibrosis, a disease characterized by recurrent and chronic pulmonary infections, suggest that ETS can exacerbate the condition. Several studies have shown an increased risk of atopy (a predisposition to develop IgE antibodies against common allergens, which can then be manifested as a variety of allergic conditions) in children of smoking mothers, though the evidence regarding this issue is mixed.

12. Of the studies examining the effect of ETS exposure on nasal sinus cancers, all three show consistent associations, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. Further study is needed to characterize the magnitude of the risk of nasal sinus cancer from ETS exposure.

13. The epidemiological and biochemical evidence suggest that exposure to ETS may increase the risk of cervical cancer. Positive associations were observed in two of three case-control studies and a statistically nonsignificant positive association was observed in the only cohort study conducted. Findings of DNA adducts in the cervical epithelium as well as nicotine and cotinine in the cervical mucus of ETS-exposed nonsmokers provides biological plausibility.

14. Studies on ETS exposure and breast cancer suggest an association, but the associations were present only in select groups, or there is either no association between active smoking and the risk of breast cancer or the association for active smoking is weaker than for passive smoking. However, there is no indication of increasing risk with increasing intensity of ETS exposure. Still, results from a recent study suggest that tobacco smoke may influence the risk of breast cancer in certain susceptible groups of women, and this requires further investigation.

15. In summary, ETS exposure is causally associated with a number of fatal and non-fatal health effects. Heart disease mortality, sudden infant death syndrome, and lung and nasal sinus cancer have been causally linked to ETS exposure. Serious impacts of ETS on the young include childhood asthma induction and exacerbation, bronchitis and pneumonia, middle ear infection, chronic respiratory symptoms, and low birth weight. In adults acute and chronic heart disease morbidity is causally associated with ETS exposure. ETS also causes eye and nasal irritation and odor annoyance.

16. Effects for which evidence is suggestive of an association, but further research is needed for confirmation, include: spontaneous abortion, adverse neuropsychological development, cervical cancer, exacerbation of cystic fibrosis, and decreased pulmonary function.

17. It is not possible to judge on the basis of the current evidence the impact of ETS on a number of endpoints, including congenital malformations, changes in female fertility and fecundability, male reproductive effects, rare childhood cancers and cancers of the bladder, breast, stomach, brain, hematopoietic system, and lymphatic system.

18. Many Californians are exposed to ETS, and the number of people adversely affected is correspondingly large. Each year ETS contributes to asthma exacerbation in 48,000 to 120,000 children, 960 to 3120 new cases of asthma in children, 78,600 to 188,700 physicians office visits due to middle ear infections in children, 18,000 to 36,000 cases and 900 to 1800 hospitalizations from bronchitis or pneumonia in toddlers and infants, and 1,200 to 2,200 cases of low birth weight. Annual mortality estimates associated with ETS

exposure in California are: Approximately 120 deaths from SIDS, 16-25 deaths in toddlers and infants from bronchitis and pneumonia, approximately 360 deaths from lung cancer, and 4,200 - 7,440 deaths from ischemic heart disease. Thus, ETS has a major public health impact.

After careful review of the February 1997 draft of the OEHHA report, "Health Effects of Exposure to Environmental Tobacco Smoke," we find the draft, with the changes specified by OEHHA in our June 19, 1997 meeting, as representing a complete and balanced assessment of current scientific understanding. Based on the available evidence we conclude ETS is a toxic air contaminant.

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on June 19, 1997

James N. Pitts, Jr., Ph.D.
Chairman, Scientific Review Panel

4

Introduction

1.0 IMPACT OF ETS ON THE HEALTH OF CALIFORNIANS

Disease risks due to inhalation of tobacco smoke are not limited to smokers, but extend to nonsmokers who inhale environmental tobacco smoke (ETS) at home, at work, or in public places. Authoritative reviews over the past 2 decades have presented scientific evidence linking ETS exposures to a number of adverse health outcomes. *Smoking and Health: A Report of the Surgeon General* (U.S. DHEW, 1979) noted several adverse respiratory outcomes in children and adults, as well as some acute cardiovascular effects associated with involuntary exposure to tobacco smoke. The 1982 *A Report of the Surgeon General* (U.S. DHHS, 1982), which focused on the carcinogenic effects of active smoking, raised the concern that involuntary smoking may cause lung cancer. The large series of epidemiological investigations following the publication of that report provided compelling evidence of a causal relationship, and subsequently the 1986 *Report of the Surgeon General* (U.S. DHHS, 1986), as well as reviews by the National Research Council (NRC, 1986) and the U.S. Environmental Protection Agency (U.S. EPA, 1992), concluded that ETS exposure causes lung cancer. The NRC (1986) and U.S. EPA (1992) also found ETS exposure to be associated with lower respiratory tract illnesses in young children, as well as with other adverse respiratory outcomes.

Many people are exposed to ETS. Table 1.1 presents estimates of impacts for some of the health effects associated with ETS exposure and predictions of the numbers of people potentially affected in California, mainly based on extrapolations from national estimates. Recent state and local restrictions on smoking at work and in public places in California, in addition to the California Department of Health Services' (CDHS) advertisement campaign by the Tobacco Control Program, have significantly reduced ETS exposures of nonsmokers in California. Thus the predictions in Table 1.1 may overstate the number of Californians adversely impacted by ETS. Results of the California Adult Tobacco Survey (CDHS, 1995) suggest, however, that it is doubtful that the risks are overstated by more than two-fold. Exposure to ETS therefore remains a significant public health concern in California.

Evidence on ETS-related effects has expanded considerably since the major comprehensive reviews contained in the Reports of the Surgeon General and published by the U.S. EPA and NRC. The State of California has therefore undertaken a broad review of ETS covering the major health endpoints potentially associated with ETS exposure.

Table 1.1
Estimated Annual Morbidity and Mortality in Nonsmokers Associated with ETS Exposure

Condition	Source	Number of Cases Annually[a]	
		United States	California
Developmental Effects			
Low birthweight	Windham *et al.*, 1995	9,700-18,600[b]	1,200-2,200[b]
Sudden Infant Death Syndrome (SIDS)	Klonoff-Cohen *et al.*, 1995	1,900-2,700 deaths[b]	120 deaths[b]
Respiratory Effects in Children			
Otitis media	Etzel, 1992	0.7 to 1.6 million physician office visits[b]	78,600-188,700 physician office visits[b]
New asthma cases	U.S. EPA, 1992	8,000- 26,000[c]	960-3,120[c]
Asthma exacerbation	U.S. EPA, 1992	400,000- 1,000,000[c]	48,000-120,000[c]
Acute lower respiratory illness (LRI) in children up to 18 months	U.S. EPA, 1992	150,000-300,000 cases of bronchitis and pneumonia[c] 7,500 to 15,000 hospitalizations[c]	18,000-36,000 cases of bronchitis and pneumonia[c] 900 to 1,800 hospitalizations[c]
	DiFranza and Lew, 1996	136-212 deaths[c]	16-25 deaths[c]
Lung Cancer	U.S. EPA, 1992	3,000 deaths[c]	360 deaths[c]
	NRC, 1986	2,590-4,040 deaths in 1985	310-485 deaths
Cardiovascular Effects			
Ischemic heart disease	Wells, 1994; Glantz and Parmley, 1991; Steenland, 1992; Wells, 1988	35,000-62,000 deaths[c]	4,200-7,440 deaths[c]

[a] *The numbers in the table are based on maximum likelihood estimates of the relative risk. As discussed in the body of the report, there are uncertainties in these estimates, so actual impacts could be somewhat higher or lower than indicated in the table. The endpoints listed are those for which there is a causal association with ETS exposure based on observations of effects in exposed human populations.*

[b] *California estimates for low birthweight, SIDS, and middle ear infection (otitis media) are provided in Chapters 3, 4, and 6 respectively. U.S. estimates are obtained by dividing by 12 percent, the fraction of the U.S. population residing in California.*

[c] *Estimates of mortality in the U.S. for lung cancer and respiratory effects, with the exception of middle ear infection (otitis media), come from U.S. EPA (1992). U.S. range for heart disease mortality reflects estimates reported in Wells (1988 and 1994), Glantz and Parmley (1991), Steenland (1992). California predictions are made by multiplying the U.S. estimate by 12 percent, the fraction of the U.S. population residing in the state. Because of decreases in smoking prevalence in California in recent years, the number of cases for some endpoints may be somewhat overestimated, depending on the relative impacts of current versus past ETS exposures on the health endpoint.*

1.1 ORGANIZATION OF THE REPORT The review begins with introductory material on definitions and the methodology of the review. In Chapter 2, an overview is presented on measurements of ETS exposure, particularly as they relate to characterizations of exposure in epidemiological investigations, and on prevalence of ETS exposure found in studies conducted in California and nationally. Chapters 3 through 5 address the developmental and reproductive effects of ETS exposure. Perinatal manifestations of developmental toxicity are addressed in Chapter 3, postnatal manifestations in Chapter 4, and male and female reproductive effects in Chapter 5. In Chapter 6, acute and chronic respiratory health effects are described, including some that, under standard definitions (U.S. EPA, 1991; CDHS, 1991), are considered to be developmental effects, such as pulmonary development and childhood asthma induction. Chapter 7 describes the evidence for carcinogenic effects of ETS exposure; beginning with a discussion of all sites combined for children and adults, the chapter then describes the evidence for specific sites: lung, nasal sinus, cervical and bladder cancer (sites for which active smoking has been causally linked to cancer induction), and breast, stomach, brain, leukemia, lymphomas, non-Hodgkin's lymphomas, and other rare childhood cancers (sites for which there is equivocal evidence for an etiologic role for active smoking). Chapter 8 reviews the evidence for the impact of ETS exposure on coronary heart disease.

1.2 DEFINITION OF ETS ETS is also called "second-hand smoke," and ETS exposure is frequently used interchangeably with "involuntary smoking" and "passive smoking." ETS is formed from the smoldering of a cigarette or other tobacco product and from smoke exhaled by the smoker (NRC, 1986). There are other minor contributors, such as the smoke that escapes while the smoker inhales and some vapor-phase components that diffuse into the environment. Once released into the environment of the smoker, components are diluted by the ambient air, diffusing in and being transported through it. These smoke constituents may also aggregate with other components in the air and further age and change in character. This complex mixture is defined as ETS, and inhalation of it, as ETS exposure. In some ways this definition may be overly restrictive when it comes to assessing effects from prenatal smoke exposures. Because the fetus cannot actively smoke, all of its exposure to tobacco smoke constituents is "passive" or "involuntary." Nonetheless, exposure of the fetus due to maternal smoking during pregnancy is not considered to be ETS exposure in this report.

1.3 METHODOLOGY This review is based on exhaustive searches of the literature, including electronic searches (*e.g.*, Medline, Toxline), formal requests for information through an initial "data call-in" through mailed notices, and a *California Regulatory Notice Register* announcement and less formal requests at a number of public workshops, as well as through the public review process. While published, peer-reviewed literature serves as the primary source of data, additional sources, for example abstracts of meeting presentations or doctoral dissertations, may be included, particularly if they provide information in an area where data are lacking.

Methodological issues that were considered in the review of the epidemiologic literature include: 1) the sample size of the study, which affects the power to detect an effect; 2) the extent to which the analysis or design takes into account potential confounders or other risk factors; 3) selection bias, or whether the study groups were comparable; and 4) the potential for bias in ascertaining exposure. These factors were considered when identifying those studies of highest quality.

An important consideration in exploring the effects of ETS exposure is the biological plausibility of an effect. This issue is addressed by comparing findings from studies of ETS exposure to those of active smoking, and by examining the results of animal studies, short term tests, and biomarker investigations.

1.3.1 Measures of Exposure in Epidemiological Studies Characterization of ETS exposure in most epidemiological studies is limited to broad categories (*e.g.,* yes/no, number of hours per week). Accurate categorization is difficult given the large variation in exposures individuals experience. Exposure has generally been determined in three ways: ascertainment of spousal smoking status; estimation of the number of hours a person is exposed (at home, at work, or elsewhere); or measurement of biomarkers. Interviews or questionnaires are often used to collect the first two types of information. Some of the limitations of assessing ETS exposure are briefly discussed below, while Chapter 2 provides more detail on exposure measurement using biomarkers and examines issues regarding the use of questionnaires.

Misclassification is an important consideration when reviewing epidemiologic studies. Misclassification of exposure status occurs when individuals are categorized as having been more or less exposed than they actually were. If the likelihood of misclassification does not depend on whether the study subjects are diseased or not (that is, misclassification is "nondifferential"), then an association between ETS and the disease will be more difficult to detect. Misclassification is a concern in studies which rely on the ascertainment of spousal smoking status because ETS exposures also occur outside the home. In addition, the amount smoked by the spouse outside and inside the home, as well as the time spent in the home by the nonsmoking spouse, varies from couple to couple. Other considerations include size and ventilation of the subjects' residences. Misclassification can occur when exposures observed at one point in time are assumed to apply to other time periods. Misclassification can also be an issue when exposure is determined by asking subjects about the number of hours they are exposed, for example, at home or at work. While questions on number of hours exposed provide more information about multiple exposure sources, respondents may vary in their awareness of and ability to quantify their exposure (Coultas *et al.*, 1989). The tendency is toward underestimation of hours exposed (Emmons *et al.*, 1992). Few studies of this type attempt to verify self-reported exposures.

To minimize misclassification errors, the occurrence and duration of exposure to all sources of ETS should be ascertained as completely as possible. More recent studies have used measurement of biomarkers of exposure to improve assessment of ETS exposure. The biomarker cotinine, a metabolite of nicotine with relatively short half-life (20-30 hours in blood plasma), is useful in categorizing and verifying recent exposure. However, because it only reflects exposures of the past day or two, it is less useful in evaluating chronic exposure. Measurement of cotinine can also be useful for identifying active smokers, as levels generally differ between smokers and nonsmokers exposed to ETS by one to two orders of magnitude.

Characterization of ETS exposure in studies of developmental effects which manifest perinatally or in the first year of life can be particularly challenging. Because of the pronounced effects of maternal smoking during pregnancy on some of the outcomes of interest, studies that can distinguish pre- and postnatal ETS exposure from *in utero* exposure due to maternal active smoking are given more weight. Some studies have attempted to control for maternal active smoking during pregnancy through statistical analyses. However, as spousal smoking habits are correlated, it is difficult to control for the effect of only one partner's smoking. In addition, almost all women who smoke throughout pregnancy continue to smoke after their babies are born (Fingerhut *et al*., 1990) and thus expose their children both to mainstream tobacco smoke components prenatally and to ETS after birth.

Assessment of current ETS exposure of children is somewhat less problematic. Although concerns similar to those discussed above regarding misclassification remain, children, especially infants and young children, are likely to be exposed to tobacco smoke in fewer circumstances than adults. Cotinine concentrations in children are well correlated with smoking by the mother (Greenberg *et al*., 1989; U.S. DHHS, 1986); thus, information on cigarette consumption by the mother is likely to provide a reasonable proxy for a young child's ETS exposure. This may not be the case if the mother is not the primary caregiver. The use of paternal smoking alone as a proxy for ETS exposure of infants and children can be problematic, as fathers are generally less likely to be the primary caregiver.

1.3.2 ETS Exposure in Animal Studies

Two main exposure issues arise in examining animal studies of tobacco smoke effects. First, there are no direct analogues of active smoking in animals; in all cases the smoke is dispersed in the air rather than pulled from a cigarette into the lungs. Secondly, in many study reports, not enough methodological detail is provided to determine whether the smoke generated can be classified as "mainstream" or "sidestream" smoke, and thus its relevance to ETS exposure is unclear. The majority of the studies available have attempted to simulate active smoking by using mainstream smoke, and some delivered the smoke in bursts or "puffs." A few recent studies have used exposures characterized as "sidestream smoke," which is considered more relevant to the assessment of the effects of ETS exposure.

Animal models have not been prominent in providing evidence concerning the toxicity of active smoking. In contrast to humans, rodents, the most commonly used animals in laboratory experiments, are obligatory nose breathers and cannot inhale through the mouth. In addition, lung and nasal cavity morphometry (*e.g.*, shape) differ significantly between laboratory rodents and humans, leading to differences in distribution and absorption of particulates (Harkema, 1991; Snipes *et al.*, 1989). Also, methods of exposing animals to tobacco smoke comparable to human active smoking have not been available. To address this issue, "smoking machines" were developed that provided "puffs" of smoke drawn through lit cigarettes (Guerin *et al.*, 1979). This smoke could be dispersed in a chamber or delivered via "nose only" exposure in which the animal's head was confined in a separate area to which the smoke was delivered. "Nose only" exposures are considered superior to chamber exposures. In chambers, smoke constituents could condense on fur and subsequently be ingested during grooming, although this has not been demonstrated.

Animal models for ETS exposure have been recently developed and studies using such models are being released (Witschi *et al.*, 1997a & b). Typically, "sidestream" smoke is smoke produced from the lit end of a cigarette, while "mainstream" smoke is that produced when air is drawn through a lit cigarette. Aging and dilution are provided prior to exposure to simulate constituent profiles similar to those described for human ETS exposure (Coggins et al., 1992). Few studies using exposures specifically designed to simulate human ETS exposure have as yet been published, however.

1.3.3 Measures of Effect The association of ETS exposure and a specific outcome in an epidemiologic study is usually reported as an odds ratio or a rate ratio with a confidence interval, if available from reported studies. Odds and rate ratios adjusted for potential confounders in the original studies are included when available. If not presented in the published report and sufficient data were provided for doing so, crude rate ratios or odds ratios and confidence intervals were calculated. An important consideration in examining causality is whether a dose-response effect was found, so when available those findings are included.

In general, when evaluating the findings of a study, the statistical significance of single comparisons, as indicated by the *p*-value, is considered. However, when evaluating a body of epidemiologic literature, basing interpretation only on the tallying of statistically significant findings can be misleading (Greenland, 1987; Frieman *et al.*, 1978). One problem is that epidemiologic data seldom satisfy the criteria of randomized experimental trials, for which the statistical testing methods were designed. Furthermore, statistical significance is influenced by sample size; not all studies may be large enough to detect a significant association of a given magnitude. This is especially the case if the effect is expected to be of relatively small magnitude, as is anticipated for several of the potential ETS endpoints. Finally, comparisons simply on the basis of *p*-values do not take into account possi-

ble sources of bias in the studies. Therefore, in evaluating causality for a particular endpoint, the overall body of evidence is carefully considered.

1.3.4 Attributable Risk To provide a context for judging the importance of effects caused by ETS exposure, estimates of ETS-related morbidity and mortality are provided. The estimates are derived from data on prevalence and relative risk through assessing the attributable fraction, also called the attributable risk (Breslow and Day, 1980; Kelsey *et al.*, 1996). The attributable fraction is the proportion of disease occurrence potentially eliminated if exposure was prevented. U.S. EPA (1992) used an attributable fraction approach in estimating national figures for ETS-related respiratory health effects. In fact, the national figures derived by U.S. EPA (1992) are used as the basis for deriving California-specific values for childhood asthma induction and exacerbation, bronchitis or pneumonia in young children, and lung cancer—the U.S. estimate is multiplied by 12 percent, the fraction of the U.S. population residing in the state. U.S. statistics reported in the published literature for ETS-related heart disease mortality (Wells, 1988 and 1994; Steenland, 1992; Glantz and Parmley, 1991) are similarly used to estimate California-specific impacts. In this report, California-specific values are calculated for SIDS, low birth weight, and otitis media using California prevalence data and relative risk values to first estimate the attributable fraction.

To the extent that smoking prevalence and ETS exposure have been declining in recent years and that California differs from the rest of the country, the California-specific values derived from U.S. estimates may be slightly elevated, depending on the relative impacts of current versus past ETS exposures on the health endpoint. Cases of lung cancer occurring today are a consequence of ETS exposures over past decades, and since smoking prevalence in California was near national levels until the mid-1980s, the differences noted should not significantly impact the accuracy of the California estimate. For heart disease mortality this issue is more difficult to judge, since the importance of current versus past exposures is not clearly understood. Other sources of uncertainty in estimates based on the attributable fraction method include limited information on prevalence of current and past smokers and relative risks of disease associated with smoking status. Methods to describe the sensitivity of these factors to morbidity and mortality estimates derived using an attributable risk formulation have recently been discussed (Taylor and Tweedie, 1997).

1.4 WEIGHT-OF-EVIDENCE EVALUATIONS

A "weight-of-evidence" approach has been used to describe the body of evidence and to determine whether or not ETS exposure causes a particular effect. Under this approach, the number and quality of epidemiological studies, as well as other sources of data on biological plausibility, are considered in making a scientific judgment. Associations that are replicated in several studies, either of the same design or using different epidemiological approaches or considering different sources of exposure, are more likely to represent a

causal relationship than are isolated observations from single studies (IARC, 1996). If there are inconsistent results among investigations, possible reasons are sought (such as adequacy of sample size or control group, methods used to assess ETS exposure, range in levels of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound. General considerations made in evaluating individual studies include study design, appropriateness of the study population, methods used to ascertain ETS exposure, and analytic methods such as the ability to account for other variables that may potentially confound the ETS effect (see for example: IARC, 1996). Increased risk with increasing levels of exposure to ETS is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship (IARC, 1996).

An effect is judged to be causally associated with ETS exposure when a positive relationship between ETS exposure and the effect has been observed in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Effects considered to have suggestive evidence of a causal association with ETS exposure are those for which a causal interpretation can be considered to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence. For several effects, it is not possible to judge whether or not ETS exposure affects the severity or prevalence of their occurrence. Either too few studies are available to evaluate the impact, or the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion.

Unlike those of most of environmental contaminants, ETS-related health impacts are directly observable through studies of people in exposure situations similar to those experienced by the general population. Still, the relative risks observed can be small, requiring a number of studies or large studies to confirm the effect. Some endpoints have not been sufficiently studied epidemiologically, in which case the finding of inadequate evidence should be seen as preliminary. Because the epidemiologic data are extensive, they serve as the primary basis on which findings of ETS effects are made. Experimental data are reviewed to determine the extent to which they support or conflict with the human data. With regard to addressing biological plausibility, analyses based on particular biomarkers should be considered with caution. Presumption of a linear dose-response relationship between ETS exposure as indicated by biomarker measurements and effect can be problematic. The ratio of constituents in mainstream smoke differs from that in ETS, and the constituents themselves differ in their pharmacokinetic properties and in their dose-effect relationships.

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Exposure Measurement and Prevalence

2.1 INTRODUCTION This chapter provides background information on the prevalence and measurement of exposure to ETS and emphasizes investigation and monitoring methods used in epidemiological evaluations of health effects. Section 2.2 briefly reviews the physical and chemical properties of ETS and identifies some of the important biologically active constituents present in ETS. Section 2.3 discusses various techniques that have been used to measure ETS concentrations in indoor environments. Determination of ETS contamination is a challenge, as ETS is a complex mixture of over 4,000 compounds, and it is neither feasible nor practical to characterize every individual constituent of ETS. Given the complex nature of ETS, markers and tracers of ETS are measured to assess ETS exposures. The role and limitations of some ETS markers, such as nicotine, particulate matter in air, and polycyclic aromatic hydrocarbons, are discussed in this section. Section 2.4 addresses the use of biomarkers to measure ETS exposure. In addition to being dependant on ETS concentration in air, the measured level of biomarker varies with an individual's uptake, distribution, metabolism, and excretion of the chemical of interest. This section describes the use and limitations of some of the biomarkers, such as nicotine and cotinine in physiological fluids, in determining ETS exposure.

One problem with ETS markers and biomarkers is that most of them are only capable of estimating ETS exposure over a relatively short period of time, from a few hours to several weeks, whereas many health effects of ETS are believed to be associated with long-term exposures that are measured in months, if not years. In order to address this difficulty, most epidemiological studies cited in this report used questionnaires or interviews to determine the status of the subjects regarding long-term exposure to ETS. Some studies also used measurements of ETS markers and biomarkers as supplemental information. And just like any epidemiological study that relies on questionnaires or interviews for exposure information, these studies are subjected to the problem of misclassification. Section 2.5 of this chapter describes some of the difficulties associated with classifying subjects into exposure categories based on the smoking status of other household members. As of today, no perfect method for quantifying ETS exposure has been found. Yet, as demonstrated by many studies cited in other chapters of the report, epidemiologists are able to use the information obtained from questionnaires or interviews in classifying the subjects into categorical groups of ETS exposure (*e.g.*, none, low, medium, or high). The categorical exposure information is then used to evaluate health risks associated with ETS exposure. However, one drawback of this approach is that it decreases the sensi-

tivity or power of a study—*i.e.,* it will not show a positive association when a health effect is only moderately related to ETS exposure.

Though many ETS monitoring methods (*e.g.*, nicotine and respirable suspended particulates in air, cotinine in body fluids) are discussed in this chapter, risk assessment of ETS exposure is seldom performed based on monitoring results. Some of the reasons include short sampling duration in most studies, large uncertainty in extrapolating the ETS levels measured at a specific location to the general population, and large uncertainty in estimating the frequency and duration of ETS exposure of the general population. Consistent with the approach used by the National Research Council (NRC, 1986), U.S. EPA (1992), DiFranza and Lew (1996), and Wells (1994), this report uses prevalence assessment for the estimation of health risks that are associated with past or recent ETS exposure. Epidemiologists often use prevalence assessment, which makes use of semi-quantitative exposure information, such as job classification or duration of exposure, for the estimation of health risks associated with occupational and environmental hazards.

Section 2.6 discusses the prevalence of ETS exposures and factors affecting prevalence, especially in California. In support of the assessment of reproductive and developmental effects presented in the chapters addressing these effects, information on both measurement and prevalence of ETS exposures of the developing child (*in utero*, during infancy, and during childhood) is described when available.

2.2 PROPERTIES OF ETS AND ITS CONSTITUENTS

2.2.1 Physical and Chemical Properties of ETS[1]

ETS is a complex mixture of chemicals generated during the burning of tobacco products. The principal contributor to ETS is "sidestream smoke," the material emitted from the smoldering tobacco product between puffs. Other components of ETS include exhaled mainstream smoke, mainstream smoke emitted at the mouthpiece during puff drawing, and compounds diffused through the wrapper. "Mainstream smoke" is the complex mixture that exits from the mouthpiece of a burning cigarette when a puff is inhaled by the smoker.

When a cigarette is smoked, approximately one-half or more of the smoke generated (by weight) is sidestream smoke emitted from the smoldering cigarette. The chemical composition of mainstream smoke has been more extensively characterized than that of sidestream smoke, but they are produced by the same fundamental processes, such that many chemical constituents are present in both. Over 4,000 individual constituents have been identified in mainstream smoke, and approximately 400 compounds have been measured quantitatively in both mainstream and sidestream smoke.

[1] The U.S. EPA (1992) report is the primary source of information presented in this section; unless a specific reference is provided, the information in this section has been taken from that report.

The large number of constituents results from the chemical composition of tobacco and the variety of chemical and physical processes that occur as a cigarette is smoked. The majority of the compounds present in mainstream smoke are formed during combustion, in a pyrolysis-distillation zone just behind the heat-generating combustion zone (Baker, 1981). Estimates have been made that the total number of constituents in mainstream smoke actually may be 10 to 20 times the number identified to date; that is, mainstream smoke may comprise over 100,000 constituents. However, these unidentified components comprise less than 5 percent of the mass of mainstream smoke and would be present only at very low concentrations (Guerin *et al.,* 1992).

Although many constituents present in mainstream and sidestream smoke are the same, there are important differences in their rates of emission into the air due to physical and chemical differences in the burning conditions present during their generation. As discussed in *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (U.S. EPA, 1992: pages 3-2 to 3-10), some constituents have a higher rate of release into sidestream than mainstream smoke, while for others the reverse is true. Once emitted into the air, sidestream smoke may undergo various physical and chemical changes. Dilution, chemical reactions, deposition, and other removal processes may decrease the concentration of the airborne constituents of ETS, alter the size distribution of suspended particles, and chemically modify some of the more reactive constituents of ETS.

The delivery of selected agents in the mainstream smoke of nonfilter cigarettes and the ratios of the relative distribution of these agents in sidestream to mainstream smoke are given in U.S. EPA (1992: Table 3-1). As discussed by U.S. EPA (1992: pages 3-4 to 3-6), sidestream to mainstream ratios are highly variable and can be misleading, as a number of factors affecting cigarette design (*e.g.*, presence of a filter and filter ventilation) and smoking patterns (*e.g.*, puff volume) have a substantial impact on the emissions of mainstream smoke. In contrast, sidestream smoke emissions show relatively little variability as a function of most of these same factors. A study of the influence of puff volume and filter ventilation on sidestream and mainstream deliveries illustrates this point (Browne *et al.,* 1980). The mainstream delivery of particulate matter and carbon monoxide increases with puff volume, but decreases with increasing filter ventilation. Because the sidestream delivery of these constituents remains relatively constant, the corresponding sidestream to mainstream ratios will decrease or increase as a function of the specific condition and constituent examined (Table 2.1).

Data on sidestream emission rates from filtered and commercial cigarettes for many compounds of public health interest are tabulated in U.S. EPA (1992: Table 3-2). While the data are limited, they suggest that sidestream deliveries are relatively constant across a number of products, with differences ranging two- to three-fold when measured under standard smoking conditions. These results are consistent with the finding that side-

Table 2.1

Influence of Puff Volume and Filter Ventilation on Deliveries of Particulate Matter and Carbon Monoxide in Mainstream and Sidestream Smoke

		Milligrams per Cigarette and SS/MS ratio					
	# of	Particulate Matter			Carbon Monoxide		
Variable[a]	Puffs	MS	SS	SS/MS	MS	SS	SS/MS
Puff Volume							
None, Free burn	0	--	23	--	--	58	--
17.5 cc	9.6	29	23	0.8	9	63	7
35 cc	8.7	46	20	0.4	19	50	2.6
50 cc	7.4	55	21	0.4	20	56	2.8
Filter Ventilation[b]							
0%	8.7	46	20	0.4	19	50	2.6
33%	8.8	32	21	0.6	13	49	3.8
48%	9.8	21	21	1.0	7	58	8.3
83%	10.6	12	21	1.8	2	56	2.8

Browne et al. (1980)

[a] *USA blend cigarette, FTC smoking conditions unless otherwise noted.*
[b] *Percentage of mainstream puff air entering through periphery of filter.*

stream deliveries are primarily related to the weight of the tobacco and paper consumed during smoldering, rather than to cigarette design (Guerin *et al.,* 1992).

2.2.2 Biologically Active Constituents of ETS A number of chemicals known or suspected to contribute to adverse health effects are present in tobacco smoke (mainstream and sidestream smoke), including eye and respiratory irritants, systemic toxicants, mutagens, carcinogens, and reproductive toxicants. It is outside the scope of this review to assess exposure to each of the numerous individual constituents of ETS or their specific contribution to the health effects associated with ETS. This section provides a brief discussion of some of the more toxicologically significant compounds identified in tobacco smoke.

2.2.2.1 Toxicants with Acute Effects Irritants and toxicants with other acute health effects have been identified in ETS, including ammonia, acrolein, carbon monoxide, formaldehyde, hydrogen cyanide, nicotine, nitrogen oxides, phenol, and sulfur dioxide. Ammonia, formaldehyde, and sulfur dioxide are respiratory irritants and may exacerbate the condition of people with breathing difficulties. Several components, including acrolein, crotonaldehyde, formaldehyde, and hydrogen cyanide, affect mucociliary function, and at a sufficiently high concentration can inhibit clearance of smoke par-

Table 2.2

Chemical Constituents of Tobacco Smoke That Have Been Classified or Identified as to their Carcinogenicity, Reproductive Toxicity, or Other Health Hazard

COMPOUND	IARC Classification[a]	U.S. EPA Classification[b]	CAL/EPA Prop 65[c]/TAC[d]
Organic Compounds			
Acetaldehyde	2B	B2	yes//yes
Acetamide	2B		yes//yes
Acrolein	3	C	--- //yes
Acrylonitrile	2A	B1	yes//yes
4-Aminobiphenyl	1		yes//yes
Aniline	3	B2	yes//yes
o-Anisidine	2B		yes//yes
Benz[a]anthracene	2A	B2	yes//yes
Benzene	1	A	yes//yes
Benzo[b]fluoranthene	2B	B2	yes//yes
Benzo[j]fluoranthene	2B		yes//yes
Benzo[k]fluoranthene	2B	B2	yes//yes
Benzo[a]pyrene	2A	B2	yes//yes
1,3-Butadiene		B2	yes//yes
Captan	3		yes//yes
Carbon disulfide[e]			yes//yes
Carbon monoxide[e]			yes//---
Chrysene	3	B2	yes//yes
DDT	2B		yes//---
Dibenz[a,h]acridine	2B		yes//yes
Dibenz[a,j]acridine	2B		yes//yes
Dibenz[a,h]anthracene	2A	B2	yes//yes
7H-Dibenzo[c,g]carbazole	2B		yes//yes
Dibenzo[a,e]pyrene	2B		yes//yes
Dibenzo[a,h]pyrene	2B		yes//yes
Dibenzo[a,i]pyrene	2B		yes//yes
Dibenzo[a,l]pyrene	2B		yes//yes
1,1-Dimethylhydrazine	2B		yes//yes
1-Naphthylamine	3		yes//---
2-Naphthylamine	1		yes//---
Nicotine[e]			yes//---
2-Nitropropane	2B		yes//yes
N-Nitrosodi-n-butylamine	2B	B2	yes//---
N-Nitrosodiethanolamine	2B	B2	yes//---
N-Nitrosodiethylamine	2A	B2	yes//---
N-Nitroso-n-methylethylamine	2B	B2	yes//---
N'-Nitrosonornicotine	2B		yes//---
N-Nitrosopiperidine	2B		yes//---
N-Nitrosopyrrolidine	2B		---//yes
Styrene	2B		---//yes
Toluene[e]			yes//yes
2-Toluidine	2B		yes//yes
Urethane	2B		yes//---
Vinyl chloride	1		yes//yes

Table 2.2 (*Continued*)

COMPOUND	IARC Classification[a]	U.S. EPA Classification[b]	CAL/EPA Prop 65[c]/TAC[d]
Inorganic Compounds			
Arsenic	1	A	yes//yes
Cadmium	2A	B1	yes//yes
Chromium V1	1	A	yes//yes
Lead[e]	2B	B2	yes//yes
Nickel	1	A	yes//yes

Sources: ARB (1993); IARC (1985, 1986, 1987, 1992); California Code of Regulations (1994); U.S. EPA (1994)

[a] *International Agency for Research on Cancer (IARC) Classification: 1, carcinogenic to humans; 2A, probably carcinogenic to humans; 2B, possibly carcinogenic to humans; 3, not classifiable as to its carcinogenicity to humans.*

[b] *U.S. EPA Classification: A, human carcinogen; B1, probable human carcinogen (primarily on the basis of epidemiological data); B2, probable human carcinogen (primarily on the basis of animal data); C, possible human carcinogen.*

[c] *Chemicals listed under Proposition 65 are known to the State to cause cancer or reproductive toxicity (California Health and Safety Code Section 25249.5 et seq.).*

[d] *Substances identified as Toxic Air Contaminants by the Air Resources Board (ARB), pursuant to the provisions of AB 1807 and AB 2728 (includes all Hazardous Air Pollutants listed in the Federal Clean Air Act Amendments of 1990).*

[e] *Reproductive toxicant*

ticles from the lung (Battista, 1976). Nicotine, which is the principal alkaloid in tobacco, is a major contributor to the addictive properties of tobacco. Nicotine has diverse pharmacologic and toxicological actions, ranging from acute poisoning to chronic effects, some of which may be responsible for some of the adverse health effects associated with smoking.

2.2.2.2 Toxicants with Carcinogenic Effects

Over 50 compounds have been identified in tobacco smoke that are recognized as known or probable human carcinogens. These compounds, which may occur naturally in tobacco or which are formed during combustion, reside mainly in the particulate phase (IARC, 1986). Most of the major classes of carcinogens, including both organic and inorganic constituents, are represented. Table 2.2 lists those compounds detected in tobacco smoke for which there is evidence of animal or human carcinogenicity, as evaluated by the U.S. EPA or the IARC. Also in Table 2.2 are compounds listed as carcinogens under California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Code of Regulations, Title 22, Section 12000) and a number of tobacco smoke constituents that have been identified as toxic air contaminants by the California Air Resources Board (ARB, 1993). Tobacco smoke itself is listed as a carcinogen under Proposition 65.

Conditions in the burning cone of a cigarette are favorable for the formation of polycyclic aromatic hydrocarbons (PAHs). Over 35 different PAHs have been identified in tobacco smoke (IARC, 1986), several of which are carcinogenic (*e.g.*, benz[a]anthracene, benzo[a]pyrene, and dibenz[a,h]anthracene). *N*-Nitrosamines are formed during the curing (drying) of the tobacco leaf and in large part during combustion while smoking. *N*-Nitrosamines identified in tobacco smoke include volatile (*e.g.*, *N*-nitrosodimethylamine), nonvolatile (*e.g.*, *N*-nitrosodiethanolamine), and tobacco-specific compounds (*e.g.*, *N*-nitrosonornicotine), formed by *N*-nitrosation of nicotine and other pyridine alkaloids. Most of the identified nitrosamines are carcinogens in experimental animals and some (*e.g.*, *N*-nitrosodimethylamine) are present in sidestream smoke in amounts 10 to 200 times greater than in mainstream smoke (U.S. DHHS, 1986; Löfroth, 1989). By weight, the tobacco-specific nitrosamines are the most prominent of the suspected carcinogens identified thus far (IARC, 1986). In addition, the inhalation of nitrogen oxides and amines in tobacco smoke may contribute to the endogenous formation of carcinogenic *N*-nitrosamines (Hoffmann and Brunneman, 1983; Ladd *et al.,* 1984). Other well-established organic carcinogens identified in tobacco smoke are aromatic amines (*e.g.*, 4-aminobiphenyl, 2-naphthylamine and *o*-toluidine), benzene, hydrazine, and vinyl chloride.

Like other plant tissues, tobacco contains minerals and other inorganic constituents derived from soil, fertilizers, agricultural sprays, and polluted rainfall. Upon combustion, most metals remain in the ash; however, some are vaporized or carried in fragments of ash and thus are also found in tobacco smoke. Several of these metals, including arsenic, cadmium, and chromium, are known to be carcinogenic to humans following inhalation.

Tobacco contains a number of naturally occurring radionuclides, of which the most important is the alpha-emitter polonium-210 (Cohen *et al.,* 1980). Polonium-210 and lead-210 in tobacco originate from phosphate fertilizers (Tso, 1966) and/or from airborne particles containing lead-210 that are trapped by the trichomes of tobacco leaves (Martell, 1974). Although not a direct source of radon, ETS in indoor environments is associated with an increase in the airborne concentrations of radon decay products, presumably because newly formed decay products are more likely to attach to smoke particles than to other surfaces in a room (Bergman *et al.,* 1986). All radioactive chemicals can cause cancer in humans and animals.

Though not all mutagens are carcinogens, mutagenicity tests have proven to be useful in identifying chemicals that can alter the integrity of genetic materials and may thus have carcinogenic potentials. Several studies have shown that the semivolatile and particle-bound organic fractions of sidestream smoke are mutagenic in bacterial systems (Löfroth *et al.,* 1983; Ong *et al.,* 1984; Löfroth and Lazaridis, 1986; Ling *et al.,* 1987; Claxton *et al.,* 1989). The results from a variety of short-term tests for genetic endpoints on mainstream smoke and tobacco smoke condensate have been reviewed by DeMarini (1983), Obe *et al.,* (1984), and IARC (1986). In addi-

tion, many of the individual constituents of ETS are positive in one or more short-term tests for genetic activity (Claxton *et al.,* 1989).

2.2.2.3 Toxicants with Effects on Development and Reproduction

Several compounds listed as developmental or reproductive toxicants under California's Proposition 65 have been detected in tobacco smoke (Table 2.2). ETS constituents identified as developmental toxicants under Proposition 65 are carbon disulfide, carbon monoxide, lead, nicotine, cadmium, and toluene. Lead and carbon disulfide have also been identified as agents causing male and female reproductive toxicity. Additional ETS constituents investigated as possible mediators of the developmental or reproductive toxicity of tobacco smoke include PAHs, which have been found to cause developmental and reproductive effects in experimental animals. Exposure to tobacco smoke due to active smoking has been listed as a developmental toxicant as well as a female and male reproductive toxicant under Proposition 65 (listed as "tobacco smoke (primary)"); however, ETS has not been listed.

2.3 EXPOSURE MEASUREMENT: ETS CONCENTRATIONS IN INDOOR ENVIRONMENTS

2.3.1 Introduction to Exposure Measurement

This section summarizes a number of different techniques used by researchers for estimating the degree of ETS exposure of their subjects. In order to investigate the health effects of ETS exposure, epidemiologists characterize the exposure level of their subjects to determine the extent to which exposure is correlated with an adverse health effect. Given the extreme spatial and temporal variation of ETS concentration in indoor and outdoor environments, it is not technically or economically feasible to accurately determine the long-term ETS exposure history of an individual. Yet often times it is the long-term exposure to ETS that is of interest in examining health effects such as developmental effects and cancers. Epidemiologists circumvent this difficulty by using questionnaires or interviews to determine the status of the subjects with respect to long-term exposure to ETS and then classifying the subjects into categorical groups of ETS exposure (*e.g.*, none, low, medium, or high). In this way, they make the best use of the semi-quantitative exposure information available without compromising the validity of the study results. One drawback of this approach is that it decreases the sensitivity or power of the study—*i.e.,* a study will not show a positive association when ETS exposure and an adverse health effect are only moderately related. Some of the indirect and direct methods used by researchers in the study of ETS exposure are discussed in the following sections.

Indirect methods for assessing exposure include measurements of indoor air concentrations of ETS constituents (discussed in this section), and population surveys and questionnaires used to assess the characteristics, patterns, and extent of exposure (Section 2.5). Direct methods for assessing ETS exposure include the use of personal monitors (discussed in this section and in Section 2.4) and measurement of biomarkers of exposure. Personal monitors measure concentrations of ETS constituents at or near the breathing zone and can be worn by individuals to assess exposures

occurring in a specific location or accumulated throughout the day, thus providing an integrated measure of short-term exposure. They are often used in conjunction with other methods to compare or validate assessment of exposure. Measurement of biomarkers, ETS constituents or their metabolites in physiological fluids (such as urine, serum, and saliva), is the most direct assessment of ETS exposure available (Section 2.4). Biomarkers are often used to study exposure prevalence and to evaluate the degree of misclassification in epidemiologic studies.

Modeling exposure on the basis of measured or modeled air concentrations, and the time an individual spends in a specific environment, is another indirect method for assessing ETS exposure. Recently, some researchers have developed and successfully applied models for predicting airborne ETS constituent concentrations (Ott *et al.*, 1992). For example, using an estimated cigarette source strength, air exchange rate and volume of the room, Klepeis *et al.* (1996) were able to predict minute-by-minute indoor time series and time-averaged respirable suspended particle concentrations from ETS. However, airborne ETS constituent concentrations derived from this type of model are location- and situation-specific, and cannot be easily applied to the general population. Such air models are not discussed further in this document.

2.3.2 Indoor Air Measurements of ETS

Given the complex chemical composition of ETS[2], air concentrations are typically assessed by measuring individual ETS constituents referred to as tracers, markers, or proxy compounds. Nicotine and respirable suspended particulates (RSP)[3] are the most widely used markers for the presence and concentration of ETS in indoor environments. Recently, some researchers have used 3-ethenylpyridine, solanesol, and ultraviolet particulate matter as markers of ETS and suggested that they may be better correlated with other constituents of ETS than nicotine and RSP (Hodgson *et al.*, 1996; Jenkins *et al.*, 1996).

Airborne nicotine is specific to tobacco combustion and is emitted in large quantities in ETS. Although not specific to tobacco combustion, large quantities of RSP are emitted during cigarette smoking, resulting in measurable increases over background levels even under conditions of high ventilation and low smoking rates. There are other common combustion-related sources of indoor RSP, such as wood-burning fireplaces, gas stoves, and kerosene space heaters, but the levels of RSP produced by these sources are much lower than that produced by tobacco smoke. Other ETS constituents have been measured in field studies assessing the contribution of

[2] The information presented refers primarily to ETS derived from cigarettes because few data are available for cigars and pipes.

[3] The term respirable suspended particulates (RSP) has been inconsistently applied in the literature. Typically, it is used to refer to PM2.5 or PM10, *i.e.*, particles for which the mean aerodynamic diameter is 2.5 or 10 microns, respectively. Particles associated with ETS are typically smaller than 1 micron, and are included in both PM2.5 and PM10.

smoking to indoor air quality. Typically, these constituents are not unique to ETS, but studies indicate that concentrations of some constituents are higher in environments where smoking takes place as compared to those where it does not.

While fixed location measurements of air concentrations of ETS constituents indicate the presence of ETS and allow an estimation of the contribution of ETS to indoor air contaminant levels, such measurements do not constitute a direct measure of an individual's total ETS exposure. During the course of a single day, an individual spends varying amounts of time in a number of different environments; for that individual, the total exposure is the sum of the concentration at each location multiplied by the time spent at that location. Further, for different individuals exposed to the same concentration levels of ETS constituents in the same room, the actual dose will vary as a function of a number of factors, including gender, age, specific activity level, and breathing rate at the time of exposure.

The data presented in the following sections on individual ETS constituents have been summarized from a large number of studies of different microenvironments, primarily within the United States. The measured concentrations of individual constituents in homes and other indoor environments show marked spatial and temporal variation as a result of the complex interaction of factors related to the introduction, removal, and dispersion of ETS constituents. These factors include the rate of tobacco consumption, room size, the location at which smoking occurs, the placement of air monitors, the ventilation or infiltration rate, air mixing, and removal of contaminants by air filters or deposition. With few exceptions, studies were not designed to determine representative ETS concentrations within a particular environment or area of the country. However, it is expected that the ranges reported are typical of similar environments within California. Measurements from the few studies specific to California are reported separately.

2.3.3 Indoor Air Concentrations of Nicotine

Over 25 separate studies have measured concentrations of nicotine in well over 100 different indoor microenvironments. The results of these studies are summarized in U.S. EPA (1992: Section 3.3.1 and Figures 3-4 and 3-7). An extensive compilation of measured nicotine concentrations in various indoor environments is also given in Guerin *et al.* (1992). Because airborne nicotine is generally specific to the combustion of tobacco, any detectable concentrations can be attributed to ETS (the few exceptions include areas such as work environments in which tobacco is processed). Both chamber studies (Baker and Proctor, 1990; Eatough *et al.,* 1990; Nelson *et al.,* 1992) and indoor air measurements (Löfroth, 1993) suggest that nicotine disappears from air faster than other ETS constituents, and hence, its use as a marker may underestimate the relative concentrations of other constituents.

Measurements taken in a wide variety of indoor environments in the U.S. indicate that most average concentrations of nicotine range about

100-fold, from 0.3 to 30 µg/m^3. The average concentration in residences with one or more smokers typically ranges from 2 to 10 µg/m^3, with high values of up to approximately 14 µg/m^3. Measured concentrations are typically higher in the winter than in summer months. In data collected from the mid-1970's through 1991, concentrations of nicotine in the workplace were similar to those measured in residences, with the range of average concentrations showing considerable overlap for the two locations. However, the maximum values for workplaces were considerably higher than in residences. In a recent paper, Hammond *et al.* (1995) showed that ETS exposures in workplaces that allow smoking are comparable with, and often greater than, ETS exposures in smokers' homes. The highest nicotine concentrations in indoor environments were measured in bars and in the smoking sections of airplanes, with levels reaching as high as 50 to 75 µg/m^3 (U.S. EPA, 1992). (Note: for several years, smoking has been prohibited on domestic flights of commercial airplanes). In a comprehensive survey of indoor measurements, the maximum nicotine concentrations were 30 µg/m^3 or less in over 50 percent of the studies examined, and less than 100 µg/m^3 in 90 percent of the studies (Guerin *et al.,* 1992). The highest reported level in the survey was 1010 µg/m^3, measured in a passenger car with the ventilation system shut off. In selected studies using controlled and field conditions, the concentrations of nicotine were found to increase as a function of the number of smokers present and the number of cigarettes consumed (U.S. EPA, 1992: Section 3.3.1.2 and pages 3-32 to 3-33).

Results of four studies (three in the U.S.) using personal monitors to assess exposure of nonsmokers to nicotine are presented in U.S. EPA (1992: page 3-37). The average personal exposures associated with the specific microenvironments in the U.S. for which measurements were taken ranged from 4.7 to 20.4 µg/m^3. In comparing the levels determined from stationary and personal samples, Guerin *et al.* (1992) reported that in one study, concentrations determined by the stationary sampler were higher than those from the personal monitor. In a second study, the reverse was found to be true. In a more recent study (Jenkins *et al.*, 1996), breathing zone air samples were taken of approximately 100 nonsmoking individuals in each of 16 metropolitan areas of the U.S. The mean 24-hour time-weighted average nicotine concentration for those who were exposed to ETS at work and away from work (3.27 µg/m^3) was higher than those who were only exposed to ETS away from work (1.41 µg/m^3) or those who were only exposed at work (0.69 µg/m^3). The mean nicotine concentration measured by personal monitoring for those who were not exposed to ETS was 0.05 µg/m^3.

Nicotine measurements in California residences were included in a large-scale field study of particle exposure in Riverside in 1990, in which 178 nonsmokers over the age of 10 wore personal particle monitors for two consecutive 12-hour periods (Ozkaynak *et al.,* 1994). Particle samples were taken concurrently in indoor and outdoor air. Due to budget constraints, only a portion of the samples from nonsmoking homes was analyzed for nicotine, while all samples from smoking homes were analyzed.

Approximately 30 percent of all personal and indoor samples analyzed were above the detection limit (about 0.05 µg/m^3), with 76 percent of the personal samples from individuals reporting one or more minutes of exposure to ETS above the limit of detection. For those samples exceeding the detection limit, the mean personal 12-hour nicotine concentration for individuals reporting exposure to ETS was 0.96 µg/m^3, and 0.11 µg/m^3 for individuals with no reported exposure. The mean indoor concentration of nicotine in homes in which at least one cigarette was smoked (1.07 µg/m^3) was significantly higher than in homes with no reported smoking (0.10 µg/m^3).

2.3.4 Indoor Air Concentrations of Particulate Matter

A large number of studies have measured concentrations of ETS-associated RSP in indoor microenvironments. These studies are summarized in U.S. EPA (1992: Figures 3-5, 3-8, and 3-10). An extensive compilation of RSP measurements is also given in Guerin *et al.* (1992). In contrast to nicotine, RSP is not specific to ETS and thus RSP measurements in environments where smoking occurs must be compared to concentrations in comparable environments where smoking does not occur. Similar to nicotine, measured concentrations of ETS-associated RSP range about 100-fold, from 5 to 500 µg/m^3 over a wide variety of indoor environments. In residences with one or more smokers, average daily or weekly concentrations of ETS-associated RSP are increased about 20 to 100 µg/m^3 over concentrations in similar nonsmoking environments. Somewhat lower levels are reported in the workplace (offices), with average concentrations ranging from approximately 2 to 60 µg/m^3 over concentrations in similar nonsmoking environments. Both the maximum reported concentration (1,370 µg/m^3) measured in any environment and the highest range of average concentrations (approximately 35 to 986 µg/m^3) were for restaurants (U.S. EPA, 1992: Figure 3-8).

Studies comparing RSP concentrations in similar locations in which smoking does and does not take place consistently show higher RSP concentrations in environments where smoking occurs. Typically, the differences range from less than 10 percent to approximately three-fold higher, although larger differences have been reported (Guerin *et al.,* 1992). Under selected and controlled field conditions, the concentration of ETS-associated RSP has been found to increase with increased smoking (U.S. EPA, 1992: page 3-34).

Recently, Ott *et al.* (1996) measured RSP in a large sports tavern in Northern California on 26 dates between 1992 and 1994 during which smoking was allowed, and subsequently made additional measurements during the year after smoking was prohibited. Though the degree of active smoking in the tavern was characterized as low by the authors, they reported that the average RSP concentration indoors was 56.8 µg/m^3 above the outdoor concentration. After smoking was prohibited, another set of 26 follow-up visits (matched to the earlier smoking visits by time of day, day of the week, and season), yielded an average RSP concentration that was 77 percent of the average concentration during the smoking period. No decrease in tavern attendance was evident after smoking was prohibited.

Results of five studies using personal monitors to assess exposure of nonsmokers to RSP are presented in U.S. EPA (1992: page 3-38). Only three studies reported exposures integrated over several different environments, with exposure to ETS-associated RSP resulting in increased concentrations of 18 to 64 μg/m^3. Those individuals reporting exposure to ETS had substantially increased exposure to RSP as compared to individuals reporting no ETS exposure. In a more recent study, Jenkins *et al.* (1996) took breathing zone air samples of approximately 100 nonsmoking individuals in each of 16 metropolitan areas of the U.S. The mean 24-hour time-weighted average RSP concentration for those who were exposed to ETS at work and away from work (47 μg/m^3) was higher than for those who were only exposed to ETS away from work (33 μg/m$^{3)}$ or those who were only exposed at work (28.7 μg/m^3). The mean RSP concentration measured by personal monitoring of those who were not exposed to ETS was 18.1 μg/m^3.

Data specific to California are available from one field study conducted in 178 randomly selected homes in the city of Riverside (Pellizzari *et al.,* 1992). Indoor air concentrations of particles 10 micrometers or less in aerodynamic diameter (PM10) were significantly higher in homes in which smoking occurred (n = 28 homes for daytime measurement, 30 for nighttime), as compared to the homes without smoking (n = 139 homes for daytime measurement, 131 for nighttime)—samples from a few homes were lost due to pump or power failure, or quality control concerns. Mean PM10 levels in the homes with smoking were elevated (125.6 μg/m^3 for the 12-hour daytime measurement, 92.9 μg/m^3 nighttime) above those in homes without smoking (87.8 μg/m^3 daytime, 54.6 μg/m^3 nighttime) by a consistent amount (approximately 38 μg/m^3; Pellizzari *et al.,* 1992). Average personal exposures to PM10 were significantly higher for those persons (n = 29) reporting exposure to ETS during the nighttime period as compared to persons (n = 139) reporting no ETS exposure during the nightime (104.2 versus 71.4 μg/m^3). However, no significant difference in average personal exposures to PM10 was found for the daytime period (n = 61 ETS-exposed, 110 unexposed; 155.2 μg/m^3 versus 146.8 μg/m^3).

2.3.5 Indoor Air Concentrations of Other ETS Constituents

Numerous field studies have been conducted to assess the contribution of smoking to indoor air pollution. Data for select constituents of public health concern, including *N*-nitrosamines, benzene, benzo[a]pyrene and total PAHs, carbon monoxide, formaldehyde, and toluene are presented in U.S. EPA (1992: Table 3-3 and Figure 3-3), as are references to the literature (U.S. EPA, 1992: Section 3.3.1). An extensive compilation of data from measurements of a variety of ETS-derived constituents is also given in Guerin *et al.* (1992).

Because sources other than ETS exist for many of these constituents, it has been difficult for studies to consistently demonstrate elevated concentrations in smoking environments. For example, formaldehyde, which is present in a number of consumer products and building materials, is emitted from these sources at rates usually exceeding those from smoldering cigarettes. Carbon monoxide (CO) is also released from other sources,

including gas stoves and heaters, and may be found indoors from air exchange with outdoor air contaminanted by vehicle exhaust; thus, it is often difficult to ascertain the contribution to indoor CO levels due to cigarette smoke (Guerin *et al.,* 1992). However, for many constituents, concentrations in environments where smoking occurs are elevated above levels in comparable environments where smoking does not occur, particularly for those environments in which heavy smoking occurs. Concentrations of ETS-associated constituents measured in different indoor environments are highly variable, depending on factors such as extent of smoking, air exchange rates, and room size.

2.3.5.1 Polycyclic Aromatic Hydrocarbons

Concentrations of a variety of toxic air pollutants have been measured in California homes. Indoor concentrations of 13 PAHs measured in the homes in the Riverside field study (Pellizzari *et al.,* 1992) described in Section 2.3.4 were reported by Sheldon *et al.* (1992b). The oncentrations of most of the PAHs analyzed were significantly higher (approximately 1.5- to 2-times higher) in homes in which smoking occurred, as compared to the concentrations in homes without smoking (number of samples in homes with smoking/homes without: daytime, 17/93; nighttime, 21/85). Included in the analyses were five PAHs (benzo[a]anthracene, benzo[a]pyrene, benzo[k]fluoranthene, chrysene, and indeno[1,2,3-cd]pyrene) which are listed as carcinogens under Proposition 65 and detected in ETS. As an example of the magnitude of the concentrations measured, the average 12-hour daytime indoor concentration of benzo[a]pyrene was 0.51 ng/m^3 in homes in which smoking occurred and 0.20 ng/m^3 in homes without smoking (Sheldon *et al.,* 1992b).

A second field study in California (Sheldon *et al.,* 1993) examined the relationship between indoor concentrations of 14 PAHs and different combustion sources (tobacco smoking, fireplaces, woodstoves, and gas heaters); measurements were taken in 280 homes in Placerville and Roseville. Indoor PAH concentrations in the 64 homes in which tobacco smoking occurred were significantly higher (approximately 1.5 to 4 times higher) than in the 39 homes with no specified indoor combustion source. Of the indoor combustion sources examined, tobacco smoking appeared to have the strongest effect on indoor levels of PAHs. As an example of the magnitude of the measured concentrations, the average 24-hour concentrations of benzo[a]pyrene associated with indoor combustion sources were as follows: tobacco smoking, 2.2 ng/m^3; woodstove use, 1.2 ng/m^3; fireplace use, 1.0 ng/m^3; gas heat use, 0.41 ng/m^3; and no specified indoor combustion source, 0.83 ng/m^3 (Sheldon *et al.,* 1993).

2.3.5.2 Other Organic Compounds

Other toxic air pollutants (30 volatile and semivolatile organic compounds) were measured in a study of 128 homes in the city of Woodland. Indoor samples were collected in all homes and personal monitoring samples for volatile organic compounds were collected for 93 individuals. About 61 percent of the homes were nonsmoking homes, and smoking occurred in about 39 percent of the homes during the monitoring period. Homes (n = 15) in which heavy smoking (>20 cigarettes

smoked/24-hour period) occurred had elevated concentrations of benzene, para-dichlorobenzene[4], tetrachloroethylene, trichlorethylene[4], and xylene (ortho and meta/para) as compared to homes with no smoking. Personal monitoring air concentration samples of benzene and para-dichlorobenzene were also higher for persons in homes with "any smoking" and those with "heavy smoking" compared to homes with no smoking. However, for both the indoor and personal air measurements, these differences were not statistically significant at the $p = 0.05$ level, as determined using pairwise t tests (Sheldon *et al.,* 1992a). Hodgson *et al*. (1996), using 3-ethenylpyridine as a tracer, investigated the contribution of ETS to the measured volatile organic compounds concentrations in several environments in California where smoking was allowed. In their report, ETS was estimated to contribute 57-84 percent of the formaldehyde concentrations, 43-69 percent of the 2-butanone concentrations, 37-58 percent of the benzene concentrations, and 20-70 percent of the styrene concentrations. The fractional contributions of ETS to the concentrations of acetone, toluene, ethylbenzene, xylene isomers, and d-limonene were all less than 50 percent (Hodgson *et al*., 1996).

2.4 EXPOSURE MEASUREMENT: BIOLOGICAL MARKERS

This section addresses use of biomarkers to measure ETS exposure, with a focus on nicotine and cotinine. Topics covered include: measured concentrations in physiological fluids of adults; comparisons of levels in smokers, ETS-exposed nonsmokers, and unexposed nonsmokers; and concentrations in physiological fluids of infants and children, and in breast milk and amniotic fluid. The use of levels of exhaled carbon monoxide and blood levels of carboxyhemoglobin, as well as thiocyanate levels in blood, urine, and saliva as biomarkers of ETS exposure are also addressed. Measurement of DNA and protein adducts, and other approaches to assessing tobacco smoke exposure, are discussed briefly. Other sections of this chapter summarize studies of exposure prevalence as determined by the presence of nicotine or cotinine in body fluids (Section 2.6) and studies using biomarkers to ascertain smoking status and estimate the degree of misclassification in epidemiological studies (Section 2.5).

2.4.1 Introduction to Biological Markers of ETS Exposure

Exposure to ETS can be assessed directly by the analysis of physiological fluids (urine, saliva, and serum) for tobacco smoke constituents or their metabolites, referred to as "biomarkers." Nicotine, cotinine, thiocyanate, carboxyhemoglobin, hydroxyproline, *N*-nitrosoproline, aromatic amines, and certain protein or DNA adducts have been used as indicators of exposure to tobacco smoke. These biomarkers do not indicate the presence of disease, however, or of an individual's susceptibility to disease due to exposure to tobacco smoke. The appropriateness of a given biomarker depends on the nature of the study and the type of exposure being assessed (*e.g.*, recent or long-term). Ideally, the biomarker should be specific to tobacco smoke, although few markers fully meet this criterion.

[4] Although measured at elevated concentrations in homes with heavy smoking, para-dichlorobenzene and trichloroethylene are not expected to be associated with ETS (Guerin *et al.,* 1992)

The relationship between a biomarker and exposure is complex, and varies as a function of both environmental and physiological factors. As previously discussed (Section 2.3), the degree of exposure is a function of the time an individual spends in each setting and the air concentration of tobacco-related constituents in that environment. Factors affecting air concentrations include smoking intensity, room size, and room ventilation. For a given air concentration, several factors will affect an individual's intake, such as gender, age, weight, and activity level (and corresponding inhalation rate) at the time of exposure. In addition, individual differences in uptake, distribution, and metabolism will affect the biomarker concentration in physiological fluids. Although the presence of a biomarker indicates that tobacco smoke exposure has occurred, the level of biomarker measured may not be directly related to the intake level of the tobacco smoke constituent(s) potentially implicated in the effect of interest (*e.g.*, using cotinine as a biomarker of ETS exposure in a study of cancer incidence).

2.4.2 Biomarkers: Nicotine and Cotinine

2.4.2.1 Nicotine and Cotinine: General methodological issues

Nicotine and cotinine, a major metabolite of nicotine, are the most widely used biomarkers of ETS exposure. In general, the presence of nicotine or its metabolites in physiological fluids can be attributed to exposure to tobacco smoke. The few exceptions include occupational exposure to tobacco leaves (Gehlbach *et al.,* 1975) and nicotine products, use of smokeless tobacco products, chewing of nicotine gum, and use of nicotine patches or other aids for smoking cessation. Low levels of nicotine have been found in tea and in edible solanaceous plants including eggplant, green pepper, and tomato (Castro and Monji, 1986; Sheen,1988; Davis *et al.,* 1991; Domino *et al.,* 1993a & b). While some authors have claimed that dietary intake of nicotine may be of practical importance in the use of nicotine and cotinine as biomarkers of ETS exposure (Domino *et al.,* 1993a,b), others dispute this assertion (Henningfield, 1993; Jarvis, 1994; Repace, 1994; Benowitz, 1996; Pirkle *et al.*, 1996). In general, the levels of nicotine and nicotine metabolites in physiological fluids resulting from the ingestion of foods have not been found to significantly impact the levels resulting from exposure to nicotine from tobacco sources.

As biomarkers of exposure, nicotine and/or cotinine are typically measured in blood, saliva, or urine. For studies requiring a quantitative assessment of exposure, blood has been recommended as the fluid of choice, although saliva and urine are also considered acceptable (Watts *et al.,* 1990). Cotinine levels in saliva and plasma tend to be similar, whereas the ratio of urinary to plasma levels is generally a factor of 5 to 6 (Repace and Lowrey, 1993; Benowitz, 1996).

Urinary cotinine excretion is variable across and within individuals, depending on renal function, urinary flow rate, and urinary pH (Benowitz, 1983). Urinary results may be expressed as nanograms of cotinine per milligram of creatinine in order to correct, in part, for differences in dilution

effects. Because the amount of endogenous creatinine produced is a function of muscle mass, and hence, age and sex, individual excretion rates of creatinine are also variable. In particular, cotinine to creatinine ratios may not be appropriate for comparisons between males and females. In addition, low levels of creatinine in infants relative to adults may result in cotinine to creatinine ratios for infants that fall into the range reported for active smokers (Watts *et al.,* 1990). In general, it is preferable to collect urine over 24 hours, although is impracticable for most studies.

The average half-life of cotinine in different body fluids (plasma, saliva, and urine) is about the same, approximately 15 to 19 hours (Jarvis *et al.*, 1988; Benowitz and Jacob, 1994), making it a good indicator of the integrated ETS exposure over the previous 2 to 3 days. The half-life is typically longer in infants and children, averaging approximately 65 hours in neonates, 60 hours in infants under 18 months, and 40 hours in children over 18 months (U.S. EPA, 1992: page 3-41). Nicotine, with its shorter half-life of approximately 2 hours, is a good indicator of exposures occurring within the previous few hours.

An interlaboratory study of data from 11 laboratories in six countries was conducted to compare analytical results for nicotine and cotinine in serum and urine (Biber *et al.,* 1987). The results of the study indicate that both gas chromatography (GC) and radioimmunoassay (RIA) techniques reliably quantitate nicotine and cotinine in urine and serum samples and that both techniques are capable of discriminating between smokers and nonsmokers. However, interlaboratory variability was high. While the coefficient of variation for spiked samples was low (9-13 percent), the coefficient of variation for samples from smokers was fairly large, ranging from 18 to 45 percent for serum and from 21 to 59 percent for urine. In addition, cotinine levels reported for urine, as determined by RIA, were about 60 percent higher than the levels determined by GC. Besides cotinine, some less specific immunoassays can also react with other metabolites of nicotine. Cotinine levels reported for nonsmokers were extremely variable, and a number of laboratories could not detect cotinine in serum from exposed nonsmokers. Because of these various factors, caution should be used in making quantitative comparisons across studies. However, limitations in the design of this study have been noted (Watts *et al.,* 1990); additional studies are required to assess the comparability of these two assay methods and the results from different laboratories, as well as the performance of other methods (*e.g.*, high pressure liquid chromatography (HPLC)).

2.4.2.2 Nicotine and Cotinine: Measured Concentrations in Physiological Fluids of Adults

A large number of studies are available which report concentrations of cotinine in physiological fluids of smokers and nonsmokers. The levels of ETS encountered by exposed nonsmokers during their daily activities are sufficiently high that nicotine and cotinine are detected in their urine, blood, and saliva. The physiological concentrations of cotinine detected in saliva and plasma of nonsmokers typically range from 0.5 ng/ml to 10 or 15 ng/ml (Guerin *et al.,* 1992; U.S. EPA, 1992), and urinary concentrations range to

50 or more ng/ml. For example, Cummings *et al.* (1990) reported that a population of 663 self-reported nonsmokers attending a cancer-screening clinic in New York had a mean urinary cotinine concentration of 8.84 ng/ml (range: 0 to 85 ng/ml)—in the Cummings *et al.* study, a cutoff level of 90 ng/ml was used to distinguish between smokers and nonsmokers. In a population-based study of Hispanics in New Mexico, mean salivary concentrations of cotinine in various age groups ranged from 0 (not detected) to 6.0 ng/ml (Coultas *et al.,* 1987). The studies by Coultas *et al.* (1987) and Cummings *et al.* (1990) are described in Section 2.6.3. However, it is important to realize that some of the differences in cotinine levels reported here could be explained by the different analytical methods used. For example, cross-reactivity of cotinine immunoassays with trans-hydroxycotinine and/or cotinine glucuronide is probably an important contributor to the often significantly higher levels of urinary cotinine measured by this method compared to those measured by GC. Thus, in comparing cotinine levels reported in various studies, it is important to consider the analytical method employed and the specific analytes that are being measured.

Studies of individuals exposed in locations of exceptionally high concentrations of ETS provide some indication of the maximum concentrations of nicotine and cotinine reported in nonsmokers. Jarvis *et al.* (1992) reported a median salivary cotinine concentration of 7.95 ng/ml in 42 nonsmoking bar staff in England, with a maximum concentration of 31.3 ng/ml. In a study of individuals exposed on commercial airline flights, the highest average urinary cotinine concentrations among those who were measured was approximately 30 ng/mg creatinine (Mattson *et al.,* 1989).

In one of the few controlled studies in which both ambient air and biomarker concentrations were measured, uptake of nicotine and cotinine was determined in 10 nonsmoking volunteers. The subjects were exposed for 80 minutes in a 16 m^3 bare room into which sidestream smoke (generated by the machine smoking of 2 to 4 cigarettes) was continuously injected (mainstream smoke was released outside the room.) The ventilation rate was six air exchanges per hour, reported to correspond to the average ventilation conditions in offices in the U.S. Concentrations of measured ETS constituents attained stable levels within approximately 10 to 15 minutes, at which time the air concentration of nicotine from the continuous smoking of four cigarettes was 280 $\mu g/m^3$. The levels of nicotine and cotinine in urine, saliva, and serum for individuals exposed to the continuous smoking of four cigarettes are shown in Table 2.3. The average concentrations of nicotine in saliva increased significantly, reaching a maximum concentration of 880 ng/ml after 60 minutes of exposure. Following cessation of exposure, nicotine concentrations decreased rapidly, reaching pre-exposure levels in 2 to 3 hours. Cotinine concentrations continued to increase throughout the duration of the experiment, reaching concentrations of 3.4 ng/ml and 55 ng/mg creatinine in serum and urine, respectively, 6 hours and 20 minutes after exposure began (Hoffmann *et al.,* 1984).

Table 2.3
Mean Concentrations of Nicotine and Cotinine in the Saliva, Plasma, and Urine of ETS-Exposed Volunteers[a]

	Saliva (ng/ml)		Plasma (ng/ml)		Urine (ng/mg creatinine)	
Time	Nicotine	Cotinine	Nicotine	Cotinine	Nicotine	Cotinine
Minutes of exposure						
0 (baseline)	3	1.0	0.2	0.9	17	14
40	830	1.1	0.3	0.9	--[a]	---
60	880	2.1	0.3	1.2	---	---
80	730	1.4	0.5	1.3	84	28
Minutes post exposure						
30	148	1.7	0.4	1.8	---	---
150	17	3.1	0.7	2.9	100	46
240	3	2.0	1.1	3.3	---	---
300	7	3.5	0.6	3.4	48	55

Source: Hoffmann et al. (1984)

[a] *Individuals were exposed to ETS generated from continuous smoking of 4 cigarettes by machine. The air concentration of nicotine stabilized at approximately 280 µg/m³ within 10 to 15 minutes.*
[b] *Samples not taken for this exposure interval.*

Limited information on cotinine concentrations in California subjects is available from a large multinational study which included a center located in Los Angeles (Riboli *et al.,* 1990). Study subjects were 100 nonsmoking women with the following marital and employment status: 13 percent married to a smoker and employed; 39 percent married to a smoker and unemployed; 16 percent not married to a smoker and employed; and 32 percent not married to a smoker and unemployed. The mean urinary cotinine to creatinine concentration was approximately 8.5 ng/mg for the entire population and 10.5 ng/mg for those with detectable urinary concentrations. The differences in cotinine levels were found to be large and statistically significant between the 13 centers, and the concentrations at the Los Angeles center was one of the three highest of the centers in the study.

2.4.2.3 Nicotine and Cotinine: Comparison of Levels in Smokers, and ETS-exposed and Unexposed Nonsmokers

Studies comparing ETS-exposed and unexposed nonsmokers and active smokers (Matsukura *et al.,* 1979; Wilcox *et al.,* 1979; Williams *et al.,* 1979; Haley *et al.,* 1983; Hill *et al.,* 1983; Jarvis and Russell, 1984; Wall *et al.,* 1988) have consistently found that measurement of cotinine in the urine, saliva, or serum can distinguish active smokers from unexposed and ETS-exposed nonsmokers. Findings have been less consistent with regard to the use of such assays to distinguish between self-reported unexposed and

ETS-exposed nonsmokers. As discussed by Wall *et al.* (1988), potential reasons for this include intersubject variability in nicotine metabolism (Benowitz *et al.,* 1982); time of day of sample collection (Jarvis and Russell, 1984); misreporting of smoking status (Jarvis and Russell, 1984; Jarvis *et al.,* 1987); misreporting of nonsmoking status; adjustment of cigarette consumption for nicotine content (Benowitz *et al.,* 1983); and over- or underreporting of ETS exposure. Another reason is that in the past some of the methods used for cotinine analysis were simply not sensitive enough to detect the very low concentration of cotinine in saliva or serum resulting from ETS exposure.

The levels of nicotine, cotinine and other ETS biomarkers measured in a study by Jarvis and Russell (1984) are shown in Table 2.4. Study subjects were 100 outpatients, mostly elderly, attending cardiology and vascular clinics at a London hospital. Individuals reported their degree of exposure to ETS over the 3-day period preceding sample collection. In general, concentrations of nicotine and cotinine in ETS-exposed nonsmokers were higher than those in nonsmokers reporting no exposure to ETS. The levels of cotinine in all fluids were significantly higher in smokers than in ETS-exposed and unexposed nonsmokers, with cotinine levels in ETS-exposed nonsmokers approximately 1 percent of the levels found in active smokers. In this study, concentrations of plasma nicotine were not related to reported exposure.

Recently, an increasing number of epidemiological studies have used biomarkers in assessing tobacco smoke exposure. Biomarkers can be used to categorize individuals as exposed or unexposed, identify deceivers (individuals misreporting their smoking status), or estimate relative degree of exposure. In a comparison of tests to distinguish smokers from nonsmokers, Jarvis *et al.* (1987) analyzed questionnaire responses and biochemical measures of exposure to cigarette smoke in 211 hospital outpatients. The optimal cutoff levels (in plasma, saliva, and urine) for distinguishing smokers and nonsmokers as reported in that study are shown in Table 2.5. Examples of typical cutoff levels for distinguishing smokers from nonsmokers reported in studies using cotinine as the marker of exposure are shown in Table 2.6 (the use of biomarkers to ascertain smoking status and estimate the degree of misclassification in epidemiological studies is discussed in Section 2.5).

For all body fluids, the concentration distributions for smokers and exposed nonsmokers have been found to overlap; cotinine concentrations in the occasional smoker are similar to those of the heavily exposed nonsmoker. This is shown in Figure 2.1, in which the distributions of plasma cotinine concentrations for self-reported smokers and nonsmokers are shown to overlap. The distribution of values for self-reported nonsmokers is bimodal, suggesting some denial of active smoking (*i.e.*, deceivers) among the study subjects. For nicotine and other biomarkers of ETS exposure, the concentration distributions similarly overlap and are bimodal, presumably

Table 2.4
Compairison of Biomarkers in Unexposed and ETS-Exposed Nonsmokers and Active Smokers[a]

Biochemical Parameter	Unexposed Nonsmokers (*n* = 46) Mean Value	% of Active-Smokers' Value	ETS-Exposed Nonsmokers (*n* = 54) Mean Value	% of Active-Smokers' Value	Active Smokers (*n* = 94) Mean Value
CO in expired air (ppm [mg/m^3])	5.7 [6.5]	27	5.5 [6.3]	26	20.8 [24]
COHb (%)	0.9	23	0.8	21	3.9
Nicotine (ng/ml)					
in plasma	1.0	7	0.8	5.4	14.8
in saliva	3.8	0.6	5.6	0.8	672.5
in urine	3.9	0.2	12.1*	0.7	1749.9
Cotinine (ng/ml)					
in plasma	0.8	0.3	2.0*	0.7	275.2
in saliva	0.7	0.2	2.5**	0.8	309.9
in urine	1.6	0.1	7.7**	0.6	1391.0
Thiocyanate (µmol/l)					
in plasma	48	39	53	43	123
in saliva	1270	52	1327	54	2450
in urine	73	47	77	50	155

[a] *From IARC (1986) using data from Jarvis and Russell (1984).*
* *Indicates p < 0.01 between exposed and unexposed nonsmokers*
** *Indicates p < 0.001 between exposed and unexposed nonsmokers*

reflecting a certain degree of misreporting by the active smoker (Jarvis *et al.,* 1987).

2.4.2.4 Nicotine and Cotinine: Concentrations in Physiological Fluids of Infants and Children

ETS exposure of infants and children has been examined in a number of studies in which nicotine and cotinine were used as biomarkers of exposure. Infants can be exposed prenatally to tobacco smoke constituents if the mother smokes or if the mother is exposed to ETS during pregnancy. Postnatal ETS exposure may occur directly, via inhalation, and indirectly, from ingestion of breast milk.

Henderson *et al.* (1989) examined the relationship between levels of nicotine in home air and the urinary cotinine concentrations in 27 children, 11 months to 5 years of age, attending a day care center at which

Table 2.5
Cut-off, Sensitivity, and Specificity of Biomarkers for Discriminating True Smoking Status[a]

Biomarkers	Cut-of Value	% Smokers Detected	% Nonsmokers Detected	95% CI for % Accuracy[b]
Carbon Monoxide				
ECO (ppm)	8.0	90	89	86.2-91.7
COHb (%)	1.6	86	92	83.0-89.2
Nicotine (ng/ml)				
Plasma	2.3	88	99	89.4-93.8
Saliva	21.8	90	99	91.6-95.2
Urine	58.6	89	97	93.3-96.3
Cotinine (ng/ml)				
Plasma	13.7	96	100	98.3-99.1
Saliva	14.2	96	99	98.5-99.3
Urine	49.7	97	99	98.4-99.2
Thiocyanate				
Plasma (µmol/l	78.0	84	91	81.1-87.9
Saliva (µmol/l)	1.64	81	71	66.0-76.0
Urine (µmo/l)	118.0	59	89	67.0-77.0

Jarvis et al. (1987), with permission

[a] *True smokers were those who reported smoking cigarettes, pipes, or cigars (n = 90) and 21 "deceivers." Nonsmokers were the self-reported nonsmokers minus the deceivers (n = 100).*
[b] *Accuracy defined as overall % correct classification, and estimated for a population with equal proportions of smokers and nonsmokers.*

they were not exposed to ETS. Fifteen children resided in homes with smokers and 12 did not. The average concentration of air nicotine in the homes of children who did and did not live with smokers was 3.74 µg/m^3 and 0.34 µg/m^3, respectively. Urinary cotinine concentrations were greater than 30ng/mg creatinine in 12 of the 15 children who lived with smokers, whereas concentrations were consistently less than 30 ng/mg creatinine in the 12 children without home exposure to ETS; three of the exposed children had urinary cotinine concentrations consistently in the upper range of values observed in unexposed children. The average home air nicotine concentrations were related to the average log urinary cotinine to creatinine concentration ($r = 0.68$, $p = 0.006$).

Greenberg *et al.* (1984) measured the concentrations of nicotine and cotinine in the urine and saliva of 32 ETS-exposed and 19 unexposed infants less than 10 months of age visiting a primary care clinic in North Carolina. An infant was categorized as exposed if the caregiver reported at least two exposure episodes during the previous 24 hours and unexposed if

Table 2.6
Studies of Cotinine Measurements in Self-Reported Nonsmokers and Criteria Used to Distinguish Smokers from Nonsmokers

			Self-Reported Nonsmokers		
Study	**Marker**	**Assay**[a]	**Sample Size**	**Percent Misclassified**[b]	**Criteria (ng/ml)**
Wald *et al.* (1986)	Urinary cotinine	RIA	221	0.9	--[c]
Cummings *et al.* (1990)	Urinary cotinine	HPLC	669	0.9	90
Pojer *et al.* (1984)	Plasma cotinine	GC	181	3.3	42
Jarvis and Russell (1984)	Plasma cotinine	GC	215	9.8	20
Lee (1987)	Saliva cotinine	GC	808	2.5	30
Pierce *et al.* (1987)	Saliva cotinine	GC	622	7.4	25
Coultas *et al.* (1988)	Saliva cotinine	RIA	683	6.0	20
Haddow *et al.* (1988)	Serum cotinine	RIA	1,508	1.9	10
Riboli *et al.* (1990)	Urinary cotinine	RIA	1,369	3.4	50[d]
Wagenknecht *et al.* (1991)	Serum cotinine	RIA	3,445	4.2	14
Perez-Stable *et al.* (1992)	Serum cotinine	GC	189	6.3	14

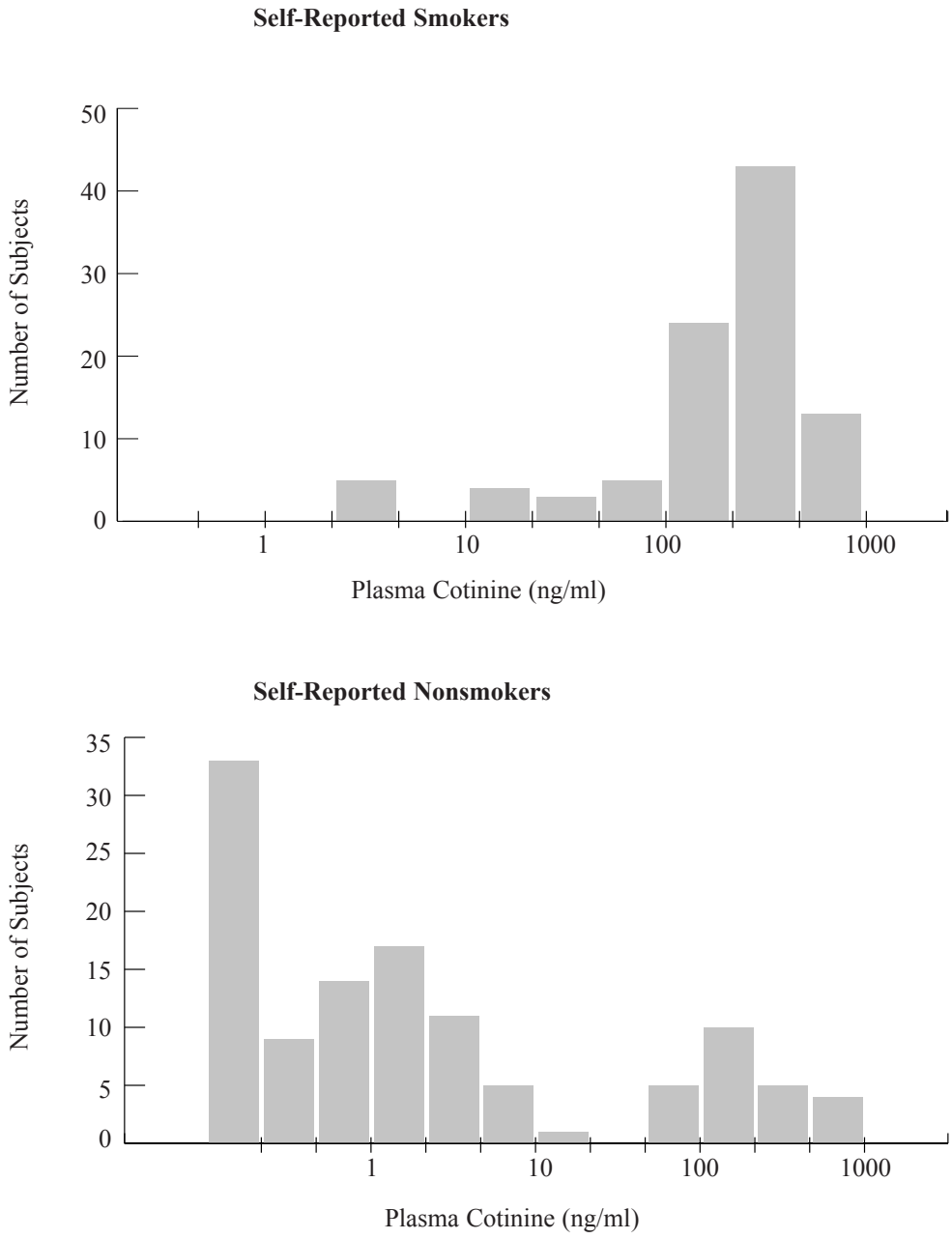
Modified from Perez-Stable et al. (1992)

[a] *Abbreviations: GC, gas chromatography; RIA, radioimmunoassay; HPLC, high pressure liquid chromatography*
[b] *percentage of self-reported nonsmokers with cotinine levels above criteria listed*
[c] *>10% smokers' median*
[d] *ng/mg creatinine*

no exposure had occurred during the previous week. Breast-fed infants were excluded from this study in order to examine inhalation exposure only. The concentrations of both nicotine and cotinine were significantly higher in the saliva and urine of the exposed group as compared to the unexposed group, with the best indicator of exposure reported to be the ratio of urinary cotinine to creatinine. The median ratio in the exposed group was 350 ng/mg as compared to 4 ng/mg in the unexposed group ($p < 0.0001$). The mother's self-reported smoking behavior (number of cigarettes smoked during the previous 24 hours) was related to infant urinary concentration ($r = 0.67$, $p = 0.0001$). In a later study from the same group (Greenberg *et al.* (1989), described in Section 2.6.3), cotinine was detected in 60 percent of the 433 infants examined; the median concentration was 121 ng/mg creatinine (range: 6 to 2,273 ng/mg).

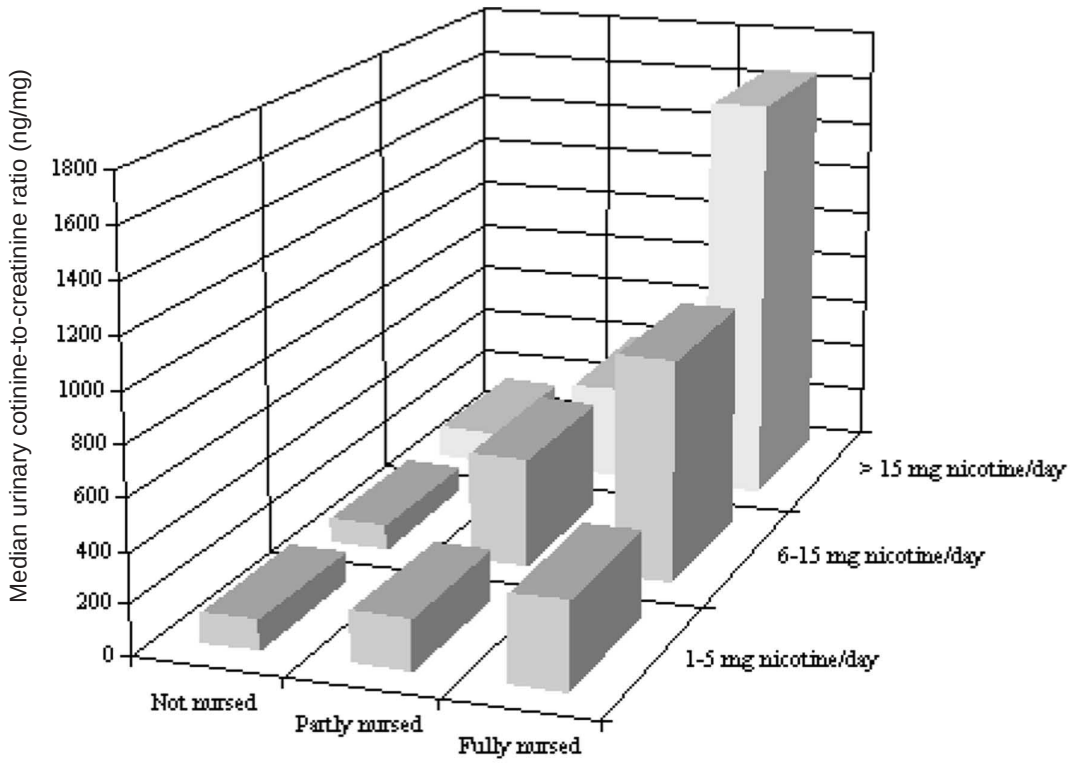
In a large population-based study of infants receiving routine well-child care in private physicians' offices in the greater Portland, Maine area, Chilmonczyk *et al.* (1990) collected urine samples from 518 infants, six to eight weeks of age, and obtained information on household smoking habits (this study is also discussed in Section 2.6.3). In the 305 households where no smoking was reported, 8 percent of the urinary cotinine values were

Figure 2.1
Plasma Cotinine Concentrations in Self-Reported Smokers and Nonsmokers



From Jarvis et al. (1987), with permission

Figure 2.2
Urinary Cotinine of Breast-Fed Infants in Relation to Maternal Cigarette Smoking



Source: Schulte-Hobein et al., 1992

equal to or greater than 10 ng/ml (the concentration of 10 ng/ml is defined by the authors on the basis of data in this study as a cutoff indicating significant ETS absorption). Median urinary cotinine concentrations in infants were 1.6 ng/ml in the 305 nonsmoking households, 8.9 ng/ml in the 96 households where a member other than the mother smoked, 28 ng/ml in the 43 households where only the mother smoked, and 43 ng/ml in the 74 households where both the mother and another household member smoked. In households where the mother smoked, breast feeding was associated with significantly higher infant urinary cotinine levels. These higher levels were seen both in the presence of other smokers in the household (median urinary cotinine: 213 ng/ml with breast feeding and 39 ng/ml without breast feeding) and in the absence of other smokers in the household (median urinary cotinine: 87 and 25 ng/ml, respectively.)

Several other studies have examined the relative contribution of inhalation versus ingestion of mother's milk to an infant's intake of nicotine and cotinine (Luck and Nau, 1985; Woodward *et al.,* 1986; Labrecque *et al.,* 1989; Schulte-Hobein *et al.,* 1992). In general, breast-fed infants whose mothers smoke were reported to have median urinary cotinine to creatinine ratios 2- to 10-fold higher than bottle-fed infants exposed only through inhalation, with the urinary cotinine levels in the infant related to the number of cigarettes smoked by the mother. Concentrations of urinary cotinine in breast-fed and bottle-fed babies as a function of the number of cigarettes smoked by the mother are shown in Figure 2.2.

2.4.2.5 Nicotine and Cotinine: Concentrations in Breast Milk and Amniotic Fluid

The observation that ingestion of breast milk is a significant contributor to infant exposure to ETS constituents (discussed above) is consistent with the findings of numerous studies in which nicotine and cotinine have been measured in milk of mothers who smoke (Ferguson *et al.,* 1976; Hardee *et al.,* 1983; Luck and Nau, 1984; Woodward *et al.,* 1986; Luck and Nau, 1987; Labrecque *et al.,* 1989; Schulte-Hobein *et al.,* 1992) and in milk of mothers exposed to ETS (Hardee *et al.,* 1983; Schulte-Hobein *et al.,* 1992). Results from these studies are summarized in Table 2.7. For smokers, mean nicotine concentrations in breast milk ranged from 5.16 to 91 ng/ml (range: 0.9 to 512 ng/ml) and mean cotinine concentrations, from 5.6 to 439 ng/ml (range: not detected to 738 ng/ml). The concentrations of nicotine measured in the breast milk of nonsmokers exposed to ETS were much lower than those reported for smokers. Nicotine and cotinine were often not detected in the milk of nonsmoking women; for samples in which these compounds were detected, nicotine concentrations ranged from 1 to 7 ng/ml (Hardee *et al.,* 1983) and cotinine concentrations from 2 to 277 ng/ml (Hardee *et al.,* 1983; Schulte-Hobein *et al.,* 1992).

The transfer of nicotine from blood into breast milk is very rapid, with milk concentrations approximately three times higher than in serum (Luck and Nau, 1984; Dahlström *et al.,* 1990). The half-life of nicotine in milk is approximately the same as that in blood (Luck and Nau, 1987). For cotinine, the reported milk/serum ratio ranges from 0.78 to 1 (Luck and Nau, 1984; Dahlström *et al.,* 1990). In general, the concentration of cotinine in milk has been found to increase with increasing nicotine consumption (Woodward *et al.,* 1986; Labrecque *et al.,* 1989; Schulte-Hobein *et al.,* 1992).

The exposure of a nursed infant to nicotine depends on the daily intake of breast milk as well as the smoking pattern of the mother, including the number of cigarettes she consumes daily, the extent to which she inhales, her smoking frequency prior to nursing, and the time interval between nursing and the last cigarette smoked (Luck and Nau, 1987). Because of the relatively short half-life of nicotine, diurnal milk concentrations are highly variable; 5- to 10-fold increases in the concentration of nicotine were observed in milk samples collected during the day, as compared to samples collected in the early morning after night time smoking

Table 2.7
Concentrations of Nicotine and Cotinine in Mothers' Milk

Study	Constituent	Concentration (ng/ml) Mean (SD)	Range	Study Population	Comments
Nonsmokers					
Hardee *et al.* (1983)	Nicotine	--	1-7	Samples from 10 nonsmoking women.	Detected in 3 women reporting work-place exposure to ETS
	Cotinine	--			
Schulte-Hobein *et al.* (1992)	Cotinine	0	0-277	Samples from 69 nonsmoking women.	Detected in 7 women who lived with partners who smoked.
Smokers					
Ferguson *et al.* (1976)	Nicotine	91	20-512	28 samples from 9 women were collected. Most subjects smoked 0.5-1.5 packs/day.	Concentrations of nicotine varied greatly in samples from the same donor taken at different times of the day.
Hardee *et al.* (1983)	Nicotine	--	20-150	Samples from 3 women	
	Cotinine	--	50-300		
Luck and Nau (1984)	Nicotine	--	2-62	44 samples from 23 women were collected. The number of cigarettes smoked per day ranged from 5-40. The time between the last cigarette smoked and the collection of samples ranged from 0.25 to 4.0 hours.	
	Cotinine	--	12-222		
Woodward *et al.* (1986)	Nicotine	8.3 (±13.0)	--	Samples from 20 women smoking 1-20 cigarettes 48 hours prior to sample collection.	
	Cotinine	84.4 (±93.3)	--		
	Nicotine	32.6 (±26.6)	--	Samples from 7 women smoking ≥21 cigarettes 48 hours prior to sample collection.	
	Cotinine	234 (±110.8)	--		

Table 2.7 (Continued)

Study	Constituent	Mean (SD)	Range	Study Population	Comments
Luck and Nau (1987)	Nicotine	8.3 (± 16)	--	Samples from all nursing periods within 24 hours.	Determinants of milk nicotine levels were the number of cigarettes consumed during the period immediately prior to nursing and the time interval between the last cigarette smoked and nursing.
	Cotinine	76 (± 33)	--	Samples from 10 women smoking 1-10 cigarettes/day.	
	Nicotine	28 (± 21)	--	Samples from 11 women smoking 11-20 cigarettes/day.	
	Cotinine	125 (± 60)	--		
	Nicotine	48 (± 25)	--	Samples from 13 women smoking 21-40 cigarettes/day.	
	Cotinine	230 (± 62)	--		
Labrecque *et al.* (1989)	Cotinine	195 (± 122)	28-256	Samples from 33 mothers smoking on average 9.8 cigarettes in the previous 24 hours.	Cotinine levels were significantly related to the number of cigarettes smoked by the mother in the previous 24 hours (r = 0.69, p = 0.0002).
Schulte-Hobein *et al.* (1992)	Cotinine	264	0-738	Samples from 69 mothers who smoked more than 5 cigarettes per day during pregnancy and continued smoking after childbirth. Samples (total = 238) were collected at monthly intervals for 1 year.	Cotinine concentrations were dependent on nicotine consumption as reported by mothers (r = 0.56, p = 0.0001)
Dahlstrom *et al.* (1990)	Nicotine	5.16	0.9-17.3	Samples from 22 mothers abstaining from cigarettes for 12 hours	
	Cotinine	112	18-388		
	Nicotine	55	10-140	Samples from 21 mothers 30 minutes after smoking at least 1 cigarette	
	Cotinine	136	31-467		
Schwartz-Bickenbach *et al.* (1987)	Cotinine	91-322	41-580	Samples from 6 mothers smoking <20 cigarettes/day.	Range of median concentrations measured 1 week to 6 months postpartum
	Cotinine	305-439	0-635	Samples from 15 mothers smoking >20 cigarettes/day.	Range of median concentrations measured 1 week to 6 months postpartum

abstinence (Luck and Nau, 1987; Dahlström *et al.,* 1990). Because of the longer half-life of cotinine, its concentrations in milk are relatively constant.

No information was available on the levels of other ETS constituents in breast milk, although it is possible that other compounds would also be transferred to breast milk. Their relative concentrations in milk would depend on a number of factors, including their concentrations in mainstream (or sidestream) smoke, biological half-life, and lipid solubility.

Cotinine has also been detected in the amniotic fluid of ETS-exposed pregnant women and in the urine of their neonates (Jordanov, 1990). Mean concentrations of cotinine in amniotic fluid collected at parturition were 15 µmol/l in unexposed nonsmokers (women not living with a smoker), 25 µmol/l in exposed nonsmokers (smoker resided in household), and 111 µmol/l in active smokers. Cotinine was also detected in the urine, collected on the first day of life, of their neonates. Neonates of nonsmokers exposed to ETS had significantly higher concentrations of urinary cotinine than neonates of unexposed nonsmokers ($p < 0.01$).

2.4.3 Biomarkers: Carbon Monoxide and Carboxyhemoglobin

Carbon monoxide, both in exhaled alveolar air and as carboxyhemoglobin in blood, originates from endogenous processes as well as from environmental sources. In addition to cigarette smoke, common environmental sources include vehicle exhaust, gas stoves and furnaces, and kerosene space heaters. Although carbon monoxide and carboxyhemoglobin have been used to distinguish smokers from nonsmokers (Ohlin *et al.,* 1976; Sillett *et al.,* 1978; Jarvis *et al.,* 1983 and 1987), they are generally not good indicators of ETS exposure because of their lack of sensitivity and specificity. In nonsmokers exposed to environments heavily polluted with ETS, elevated levels of exhaled carbon monoxide and carboxyhemoglobin in blood have been detected when measured within 30 minutes following cessation of exposure. However, several studies of more typical exposure situations did not find significant differences in the carboxyhemoglobin levels in subjects reporting no, low, or high levels of ETS exposure (Jarvis *et al.,* 1983; Jarvis and Russell, 1984; see Table 2.4).

2.4.4 Biomarkers: Thiocyanate

Present in the vapor phase of tobacco smoke, hydrogen cyanide is metabolized in the liver, yielding thiocyanate (SCN^-). Thiocyanate levels in blood, urine, and saliva have been used to distinguish smokers from nonsmokers, or in combination with assays for nicotine or cotinine, to distinguish smokers from individuals using smokeless tobacco or other nicotine-containing products (Haley *et al.,* 1983; Hauth *et al.,* 1984; U.S. DHHS, 1986; Jarvis *et al.,* 1987). Sources of thiocyanate are also present in the diet, particularly cruciferous vegetables (Haley *et al.,* 1983); thus, levels of thiocyanate in body fluids are not specific to exposure to tobacco smoke. In studies examining the use of thiocyanate as a biomarker of ETS exposure, it was not possible to distinguish between ETS-exposed and unexposed nonsmokers (Hauth *et al.,* 1984; Jarvis and Russell, 1984; See Table

2.4). For this reason, thiocyanate is not very useful as a biomarker of ETS and has not been widely used for monitoring ETS exposure.

2.4.5 Biomarkers: Protein and DNA Adducts

Protein and DNA adducts represent both markers of exposure and measures of a biochemical effect. One of the more common protein adducts measured is the hemoglobin adduct of 4-aminobiphenyl. Tobacco smoke is the primary source of environmental 4-aminobiphenyl. Because of the relatively long half-life of these adducts, their levels reflect exposures occurring over the previous four months. Levels of 4-aminobiphenyl in ETS-exposed nonsmokers compared to those of active smokers present an interesting contrast to cotinine levels measured in these two groups. The levels of 4-aminobiphenyl adducts in nonsmokers are approximately 10 percent to 20 percent of the levels measured in smokers. Although this finding appears to be inconsistent with the results for urinary cotinine, for which levels in ETS-exposed nonsmokers are about 1 percent of those in smokers, the results may be explained by the available information on the relative levels of emission of nicotine and 4-aminobiphenyl into mainstream and sidestream smoke (see U.S. EPA, 1992: Table 3-1). Approximately twice as much nicotine is emitted in sidestream as in mainstream smoke, whereas about 31 times as much 4-aminobiphenyl is emitted in sidestream as in mainstream smoke, and as a result, the smoker/nonsmoker ratio for 4-aminobiphenyl is about 15 times higher than that for cotinine.

Another group of protein adducts which have been measured are the albumin adducts of polycyclic aromatic hydrocarbons (PAHs). Multiple PAHs are present in tobacco smoke. Crawford *et al*. (1994) analyzed PAH-albumin levels in peripheral blood of 87 mothers and their preschool children (2-5 years of age; discussed in more detail in Chapter 7, *Carcinogenic Effects*, Section 7.1.2.1). They found PAH-albumin levels were significantly higher in the children whose mothers smoked than in the children of nonsmoking mothers ($p < 0.05$). Among the nonsmoking mothers, regression of PAH-albumin against total ETS exposure also showed a significant association with cotinine ($r^2 = 0.25$; $p = 0.04$).

DNA adducts of tobacco smoke constituents can also be measured. The distribution of DNA adducts of benzo[*a*]pyrene diol epoxide, the ultimate carcinogenic metabolite of benzo[*a*]pyrene, a PAH present in tobacco smoke, has been analyzed by Denissenko *et al*. (1996) in the *P53* tumor suppressor gene. These authors reported that exposure of human bronchial epithelial cells to benzo[*a*]pyrene diol epoxide resulted in strong and selective DNA adduct formation within the *P53* gene at mutational hotspots identified in non-radon associated human lung cancer tissues obtained from smokers. This mapping of DNA adduct formation to mutational hotspots provides a direct etiological link between a specific tobacco smoke carcinogen and human cancer.

2.4.6 Biomarkers: Other Approaches Testing for other compounds in body fluids and for the mutagenicity of those fluids has been conducted to identify other approaches to assessing tobacco smoke exposure which are potentially more relevant to health endpoints of concern (*e.g.*, cancer). In a recent study by Hecht *et al.* (1993), five male nonsmokers were exposed to sidestream cigarette smoke generated by machine smoking for 180 minutes on each of two days, six months apart. The air concentrations of nicotine to which the men were exposed were reported to be comparable to levels found in a heavily smoke-filled bar. The mean concentrations of 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide were significantly higher after exposure than at baseline (33.9 versus 8.4 ng per 24-hour urine sample). The compound NNAL and its glucuronide are metabolites of 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK), a potent lung carcinogen in rodents (IARC, 1985). NNAL is also a lung carcinogen in rodents (Castonguay *et al.,* 1983; Rivenson *et al.,* 1988). NNK is formed by the oxidation and nitrosation of nicotine during the curing (drying) and smoking of tobacco (IARC, 1985).

Body fluids from active smokers and ETS-exposed nonsmokers have been assayed for genotoxic activity in a number of studies, primarily using the Ames *Salmonella* test. While the mutagenicity of the urine of cigarette smokers has been confirmed in a number of studies (IARC, 1986), the results using the urine from ETS-exposed nonsmokers have been less conclusive. Bos *et al.* (1983) reported that mutagenic activity of the urine of nonsmokers was significantly higher ($p < 0.02$) in samples collected following exposure to ETS than in samples collected prior to exposure, when tested in the *Salmonella* assay. In other studies, however, no increases or insignificant increases in mutagenic activity were reported (Sorsa *et al.,* 1985; Husgafvel-Pursiainen *et al.,* 1987; Mohtashamipur *et al.,* 1987; Scherer *et al,* 1987). Limitations of some of these studies include small numbers of subjects tested and lack of consideration of dietary factors, which have been shown to influence urinary mutagenicity (Sasson *et al.,* 1985).

2.5 EXPOSURE MEASUREMENT: USE OF QUESTIONNAIRES Epidemiologic studies typically evaluate exposure to ETS using questionnaires in which the subject reports his or her own exposure history and smoking status. In studies using questionnaires alone to assess ETS exposure, misclassification of true exposure status can result from a number of factors, including: limited questions (*e.g.*, spousal smoking status only); possible deception in reporting spousal smoking status; or inadequate recall of exposure (*e.g.*, parental smoking status; lack of awareness of contemporary exposure). Many studies cited in this report recognized the possibility of misclassification bias and took appropriate steps to minimize its impact or adjusted the analysis to account for this source of error. This section summarizes the results of a number of studies that have examined the reliability and validity of information collected using questionnaires regarding ETS exposure and smoking status.

2.5.1 Reliability of Questionnaire Responses on ETS Exposure

2.5.1.1 Reliability: Test-retest of the Same Subject

Studies employing a "test-retest" design have been used to assess the reliability of information obtained in questionnaires on past exposures to ETS. Coultas *et al.* (1989) interviewed a sample of 149 adult nonsmokers on two occasions, 6 months apart, with regard to whether their parents had smoked during their childhood. Concordance was 94 percent for mothers' smoking, 93 percent for fathers' smoking, and 85.9 percent for maternal smoking during pregnancy. However, information provided by the subjects on the amounts smoked (*i.e.*, number of cigarettes or hours of smoking per day) was found to be less reliable.

In a study of similar design, Pron *et al.* (1988) interviewed 117 subjects (controls in a case-control study of lung cancer) on two occasions separated by an average of 6 months. Agreement of responses with regard to the subjects' residential exposure (*i.e.*, if the subject ever resided in the same household as a regular smoker) was generally good (kappa = 0.66 for all subjects combined). Smoking by spouses was reported with high reliability (kappa = 0.89 for both husband and wife). Response agreement for exposure at work (kappa = 0.46 for both sexes) was lower than for residential exposure. Similar to the findings of the preceding study by Coultas *et al.* (1989), quantitative measures of exposure (*i.e.*, number of cigarettes smoked and duration of exposure) were less reliably reported.

2.5.1.2 Reliability: Self Versus Surrogate Respondents

A number of studies have examined the quality of information provided by surrogate respondents. Use of surrogate respondents occurs frequently in studies of ETS exposure. Studies examining the effects of exposure to spousal or household smoking often ask subjects to report on the smoking habits of members of their households. In retrospective studies of adult health risks from exposures occurring early in life, subjects who are now adults are questioned concerning parental smoking habits.

The quality of parental smoking histories was evaluated in a North Carolina study of cancer risk from childhood exposure to ETS (Sandler and Shore, 1986). A total of 1,036 subjects (cases and controls, aged 15 to 59 years) were asked about parental smoking habits during the subject's childhood and prior to the subject's birth. Parents or siblings of 70 percent of the study subjects were also interviewed to obtain the same information. Interviews were conducted with 355 mothers, 33 fathers, and 261 siblings. Concordance of subjects and their mothers was greater than 93 percent on questions concerning mothers' smoking and 85 percent regarding fathers' smoking. The study found that the responses were less accurate for information provided about dates or the number of cigarettes smoked. When extent of smoking was categorized as none, less than one pack, one pack, or greater than one pack, agreement between mothers and subjects was 82 percent with respect to mothers' smoking.

Similar findings were reported by McLaughlin *et al.* (1987) in a study of the reliability of surrogate information. The responses of children about smoking by their deceased parents agreed closely with information given 10 years previously by the parents themselves, with the level of agreement ranging from 80 to 96 percent.

Of the study populations examining the quality of information on smoking habits provided by surrogate respondents, most consisted of husband-wife pairs, although other family members were included in some studies (Rogot and Reid, 1975; Kolonel *et al.,* 1977; Pershagen, 1984; Lerchen and Samet, 1986; McLaughlin *et al.,* 1987). Information was obtained directly from interviews with both members of the pair or from an interview with one individual and the medical history of the other. These studies consistently found good agreement in responses concerning spousal smoking status, ranging from 90 to 100 percent. However, similar to the findings of studies on parental histories, quantitative information on the number of years or cigarettes smoked was less accurate.

In summary, the results of these studies indicate that information on childhood exposure to ETS provided by individuals who are now adults is of good quality, particularly with regard to qualitative information. Similarly, qualitative information on spousal smoking is of good quality. However, in both cases, quantitative information on the number of years of smoking, dates of smoking, or number of cigarettes smoked per day is sometimes less reliably provided.

2.5.2 Validity of Questionnaire Responses on ETS Exposure

2.5.2.1 Validity of ETS Exposure Status Based on Spousal / Household Smoking

A number of the early epidemiologic studies classified an individual's exposure to ETS solely on the basis of spousal smoking. Information presented in Sections 2.6.2 and 2.6.3 indicates that in California and nationwide, locations outside the home are also important sources of ETS exposure. The validity of ETS exposure status based on spousal or household smoking has been examined in a number of studies (Friedman *et al.,* 1983; Coultas *et al.,* 1987; Coghlin *et al.,* 1989; Cummings *et al.,* 1990). Methods used to validate exposure status include: gathering information on the extent to which nonsmokers report exposure outside the home; comparison of ETS biomarker levels of those with smoking and nonsmoking spouses; and comparison of indoor air levels of nicotine in houses with members who do and do not smoke. Results from these studies indicate that misclassification may occur when smoking by a spouse or other household member is the basis for determining ETS exposure.

In a study by Friedman *et al.* (1983), married couples were asked about their smoking habits and weekly exposure to ETS. Over 90 percent of nonsmokers married to nonsmokers reported no weekly exposure to ETS in the home; however, 40 percent of the nonsmoking females and 49 percent of the nonsmoking males reported ETS exposures outside the home. Conversely, substantial percentages of nonsmokers married to smokers (47

percent of women, 39 percent of men) reported no weekly exposure to ETS in the home. These studies indicate that classifying an individual's exposure to ETS on the basis of spousal smoking habits may result in misclassification.

Biomarker studies have shown that a proportion of subjects reporting no exposure to ETS have measurable biomarker concentrations, indicating that the subject either forgot or was not aware of his ETS exposure. In a study of 663 nonsmokers attending a cancer-screening clinic, Cummings *et al.* (1990) reported that 84 percent of subjects not living with a smoker had detectable urinary cotinine levels. In an unpublished analysis of only those subjects who were currently employed nonsmokers in this study, 76 percent of those reporting no exposure to ETS at home reported exposure at work (Cummings, 1994). Coultas *et al.* (1987) reported that in 727 households, approximately 35 percent of adults and children not living with a smoker had detectable levels of salivary cotinine (these studies are described in Section 2.6.3).

Comparison of reported exposures and questionnaire responses has also been examined using results from air monitoring of nicotine. Coghlin *et al.* (1989) questioned 37 nonsmokers with nonsmoking spouses and 15 nonsmokers with smoking spouses about their weekly exposure to ETS at home, work, in public places, and in vehicles. Personal nicotine monitors were worn by study participants to obtain measurements of actual exposure. Of the nonsmokers with nonsmoking spouses, 22 percent had personal nicotine levels similar to those measured for smokers, while 13 percent of nonsmokers with smoking spouses had low nicotine levels. In addition, 88 percent of nonsmoking women with nonsmoking spouses reported work-related exposure and 80 percent reported social exposure.

In a study by Leaderer and Hammond (1991), measurable concentrations of nicotine were detected in 13 percent of residences reporting no smoking in the home, while nicotine was not detected in 28 percent of the households with occupants who smoked. For the latter, smoking could have occurred in rooms other than the primary activity room in which samples were taken.

In summary, studies have consistently shown that subjects are misclassified with regard to their ETS exposure status when the sole basis for classification is the smoking status of other household members. The overall impact of misclassification would be an underestimation of the health impacts of ETS exposure.

2.5.2.2 Validity of Self-Reported ETS Exposure: Biomarker Concentrations

Biomarkers have been used to examine the quantitative relationships between the degree of ETS exposure self-reported on questionnaires and concentrations of nicotine in ambient air (Coultas *et al.,* 1989; Haley *et al.,* 1989; Cummings *et al.,* 1990; Riboli *et al.* 1990). Depending on the study design and the endpoints examined, the reported correlations among the various exposure indices

ranged from moderate to high. Because of the many limitations of these studies, inconsistencies among studies is not unexpected.

Significant differences in uptake, distribution, metabolism, and excretion of nicotine are found among individuals (Benowitz *et al.,* 1982), and thus cotinine levels in biological fluids vary among individuals exposed under identical conditions. In those studies in which urinary cotinine is used as the measure of exposure, cotinine concentrations are often assessed from a single urine sample, which may not adequately represent the exposure period in question. For studies in which ambient air concentrations of nicotine serve as the exposure measure, it has been shown that air concentrations vary within the same room; intake will depend on the location of the individual relative to the smoker, the exposure duration, and the physical characteristics of the exposed individuals (*e.g.*, activity level and corresponding breathing rate).

2.5.3 Reliability and Validity of Self-Reported Smoking Status

In a test-retest study of the reliability of subjects' reports of their own smoking habits, Lee (1987) found that responses from 93 percent of 166 subjects regarding current or past smoking status were consistent with responses to the same questions asked five years earlier.

A number of studies have used biomarkers to validate self-reported smoking status (Coultas *et al.,* 1989; Haley *et al.,* 1989; Cummings *et al.,* 1990; Riboli *et al.* 1990; Perez-Stable *et al.,* 1992). Self-reported nonsmokers who appear to be smokers on the basis of biochemical measurements are generally considered "deceivers" of their true smoking status. In a summary of 11 studies in which questionnaire responses regarding smoking status were compared with cotinine or nicotine measurements (Perez-Stable *et al.,* 1992), the estimated misclassification rates (self-reported nonsmokers with elevated cotinine or nicotine levels indicative of active smoking) ranged from zero in a small study to nearly 10 percent in a sample of nonsmokers from a clinical setting. These studies are summarized in Table 2.6. Misclassification of an individual who is a smoker as a nonsmoker may increase the apparent relative risk of smoking-related diseases in nonsmokers. However, Perez-Stable *et al.* (1992) suggest that most smokers misclassified as nonsmokers are very light smokers or occasional smokers who binge.

2.6 EXPOSURE PREVALENCE AND DETERMINANTS

2.6.1 Introduction

Because the various health endpoints reviewed in other chapters of the overall ETS assessment may be the result of either acute or chronic exposures, both present and past patterns of exposure are of interest, and information on both is included here. Studies of the prevalence of ETS exposure and its demographic and social determinants summarized below (Sections 2.6.2 and 2.6.3) should be considered representative only of the general time periods covered by the study. Smoking prevalence, smoking behaviors, and other factors contributing to exposure to ETS have continued to change as smoking customs have changed in the U.S., with a number of important changes occurring within the past few years. Thus, it

is expected that the number of individuals exposed to ETS and the patterns of exposure have also changed over time (see Section 2.6.4).

For California, information is available from population-based surveys in which self-reported exposure to ETS was assessed (Friedman *et al.,* 1983; Phillips *et al.,* 1991; Wiley *et al.,* 1991a & b; Burns and Pierce, 1992; Jenkins *et al.,* 1992; Pierce *et al.,* 1994). With one exception (Friedman *et al.,* 1983), these studies relied solely on self-reported exposure and did not validate questionnaire responses using biomarker data. A certain amount of misreporting occurs in studies relying on self-reported exposure; several studies have been conducted to evaluate the relationship among self-reported exposure and other exposure indices (*e.g.*, ambient air concentrations of ETS constituents and cotinine levels in biological fluids), and these studies are discussed in Section 2.5.

For areas outside of California, information on exposure prevalence is available from a variety of studies, using either self-reported exposure or the presence of biological markers as the measure of exposure (Coultas *et al.,* 1987; Greenberg *et al.,* 1989; Chilmonczyk *et al.,* 1990; Cummings *et al.,* 1990; Overpeck and Moss, 1991; CDC, 1993b; Pirkle *et al.*, 1996). In general, only limited comparisons can be made between the findings on exposure prevalence for California and those available for other areas, primarily because of important differences in study objectives and study design. However, indirect indicators of ETS exposure suggest that the prevalence of ETS exposure in California is less than that of the rest of the U.S. population. A discussion of these indicators and other factors in California expected to affect trends in exposure prevalence are discussed in Section 2.6.4. The studies presented in the following sections are summarized in Tables 2.8 and 2.9.

Taken as a whole, the various studies discussed below indicate that, within California and the United States, exposure to ETS was widespread during the time period of the studies (1979 through 1992). Analyses of ETS exposure within California indicated that the workplace, home, and other indoor locations contributed significantly to the exposure of adults; for children, the home was the most important single location contributing to ETS exposure. In all studies using both self-reporting and a biological marker (cotinine level) as measures of exposure, prevalence was higher when determined using the biological marker.

2.6.2 Prevalence of ETS Exposure in California

Friedman et al. (1983)

In one early study, the prevalence and extent of weekly exposure to ETS was assessed from questionnaire responses of 37,881 nonsmokers and ex-smokers receiving multiphasic health checkups in 1979 and 1980 (Friedman *et al.,* 1983). The population consisted of members of the Kaiser-Permanente Medical Care Program in Oakland and San Francisco. Altogether, 63.3 percent of the respondents reported some exposure to ETS, with 28.8 percent reporting exposure durations of between 1 and 9 hours per week, 18.6 percent reporting exposure durations of between 10 and

39 hours per week, and 15.9 percent reporting exposure durations of 40 or more hours per week. The reported locations of exposure were the home (23.8 percent), other small areas (40.4 percent, defined in the study as "such as airplane, office, or car, etc.") or a large indoor area (46.5 percent, defined in the study as "such as restaurant, hotel lobby, lecture hall, etc.").

Exposure was strongly related to age, with 78.2 percent of those in their twenties reporting exposure, decreasing to 13.9 percent of those aged 80 and over. Serum thiocyanate and expired-air concentrations of carbon monoxide were determined for 267 persons who completed the questionnaire. The correlations between self-reported ETS exposure and the biomarkers were all positive, but small. While the correlations of thiocyanate levels with non-home small area, large area, and total exposure were at, or close to, the $p < 0.05$ level of statistical significance, for CO, no correlation approached statistical significance. These findings are not surprising given that sources of thiocyanate and carbon monoxide in addition to tobacco smoke are present in the environment. More recent studies indicate that, in general, they are not suitable as markers of ETS exposure (see Sections 2.4.2 and 2.4.3).

Wiley et al. (1991a & b)
Phillips et al. (1991)
Jenkins et al. (1992)

In the late 1980s, the California Air Resources Board (ARB) funded a statewide survey to obtain information on activity patterns of Californians and on their use of and proximity to air pollutant sources, including ETS (Wiley *et al.,* 1991a; Jenkins *et al.,* 1992). The study consisted of telephone interviews with 1,579 English-speaking adults and 183 adolescents (12 to 17 years of age) who were members of households with telephones in California. The interviews were conducted over four seasons—from October 1987 through September 1988. The participants completed a verbal recall diary of their activities and locations of the previous day, and for each activity and location, were asked whether anyone smoking a cigarette was present.

In a second study of similar design (*i.e.*, telephone interviews with English-speaking individuals) conducted from April 1989 through February 1990, information was obtained on the activity patterns of 1,200 children (Phillips *et al.,* 1991; Wiley *et al.,* 1991b). In this study, children from 9 to 11 years old were interviewed directly. For children 6 to 8 years of age, the interview was conducted with a parent or guardian who was encouraged to consult with the child, and for younger children, the interview was conducted with the adult household member having spent the most time with the child on the diary day. Because exposure to ETS was not the primary focus of either the adult or childhood study, the ETS responses had not been fully analyzed. At the request of the Office of Environmental Health Hazard Assessment, additional unpublished analyses of the responses on ETS exposures were conducted by the ARB for inclusion in this report (Jenkins, 1992 & 1994, personal communication; Lum, 1994a & b, 1994, personal communication).

Table 2.8
Studies with Information on ETS Exposure Prevalence in California and the United States: Adults and Adolescents

Study	Year/ Location	Description	Measure of Exposure	Exposure Prevalence (Age)	Comments
California					
Friedman *et al.* (1983)	1979-1980 Oakland and San Francisco, California	37,881 nonsmoking adults from the Kaiser-Permanente Medical Care Program.	Self-report	63.3% (≥18yrs)	Exposed individuals defined as those reporting an average exposure to ETS of one or more hours per week.
Wiley *et al.* (1991a) Jenkins *et al.* (1992)	1987-1988 California (statewide)	1,579 English-speaking adult members of house-holds with telephones.	Self-report (interview)	43% (≥18 yrs) 64% (12-17 yrs)	Activity-pattern study. Exposed individuals defined as those reporting exposure to ETS on the day preceding the interview. Prevalence given for nonsmokers.
Burns and Pierce (1992)	1990-1991 California (statewide)	Telephone interviews with 32,135 English- and Spanish-speaking households	Interview	36.5% (12-17 yrs)	Exposed individuals defined as those living in a household with at least one smoker.

Table 2.8 (Continued)

Study	Year/ Location	Description	Measure of Exposure	Exposure Prevalence (Age)	Comments
Other U.S. areas					
Coultas *et al.* (1987)	1984-1985 Albuquerque, New Mexico	698 nonsmoking adults from 727 randomly selected Hispanic households.	Salivary cotinine	39% (≥18 yrs) 48% (13-17 yrs)	Exposed individuals defined as those with salivary cotinine concentrations ranging from 0.78-20 ng/ml.
Cummings *et al.* (1990)	1986 Buffalo, New York	663 nonsmoking adults attending a cancer-screening clinic	Self-report (interview)	76% (≥18 yrs)	Exposed individuals defined as those reporting any exposure to ETS during the 4-day period preceding the interview.
			Urinary cotinine	91% (>18 yrs)	Exposed individuals defined as those with detectable concentrations of cotinine (detection limit not given).
Centers for Disease Control (1993b)	1988-1992 United States	800 nonsmoking individuals, ages 4-91 years, from 81 U.S. counties.	Serum cotinine	100% (----)[a]	Exposed individuals defined as those with detectable concentrations of cotinine. Interpretation of the study results limited by the preliminary nature of the report and the sensitive method for analyzing for cotinine (see text).

[a] *Exposure prevalence reported for entire study population*

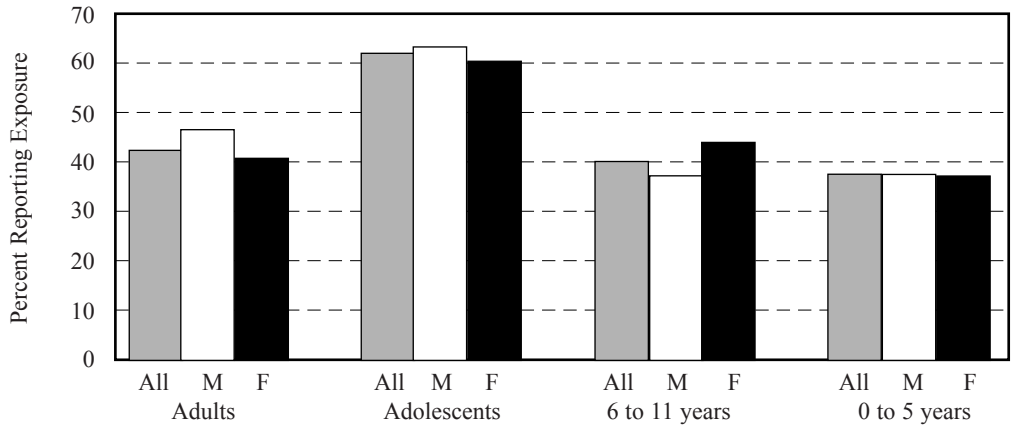
Table 2.9
Studies with Information on ETS Exposure Prevalence in California and the U.S.: Infants and Children

Study	Year/ Location	Description	Measure of Exposure	Exposure Prevalence (Age)	Comments
California					
Phillips *et al.* (1991) Wiley *et al.* (1991b)	1989-1990 California (statewide)	1,200 children (0 to 11 years old) from households with telephones and an English-speaking adult	Surrogate Report	40% (6-11yrs) 36% (0-5 yrs)	Exposed individuals defined as those reporting exposure to ETS on the day preceding the interview.
Burns and Pierce (1992)	1990-1991 California (statewide)	Telephone interviews with 32,135 English- or Spanish-speaking households	Surrogate Report	32.2%(6-11 yrs) 32.2% (0-5 yrs)	Exposed individuals defined as those living in a household with one or more smokers.
Other U.S. areas					
Coultas *et al.* (1987)	1984-1985 New Mexico	Hispanic children participating in a population-based survey of respiratory disease	Salivary cotinine	45% (6-12 yrs) 54% (0-5 yrs)	Exposed individuals defined as those with salivary cotinine concentrations ranging from 0.78 to 20 ng/ml.
Greenberg *et al.* (1989)	1986-1987 Central North Carolina	433 healthy infants	Surrogate Report	42% (8-51 days)	Exposed individuals defined as those exposed to ETS during the preceding week.
			Surrogate Report	55% (8-51 days)	Exposed individuals defined as those living in a household with one or more smokers.

Table 2.9 (Continued)

Study	Year/ Location	Description	Measure of Exposure	Exposure Prevalence (Age)	Comments
Greenberg *et al.* (1989) (continued)	1986-1987 Central North Carolina	433 healthy infants	Urinary cotinine	60% (8-51 days)	Exposed individuals defined as those with detectable concentrations of urinary cotinine.
Chilmonczyk *et al.* (1990)	1988 Portland, Maine	518 infants	Surrogate Report	41% (6-8 wks)	Exposed individuals defined as those living in a household with one or more smokers.
			Urinary cotinine	80% (6-8 wks)	Exposed individuals defined as those with detectable concentrations of urinary cotinine.
Overpeck and Moss (1991)	1988 United States	5,356 children from a cross-sectional survey of household populations	Surrogate Report	48.8% (0-5 yrs)	Exposed individuals defined as those living in a household in which one member smoked regularly at any time since the child's birth.
			Surrogate Report	42% (0-5 yrs)	Exposed individuals defined as those currently living in a household with one or more smokers.

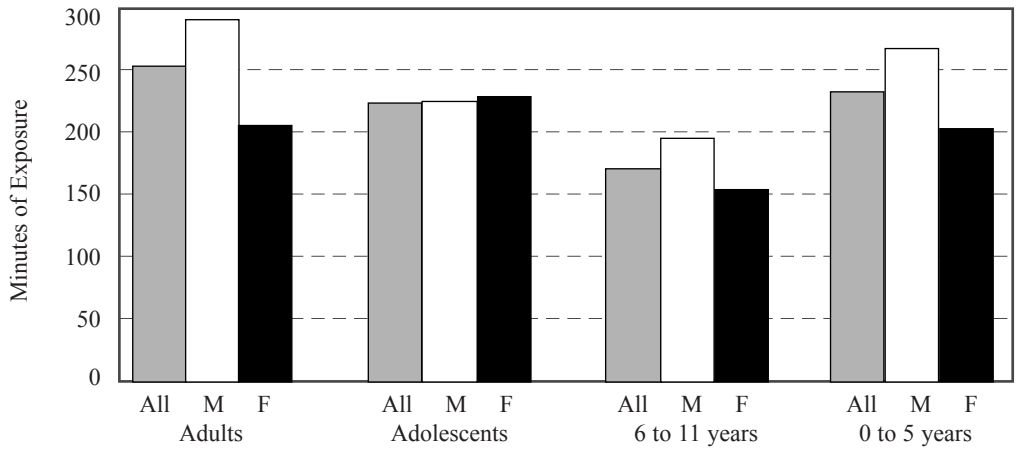
Figure 2.3
Percent of Nonsmokers in California Reporting ETS Exposure*



Source: Jenkins et al., 1992; Lum, 1994b

** Smoking status of 6 to 11 year olds not determined in the study. Data from 1989 to 1990.*

Figure 2.4
Reported Average Daily ETS Exposure Duration* in California



Source: Lum, 1994a,b

** Exposure duration is the average value for individuals reporting ETS exposure. For adults, values are for nonsmokers only. For adolescents, values are for both smokers and nonsmokers. The smoking status of 6 to 11 year olds was not determined. Data from 1989 to 1990.*

Figures 2.3 and 2.4 show the percentage of nonsmokers in California reporting exposure to ETS and the average daily duration as determined in this study. Of adult nonsmokers, 43 percent reported exposure to ETS, as did 64 percent of nonsmoking adolescents (Jenkins *et al.,* 1992). For smokers and nonsmokers combined, approximately 61 percent of adults and 70 percent of adolescents (age 12 through 17) reported exposure to ETS at some time during the day (at the time of the survey, 22.5 percent of the population reported active smoking on a given day). The groups with the lowest percentage reporting exposure were children, and infants and preschoolers, ranging from 35 percent to 45 percent, as a function of age and sex. About 38 percent of children under age 12, statewide, were exposed to ETS at some time during a typical day. Among those infants and preschoolers who were exposed to ETS, the average duration of their exposure was as long as that of adults (about four hours); children aged 6-11 years who were exposed had an average exposure duration of three hours (Lum, 1994a & b, 1994, personal communication).

A separate analysis of the survey data was conducted to determine the relative proportion of the population's ETS exposure duration (measured in person-minutes) occurring in different locations (Lum, 1994a & b, 1994, personal communication). The various locations identified in the study were grouped into three or four mutually exclusive categories for each population subgroup and the mean duration of reported exposure to ETS while in those locations was determined. For adults, the categories were home, work, other indoor, and outdoor; for adolescents and children, home, school, other indoor, and outdoor; and for infants and preschoolers, home, other indoor, and outdoor. The relative person-minutes of reported exposure at each location (*i.e.*, the product of the number of individuals reporting ETS exposure and the average reported exposure duration, divided by the total number of person-minutes of reported ETS exposure at all locations) was then calculated to provide a crude index of the relative importance of each exposure location.

Although the concentration of ETS at each location is also an important parameter in estimating exposure, measurements of ETS concentrations were not obtained in this study, which focused primarily on time-activity patterns. In other studies (see Section 2.3.3), home and workplace concentrations of nicotine (as an indicator of ETS) fall within the same general range. Thus, this location/duration index provides a rough estimate of the relative extent of the population's exposure at these locations. However, ETS concentrations at locations grouped as other indoor (*e.g.*, bars, restaurants, banks, or hospitals) are highly variable, and little information is available on concentrations in outdoor environments (*e.g.*, at parks or bus stops). Overall, the index provides an indication of the locations at which exposure occurs, but not of the relative dose incurred at each location.

The results of the analysis are shown in Figure 2.5. For adult male nonsmokers, the highest exposure index was estimated for the workplace

(46 percent), with the index at other locations (*i.e.*, the home, other indoor, and outdoor) ranging from 15 to 23 percent. For female nonsmokers, the highest indexes were for the workplace (35 percent) and other indoor locations (31 percent), followed by the home (20 percent) and outdoor locations (13 percent). Somewhat different patterns were found for adult smokers reporting exposures to ETS from someone else's smoking. For male smokers, the exposure index was similar at all locations, ranging from 21 to 29 percent. For female smokers, the highest index was for the home (53 percent), ranging from 12 to 22 percent at other locations. Different patterns were observed for adolescents and children. For adolescents, the exposure index was approximately the same for home and other indoor locations (41 to 42 percent), followed by outdoor locations (13 percent) and school (4.5 percent). (It should be noted that the values for adolescents are based on a small sample size of 183.) Not unexpectedly, for children (6 to 11 years old) and infants and preschoolers (0 to 5 years old) the highest exposure index (54 percent and 62 percent, respectively) was for the home.

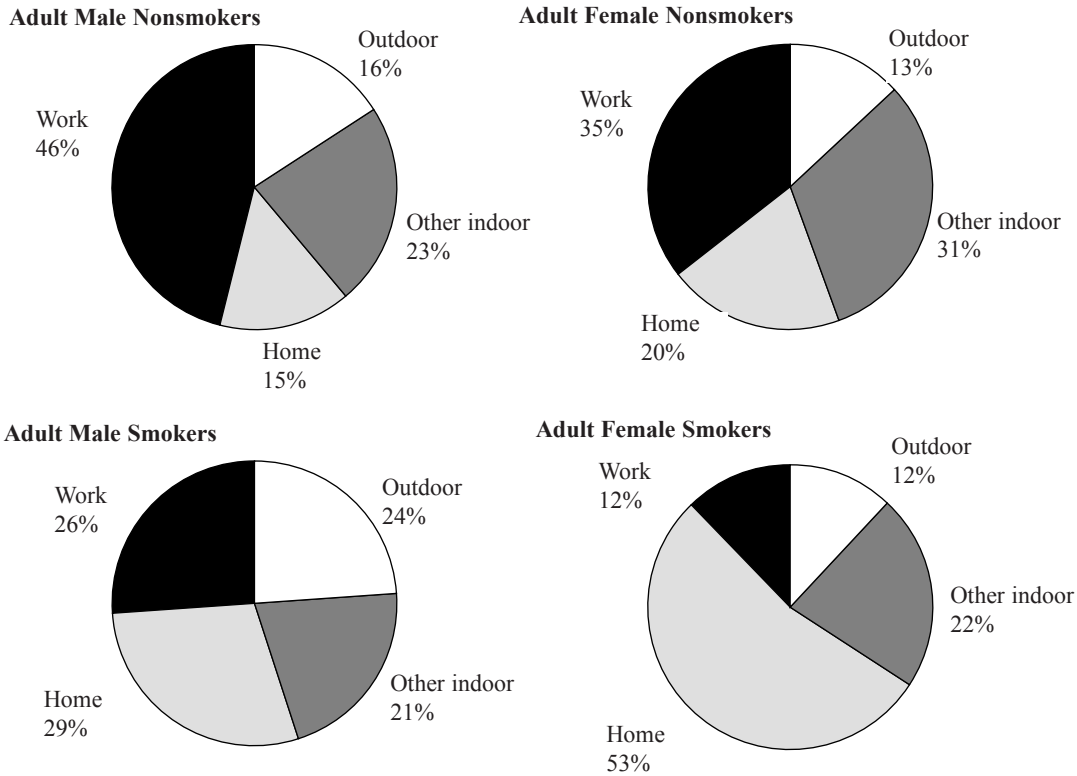
Workplace exposures to ETS were also examined (Jenkins, 1994, personal communication). Approximately 40 percent of nonsmokers working outside the home reported exposure to ETS in the workplace. While fewer nonsmoking working females (30 percent) reported exposure than nonsmoking working males (47 percent), their average exposure duration at work was somewhat longer (females, 5.8 hours; males, 5.2 hours). The proportion of the total daily reported exposure duration occurring in the workplace for these nonsmoking workers was 51 percent for males, and 38 percent for females.

Burns and Pierce (1992)
Borland et al. (1992)

Limited information on exposure to ETS is also available from a survey on tobacco use in California, conducted between June 1990 and July 1991 (Burns and Pierce, 1992). Using a stratified random-digit dialing technique, the head of household in 32,135 homes was surveyed briefly (in either English or Spanish) to enumerate household members and determine the smoking status of each household member. From this information, all adult household members who were reported as having smoked within the past five years were scheduled for an in-depth interview, as were 28 percent of nonsmokers. The prevalence of active smoking, as reported in this study, was 22.2 percent, with males (25.5 percent) smoking more than females (19.1 percent). Information was obtained on household ETS exposure of children up to 18 years of age. The study found that 32.2 percent of children under 5 years of age live in homes with one or more smokers. Similar values were reported for children 6 to 11 years old (32.2 percent) and 12 to 17 years old (36.5 percent).

Using data collected in the California tobacco-use survey (Burns and Pierce, 1992) described above, Borland *et al.* (1992) examined the extent of exposure of nonsmoking workers to ETS according to type of work-site smoking policy, work area, workplace size, and demographic characteristics. The analysis reported by Borland *et al.* is for weighted population estimates and differs slightly from that in the original report of Burns and Pierce

Figure 2.5 (Figure continues on next page)
Relative Person-Minutes of ETS Exposure* in Different Environments

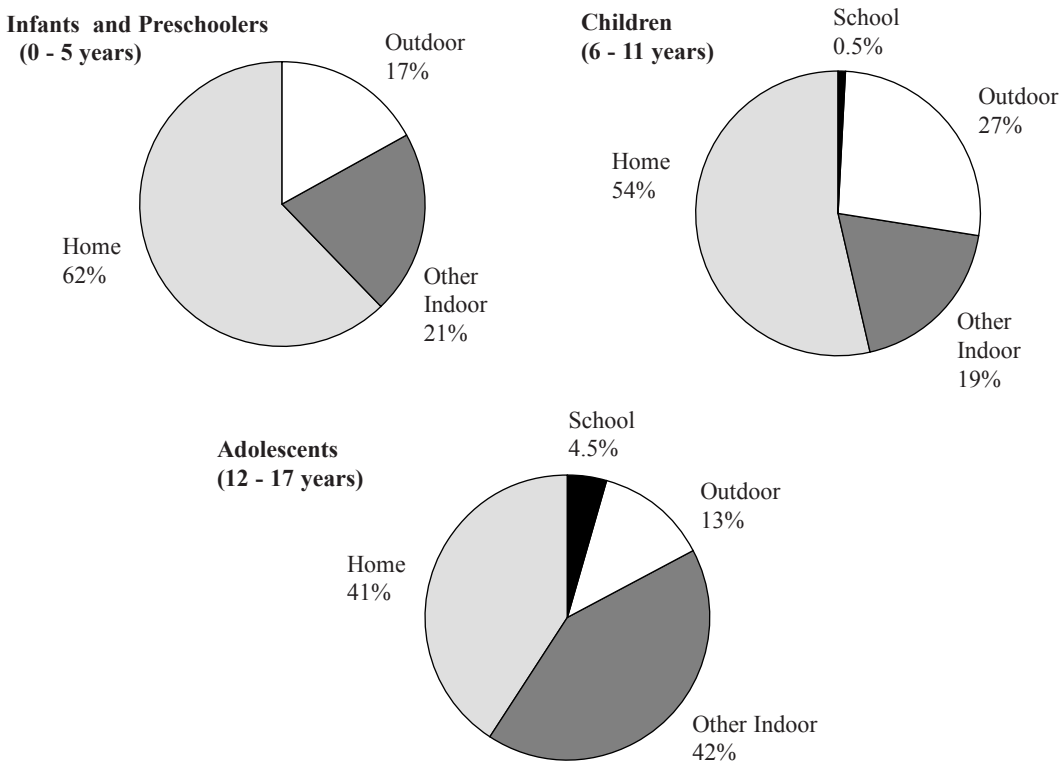


Source: Lum, 1994a,b

** Percentages may not add to 100 due to rounding errors. Data from 1989 to 1990.*

(1992). The sample consisted of 7,301 nonsmokers from the larger study who reported that they worked primarily indoors. Workplace ETS exposure of these individuals was assessed by asking the question, "During the past two weeks has anyone smoked in the area in which you work?" Additional questions were not asked to define the frequency and extent of exposure. Overall, 31.3 percent of the nonsmoking workers reported workplace ETS exposure at least once in the preceding two weeks. Examined as a function of work-site smoking policy, workplace exposure of nonsmokers was 9.3 percent for those working in a smoke-free worksite, 23.2 percent for those working where there was a work-area smoking restriction, 46.7 percent for those working where the smoking policy did not include the work area, and 51.4 percent for those working where there was no work-site smoking policy. The study also found that a greater percentage of male workers reported exposure than did female workers (35.8 percent versus 22.9 percent); that more workers under 25 reported exposure than did older workers (41.9 per-

Figure 2.5 (Continued)



Source: Lum, 1994a,b

** Percentages may not add to 100 due to rounding errors. Data from 1989 to 1990.*

cent versus 26.4 percent); and that the number of workers reporting exposure decreased with increasing level of education, from 43.1 percent of those with less than 12 years of education to 18.6 percent of those with a college education.

California Department of Health Services (1995 and 1996)
Pierce et al. (1994 and 1996, personal communication)

The California Department of Health Services (CDHS) conducts annual telephone surveys of a representative sample of Californians–the California Adult Tobacco Survey (CATS). The 1995 survey interviewed over 4,000 adults about their smoking behavior. According to 1995 data from the California Adult Tobacco Survey and an additional survey (Behavioral Risk Factors Survey), CDHS estimated that 16.7 percent of the adult population in California smokes.

Survey results from 1994 and 1995 indicate increasing percentages of nonsmoking and smoking California adults reporting that smoking is prohibited at their work sites (1994: 84 percent (nonsmokers) and 75 per-

cent (smokers); 1995: 89 percent (nonsmokers) and 78 percent (smokers)). Similarly, the percentages of nonsmoking and smoking adults in California reporting that smoking is prohibited in public areas of their work has also increased (1994: 74 percent (nonsmokers) and 63 percent (smokers); 1995: 82 percent (nonsmokers) and 85 percent (smokers)). The percentages of adults reporting a complete ban of smoking in their own homes has also increased (1994: 64 percent (nonsmokers) and 24 percent (smokers); 1995: 80 percent (nonsmokers) and 34 percent (smokers)).

The California Adult Tobacco Surveys in 1990, 1992, and 1993 were conducted for CDHS by Pierce *et al*. (1994) at the University of California, San Diego, who sampled relatively large numbers of Californians: 8,224 to 30,716 adults (18 years and older) and 1,789 to 5,040 teenagers (12-17 years of age, CDHS, 1996). From the results of those surveys, prevalence of active smoking and ETS exposure for various subpopulations can be estimated. For example, of the 2,047 women interviewed in 1992 who were pregnant over the previous 5 years, 15.1 percent smoked prior to pregnancy, and of these, 37.5 percent quit during the pregnancy; thus, a prevalence estimate of 9.4 percent for California women smoking throughout pregnancy can be obtained. Regarding ETS exposure of women of child-bearing age, Pierce *et al*. (1996, personal communication) estimated that in 1993 of the 6,513,891 women aged 18-44 in California, 634,028 were nonsmokers exposed to ETS at home, 564,411 were nonsmokers exposed indoors through their work, and 46,083 were exposed at both work and home. From this, the proportion of nonsmoking women in California of child-bearing age who are ETS-exposed is estimated to be 22.1 percent. Regarding childhood exposures, the 1993 survey suggests 19.6 percent of those age 17 and under and 17.7 percent of those under age 5 may be exposed to ETS in their homes (Pierce *et al*., 1994).

2.6.3 Prevalence of ETS Exposure in the United States

Historically, the main focus of large population-based studies of tobacco smoke exposure has been on active smoking, with little or no information obtained on exposure to ETS. More recently, several studies in the U.S. have addressed various aspects of ETS exposure, including exposure prevalence in various population subgroups. The measures of exposure used in these studies include both questionnaire responses and measured levels of biological markers (primarily cotinine). As previously noted, self-reporting can result in some degree of misclassification. The use of biomarkers can also result in some misclassification, however, in that it is not always possible to distinguish between a nonsmoker heavily exposed to ETS and a very light smoker; another concern is that, in some studies, the timing of sample collection relative to exposure may not have been appropriate. In addition, most biomarkers reflect exposures occurring within the past few days, whereas the exposure period of interest for many studies extends over a time period of many years. These factors are discussed in Section 2.4.1. For those studies summarized below in which prevalence was assessed using biomarkers, the biomarker levels detected in biological fluids are mentioned. The use of biomarkers as an exposure measure is discussed in detail in Section 2.4.

2.6.3.1 General Population Studies

Centers for Disease Control (CDC, 1993b; Pirkle et al., 1996)

As part of the Third National Health and Nutrition Examination Survey (NHANES III), the National Centers for Environmental Health and the National Center for Health Statistics of the Centers for Disease Control (CDC) measured serum levels of cotinine to assess exposure to tobacco of persons in the United States aged 4 years and older. The study was conducted from 1988 through 1994; preliminary information was available in 1993 (CDC, 1993b), and final results of the 1988 to 1991 survey were recently published (Pirkle *et al.,* 1996). In the 1988 to 1991 survey, 14,269 persons aged 4 years and older were interviewed; of those, 12,678 were examined, and of those examined, 10,642 had serum cotinine measurements taken. Reported data on ETS exposure in the home were available for 3,185 children aged 2 months to 3 years, 3,011 aged 4 to 11 years, and 878 aged 12 to 16 years. Serum cotinine levels were available on 737 adolescents and 7,740 adults with complete information on tobacco use and ETS exposure.

Of US children 11 years and younger, 43 percent lived in homes of at least one smoker, as did 37 percent of adult non-tobacco users. Serum cotinine levels, however, indicated more widespread exposure to nicotine, with 87.9 percent of non-tobacco users with detectable levels of serum cotinine. Both the number of smokers in the home and the hours exposed at work were significantly and independently associated with increased serum cotinine levels ($p < 0.001$, multiple regression t test). Identified groups with higher exposure to ETS were children, non-Hispanic blacks, and males. Dietary variables showed no consistent association with serum cotinine levels, and dietary contributions, if any, appeared to be extremely small.

Cummings et al. (1990)

Cummings *et al.* (1990) assessed the prevalence of ETS exposure of 663 nonsmokers and ex-smokers who attended the Roswell Park Memorial Institute cancer-screening clinic in Buffalo, NY in 1986. Both self-reported exposure and measured urinary cotinine were used as measures of exposure. An interviewer questioned subjects about their exposure over the 4-day period preceding the interview and a single urine sample was collected on the day of the interview. A total of 76 percent of the subjects reported some exposure to ETS during the 4 days preceding the interview. The average number of exposures over the 4-day period was 3.3 (range: 0 to 21), and for those exposed, the average daily reported exposure was 2 hours (range: <1 to 13.25 hours/day). The reported exposure locations were work (28 percent), home (27 percent), restaurants (16 percent), private social gatherings (11 percent), car or airplane (10 percent), and public buildings (8 percent). Cotinine was detected in the urine of 91 percent of samples (detection limit not given), suggesting that individuals are not always able to recall exposures or are not aware that exposure has occurred. It is also possible that for some subjects, cotinine was detected as a result of exposures that preceded the 4 days reported in the interview. The measured cotinine levels for self-reported nonsmokers ranged from 0 to 85 ng/ml (average, 8.84 ng/ml), with 92 percent of the values less than 20 ng/ml.

In a recent additional (unpublished) analysis of this study, Cummings (1994) examined ETS exposure at work among currently employed nonsmoking subjects (*n* = 339) who did and did not report exposure to tobacco smoke in the home. Of currently employed nonsmokers, substantial percentages (81 percent and 76 percent, respectively) reported ETS exposure at work, both among those who were exposed at home (*n* = 122) and those who were not (*n* = 217). Overall, exposure to ETS at home was not predictive of being exposed to ETS at work. Mean urinary cotinine values for employed nonsmoking subjects in the study were analyzed by self-reported exposure to tobacco smoke at work and at home. Subjects exposed both at work and at home had mean urinary cotinine (12.8 ng/ml) very similar to those exposed at home but not at work (11.0 ng/ml), with those exposed at work and not at home showing lower mean cotinine (7.5 ng/ml). As noted by the author, many of the subjects took time off work to attend the clinic where the study was conducted, and thus a stronger influence of home exposure on mean urinary cotinine is not surprising. Subjects reporting no exposure at work or at home had a mean urinary cotinine level (8.7 ng/ml), which is indicative of exposure to ETS.

Coultas et al. (1987) Coultas *et al.* (1987) conducted a population-based household survey of respiratory disease in 2,029 Hispanic children and adults in New Mexico, in which salivary cotinine was measured for 1,360 nonsmokers and ex-smokers. Nonsmoking status was ascertained on the basis of self-reported smoking status and a salivary cotinine concentration of less than 20 ng/ml; the reported detection limit in this study was 0.78 ng/ml saliva. Exposure prevalence, estimated using data presented in the report, was: 39 percent for adults (18 years and older), 48 percent for adolescents (13-17 years), 45 percent for children (6-12 years), and 54 percent for infants and preschoolers (5 years of age and under). The mean salivary concentrations in the various age groups ranged from 0 (not detected) to 6.0 ng/ml.

The prevalence of a detectable level of cotinine was about 35 percent for those living in a nonsmoking household and increased with the number of cigarettes smoked by household members. In a multiple logistic regression model, the major determinants of a detectable level of cotinine in children were mother's smoking (odds ratio (OR) = 3.2), father's smoking (OR = 2.1), and the smoking of other household members (OR = 4.0); the other household smokers were primarily grandparents (41 percent), siblings (26 percent), or aunts and uncles (15 percent). Among adults, the effects of spouse's smoking were smaller, with ORs of 1.3 and 1.4 for husband's and wife's smoking, respectively.

2.6.3.2 Studies of Infants and Children

Infants and young children are particularly susceptible to the adverse effects of ETS (See chapters on *Developmental and Reproductive Effects of Exposure to ETS*, and *Respiratory Health Effects of Exposure to ETS*). A number of studies have examined exposures of this population group (Greenberg *et al.,* 1989; Chilmonczyk *et al.,* 1990; Overpeck and Moss, 1991).

Overpeck and Moss (1991) In 1988 the National Center for Health Statistics collected information on household exposure to ETS for a sample of 5,356 children 5 years of age and under (Overpeck and Moss, 1991). The information was obtained as part of the National Health Interview Survey, a continuous cross-sectional survey representing the household population of the United States (the authors report that the sample is representative of 86 percent of U.S. children in this age group). Overall, the survey found that about one-half of all U.S. children 5 years of age and under are exposed to tobacco smoke constituents due to prenatal maternal smoking and/or are exposed to ETS from household members after birth. Of the total sample, 28 percent had both prenatal and postnatal exposure, 21 percent were exposed only after birth, with 1.2 percent exposed prenatally only.

Forty-two percent of the children were currently living in a household with a smoker. Of these children, a disproportionately high number lived in homes comprising the lower income and educational categories. Children in families at the lowest income level category were almost twice as likely to live in a home with a current smoker (58 percent) compared to children in families at the highest income level (30 percent). More than twice as many children whose mothers had not completed high school (61 percent) were currently exposed to household smoke as compared to children whose mother had completed one year or more of college (28 percent).

Greenberg et al. (1989) In a study of infant exposure to ETS, Greenberg *et al.* (1989) obtained detailed information on household smoking habits from mothers of 433 infants from a representative population of healthy neonates in central North Carolina during 1986 and 1987; infant urine samples were also collected. Approximately 55 percent (239) of the study infants lived in a household with at least one smoker. As determined from the questionnaire responses, 42 percent of the infants were exposed to ETS during the week preceding data collection, where exposure was defined as the production of smoke in the same room or vehicle as the infant. As in other studies, prevalence was higher when the metric of exposure was cotinine. Of the 433 infants, cotinine was detected in 60 percent of the urine samples. Measured concentrations ranged from 6 to 2,273 ng/mg creatinine, with a median concentration of 121 ng/mg creatinine (see Section 2.4.2.1 for a discussion of cotinine to creatinine ratios).

Chilmonczyk et al. (1990) In a large population-based study of infants receiving routine well-child care in private physicians' offices in the greater Portland, Maine area, Chilmonczyk *et al.* (1990) collected urine samples from 518 infants, 6- to 8-weeks of age, and obtained information on household smoking habits. Forty-one percent of the study population lived in households in which at least one household member smoked. Of the total sample, 80 percent had detectable urinary cotinine concentrations (concentrations less than 1 µg/L were reported as not detected), with concentrations greater than 2 µg/L in 64 percent of the samples. In the 305 households where no smoking was reported, 8 percent of the infants' urinary cotinine

values were equal to or greater than 10 µg/L (on the basis of data in the study, the authors defined the concentration of 10 µg/L as a reasonable estimate of significant ETS absorption). Corresponding rates of urinary cotinine ≥10 µg/L were 44 percent in infants living in the 96 households where a member other than the mother smoked, 91 percent for those in the 43 households where only the mother smoked, and 96 percent for those in the 74 households where both the mother and another household member smoked.

2.6.4 Factors Influencing Exposure to ETS Because data are not available to quantify trends in ETS exposure in California, this section examines trends in the prevalence of smoking, the results of legislative efforts to limit smoking, and other factors contributing to ETS exposure of the nonsmoker. Indirect evidence (*e.g.*, smoking prevalence trends) suggests that exposure to ETS in California is declining and that ETS exposure prevalence in California may be lower than elsewhere in the U.S.

2.6.4.1 Smoking Prevalence Trends: California versus U.S. Data from 1965 to 1985 show that there has been a continual decline in smoking prevalence among U.S. adults, with an annual rate of decline of 0.5 percent over that time period and a 1.1 percent annual decrease between 1987 and 1990 (U.S. DHHS, 1989; CDC, 1992). In a 1991 survey of a representative sample of the U.S. civilian population (18 years and older), 49.8 percent of the population were ever-smokers and 25.7 percent were current smokers (CDC, 1993a). Comparative data for the U.S. and California indicate that both smoking prevalence and cigarette consumption are lower in California than in the rest of the U.S., and that the annual rate of decline in California has been somewhat more rapid over the last decade (Figures 2.6 and 2.7; Burns and Pierce, 1992; Pierce *et al*., 1994; CDHS, 1996). Limited information is available to determine whether there have been corresponding decreases in ETS exposures of nonsmokers, either nationwide or in California. Although smoking prevalence is clearly related to ETS exposures, other factors associated with smoking behavior that contribute to exposure of nonsmokers (*e.g.*, location of smoking) must also be considered.

2.6.4.2 Smoking Prevalence Trends in Subpopulations Although overall trends in smoking prevalence and other factors suggest that ETS exposure is decreasing, this may not be true for all population subgroups, in addition, the rate of decline may differ among different groups. Patterns of cigarette smoking in the U.S. have shifted over the years among sex, race, educational, and socioeconomic groups (Fiore *et al.,* 1989; Pierce *et al.,* 1989; U.S. DHHS, 1989; Overpeck and Moss, 1991), with differential impacts on ETS exposure of the nonsmoker. As one example, although the overall prevalence rates of smoking have declined among men and women during the last decade, smoking has decreased at a slower rate among women. In 1991, it was reported that the onset of smoking for females is occurring at younger ages and until recently, smoking initiation was increasing for the least educated females. As a result, the differential risk of ETS exposure of infants and children may have changed because of the smoking patterns among

women with higher than average birth rates and those who spend more time with the developing child (Overpeck and Moss, 1991).

Teenagers are another important example of a population subgroup with smoking prevalence trends that differ from overall trends. Smoking prevalence among 16- to 18-year-olds declined fairly steadily from 1975 through 1981, and again from 1984 through 1988. After 1988, this trend was reversed and smoking prevalence among California adolescents began to increase; however, data for 1992 and 1993 indicate that the rising trend may not be continuing (Pierce *et al.,* 1994). This trend is significant because the teen years are the time when most people who become smokers start smoking. The age of smoking initiation in the U.S. has been declining and now peaks among 16- to 18-year-olds (Pierce *et al.,* 1994).

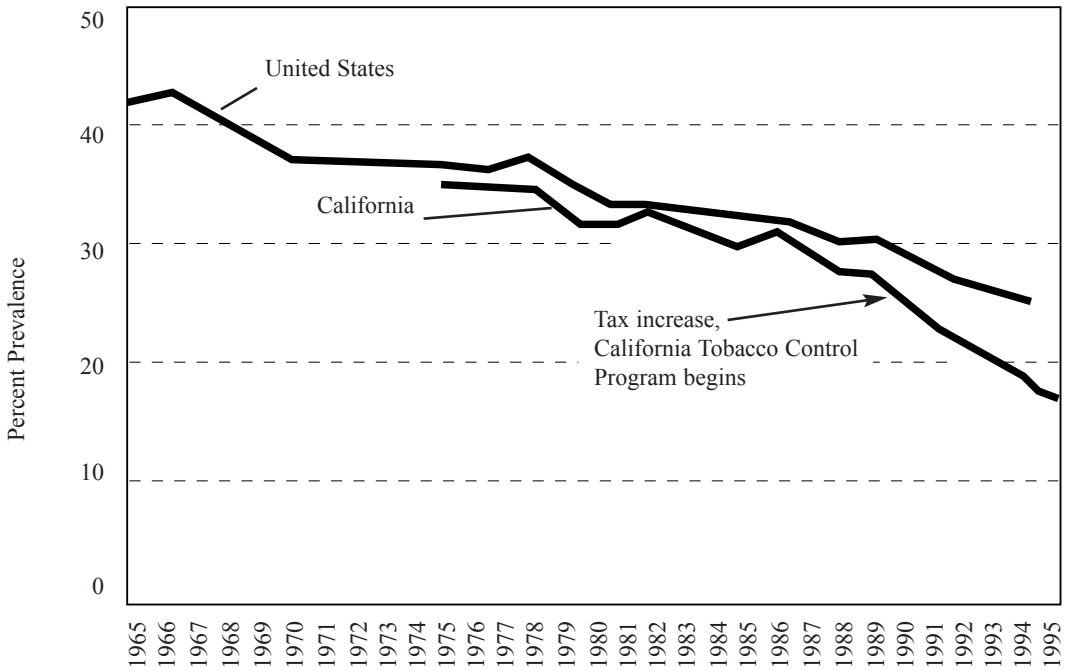
Hammond *et al.* (1995) measured occupational exposures to ETS in 25 diverse settings in Massachusetts, including offices and production areas, to evaluate the effectiveness of smoking restrictions in the workplace. Average weekly concentrations of nicotine, measured by 15 to 25 passive samplers in each worksite, were used to indicate ETS exposure. The researchers found that worksite smoking policies had a major effect on the ETS exposure, with median nicotine concentrations lowered by a factor of 6 by smoking restrictions and by a factor of 30 by smoking bans in open offices at worksites. Non-office worksites were similarly affected, with restrictions lowering exposure by a factor of 3 and bans by a factor of 10.

2.6.4.3 Factors Affecting ETS Exposure in California: Proposition 99 Efforts

Within the last several years, there has been a major public health effort in California to reduce smoking prevalence and ETS exposure of the nonsmoker. These efforts are due, in part, to the Tobacco Tax and Health Protection Act (Proposition 99) passed in 1988 by voters in California. The measure raised the tax on cigarettes by 25 cents per pack, providing funding for a statewide health education program to reduce tobacco use. Funds from this measure have also supported the collection of data on smoking behavior; telephone surveys of California households have been conducted using both cross-sectional and longitudinal designs. These California Tobacco Surveys (CTS) as analyzed by Pierce *et al.* (1994) were the main sources used to estimate the prevalence trends described below.

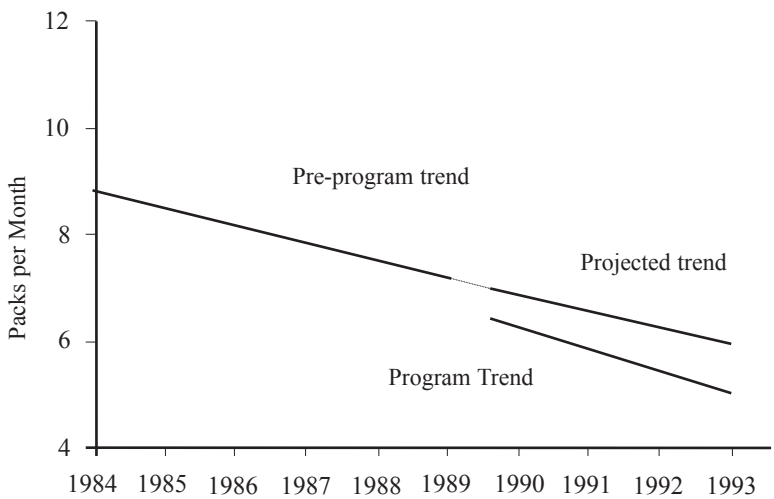
Analyses of CTS data to evaluate the effectiveness of programs implemented as a result of the passage of Proposition 99 suggest that these programs have been effective in reducing smoking prevalence (Burns and Pierce, 1992; Pierce *et al.,* 1994). Among adults, smoking prevalence in California for the year before the tax increase (*i.e.*, 1987) was 26.8 percent; the 1990 estimate was 22.2 percent, a 17 percent decline in 3 years (Burns and Pierce, 1992); the 1995 estimate is 16.7 percent (CDHS, 1996; Figure 2.6). More recent information indicates that the prevalence of smoking among adults 20 years and older has dropped even further, to an estimated 19.1 percent in 1993, while for adolescents 16 to 18 years old, prevalence is estimated to be 7.75 percent (based on 1990 data; Pierce *et al.,* 1994). If the

Figure 2.6
Adult Smoking Prevelance: California and the United States, 1965 to 1995



Source: California Department of Health Services, 1996

Figure 2.7
Linear Trend in Per Capita Consumption of Cigarettes in California Before and After Proposition 99 and Taxation Program



Source: Pierce et al., 1994

decline in smoking prevalence observed in California between 1988 and 1993 continues through the 1990s, smoking prevalence among Californian adults will be 10.2 percent by the year 1999. This rate of decline in smoking prevalence will not achieve the California Department of Health Services (CDHS) Tobacco Control Program's legislatively set goal of a 75 percent reduction in smoking prevalence (to 6.5 percent) by the year 1999 (Pierce *et al.,* 1994). Although the decline in smoking may fall short of the set goal, the program has been successful in reducing smoking prevalence among adults; the 1993 prevalence level was 16 percent lower than it would have been had the 1984 through 1988 pre-program trend continued.

A decline in per capita consumption of cigarettes in California has also been observed from 1980 through 1993 (Figure 2.7). Similar to the observations with respect to smoking prevalence, a sharp acceleration in the rate of decline in tobacco consumption was observed at the time of the Proposition 99 tax increase. As shown in Figure 2.7, the rate of change of per capita consumption appears to have leveled off following an initial rapid decline (Burns and Pierce, 1992). More recent information on cigarette consumption indicates that per capita consumption in 1992 was 5.34 packs per month, 13.82 percent lower than the 6.23 packs per month predicted if consumption trends before the passage of Proposition 99 had continued through 1992 (Glasscock *et al.,* 1992-93). Per capita cigarette consumption dropped even lower in 1993 to 4.84 packs per month (Pierce *et al.,* 1994). These declines have been attributed to the 1988 tax increase and subsequent tobacco education efforts.

Children have been a priority of the CDHS Tobacco Control Program's efforts to reduce ETS exposure and its associated health costs. The home is the primary location of exposure of young children and efforts have been made to reduce exposure at this location. Data available for the last 2 years suggest that exposure of children is decreasing—in 1992, 75.5 percent of children 18 years of age and younger lived in a smoke-free household; in 1993, this proportion had increased significantly to 80.4 percent ($p < 0.05$; Pierce *et al.,* 1994).

2.6.4.4 Factors Affecting ETS Exposure in California: Smoking Laws and Ordinances

As indicated in Section 2.6.2, the workplace represents an important ETS exposure location in California. Over the last several years, an increasing number of workplaces have adopted policies restricting smoking, and studies have shown that reported nonsmoker exposure to ETS decreases with increasing degree of worksite restriction on smoking (Borland *et al.,* 1992; Pierce *et al.,* 1994). More specifically, it is estimated that the percentage of indoor workers with smoke-free workplaces (*i.e.*, smoking is prohibited in all areas) nearly doubled in California, from 35 percent in 1990 to 65 percent in 1993; in 1993, the proportion of workers covered by at least a work-area ban on smoking (*i.e.*, smoking is prohibited in the work area) was 87.3 percent (Pierce *et al.,* 1994). Recent legislation (discussed below) can be expected to further lower these numbers. Thus, the relative importance of the workplace as an exposure location is expected to decline in California as more

workplace restrictions are imposed through the enactment of new laws or implementation of smoking policies by the private sector.

Data available for California and the United States suggest that workplace exposure in California is less than in the country as a whole, although the different time periods for which the data are available and the rapid change in workplace smoking policies limit the conclusions that can be made. Approximately 36 percent of workers (smokers and nonsmokers) in California worked in a smoke-free worksite (data for 1990), as compared to only 3 percent of workers in the U.S. population as a whole (data for 1986). Further, 71.3 percent of indoor workers in California reported some type of work-site smoking policy in 1990, compared with only 45 percent nationally in 1986 (Pierce and Hatziandreu, 1986).

In California, smoking in state-owned buildings and leased space, state prisons and hospitals, and state-owned passenger vehicles was banned in 1993 by Executive Order (W-42-93), with full compliance required by December 31, 1993 (Gov. Code, Section 19994.30). Restrictions on smoking in a wide range of workplaces in California went into effect on January 1, 1995, as the result of legislation (AB13 - Friedman) passed in 1994 and signed by Governor Pete Wilson. This addition to the California Labor Code (Section 6404.5) provides that "no employer shall knowingly or intentionally permit, and no person shall engage in, the smoking of tobacco products in an enclosed space at a place of employment." All restaurants are included under the statute. Private residences are not included under the statute, except for those licensed as family day care homes, in which case, the statute applies during the hours of operation and in those areas where children are present. The law specifies other "places of employment" which are not covered, including (for example): portions of hotels (designated lobby areas, guest rooms, and meeting rooms); bars and taverns; cabs of trucks; warehouses; and certain places of employment where fewer than five persons work. This workplace smoking prohibition could have substantial impact on ETS exposures in California.

In addition to limitations on smoking in the workplace, an increasing number of cities and counties in California have placed various types of restrictions on smoking. These include restrictions on smoking in city- and county-owned facilities, restaurants, workplaces, and other public locations; also included are restrictions on the sale or promotion of tobacco products, typically by restricting the location of vending machines, advertising, or sampling activities. As of July 1994, 77 cities and 16 counties in California have local ordinances which require all workplaces and all restaurants to be 100 percent smoke-free (Americans for Nonsmokers' Rights, 1994). An additional 72 California cities have ordinances requiring 100 percent smoke-free workplaces, and 91 have ordinances requiring 100 percent smoke-free restaurants (California Smoke-free Cities, 1994).

Smoking has also been prohibited in all day care centers and in pri-

vate residences licensed as family day care homes during hours of operation (ARB 615, 1993). A similar law, called the Pro-Children Act of 1994, was passed on the national level which prohibits smoking in any health care, day care, or early development services facility, and in facilities providing kindergarten, elementary or secondary education, or library services to children (HR 1804, Section 1041, 1994).

2.6.4.5 Other Factors Affecting ETS Exposure in California

Finally, other less quantifiable changes in smoking behavior may also be contributing to changing patterns of ETS exposure of the nonsmoker. For example, increased awareness of the potential health effects of ETS exposure and increased willingness of nonsmokers to object to smoking in their presence may result in changes in smoking behavior; for example, smokers may refrain from smoking in the presence of children, or may confine smoking to outdoor areas, even at home. Recent data indicate that half of all Californians surveyed voluntarily made their homes smoke-free by 1993, and 20 percent had some household smoking restrictions, where smoking was permitted only in certain rooms or at certain times. The number of smokers reporting a smoke-free home increased from 18.8 percent of those surveyed in 1992 to 27.1 percent of those surveyed in 1993 (Pierce *et al.,* 1994). Smokers who had young children living in the home were more likely than smokers living without children to report a smoke-free home.

2.7 CHAPTER SUMMARY AND CONCLUSIONS

ETS can be a major source of indoor air contaminants in environments where smoking occurs. Composed of both sidestream and mainstream smoke, ETS contains over 50 compounds identified as carcinogens and five identified as developmental and reproductive toxicants (under Proposition 65). Although changes in cigarette design (*e.g.*, filters) have had substantial impact on the composition of mainstream smoke, these changes have had little impact on the composition of sidestream smoke, the principal contributor to ETS.

In many indoor environments that have been monitored, ETS has been detected, and studies consistently show that concentrations of a number of toxic and carcinogenic constituents (*e.g.*, PAHs, nitrosamines) are elevated in environments where smoking is allowed as compared to those where it is not. Levels of ETS encountered by exposed nonsmokers, including infants and children, during their daily activities are sufficiently high that ETS constituents have been detected in their urine, blood, and saliva.

Although the presence of cotinine (and other biomarkers) in the fluids of nonsmokers provides evidence of the degree of exposure to ETS, the ratio of cotinine levels in ETS-exposed nonsmokers to those in smokers may not be indicative of the exposure ratio for other ETS constituents. The ratio of sidestream to mainstream emissions is not constant for all constituents, and indoor air measurements suggest that different constituents are removed from air at differing rates. In addition, differences exist in the uptake and metabolism of individual constituents.

Although nicotine and cotinine are typically used as markers of exposure to ETS, a limited number of studies have examined other biomarkers more directly related to a biological effect. For example, hemoglobin adducts of 4-aminobiphenyl (a human carcinogen) have been used as biomarkers of exposure in some epidemiologic studies. More work is needed to expand the use of biomarkers such as hemoglobin adducts of 4-aminobiphenyl, which have relevance to the health effects under study.

Questionnaires, widely used in assessing ETS exposure, provide accurate qualitative information on self-reported exposure to spousal, parental, or other household smoking, although quantitative information is less reliable. Because of the importance of the workplace and other indoor locations for adult exposures, misclassification may occur when exposure status is based solely on exposure at home. In addition, biomarker studies have shown that a proportion of subjects reporting no exposure to ETS (at work or at home) have measurable biomarker concentrations, indicating that the subject either forgot or was not aware of actual exposure. Thus, biomarker measurements may be useful in validating the questionnaire-based exposure status of ETS-exposed subjects.

Californians spend a major portion of their time indoors, where most exposure to ETS occurs. Estimates from surveys conducted in the late 1980s indicated that 43 percent of the nonsmoking adult population was exposed to ETS on any given day. In these surveys, ETS exposure was reported for approximately 40 percent of all children under the age of 12, and for approximately 64 percent of nonsmoking adolescents. The most significant location of exposure for adult nonsmokers was the workplace, although other locations (home, other indoor, and outdoors) were also important. For infants and children, the home was the most significant exposure location. Thus, at the time of these surveys, a significant proportion of the California population was exposed to ETS.

Overall trends in smoking prevalence and other factors, including an increasing number of restrictions on smoking in the workplace and public locations, suggest that exposure to ETS is decreasing in California. These decreases can be attributed, in part, to programs implemented under California's Proposition 99, passed in 1988; further decreases are expected due to the passage of AB 13, effective in January 1995, which restricts smoking in most workplaces. Lower rates of smoking and per capita consumption of cigarettes in California as compared to the entire U.S. suggest that exposure to ETS is lower in California than nationwide. However, certain subpopulations (*e.g.*, low income women, teenagers) may be experiencing different smoking trends that may affect ETS exposure rates of others (*e.g.*, infants). Because the teen years are the time when most people who become smokers start smoking, continued surveillance of this subspopulation is needed to identify public health efforts which will further reduce ETS exposures in California.

Despite the decreasing prevalence of ETS exposure of California nonsmokers due to increasing restrictions on smoking in the workplace and public locations, exposure of young Californians, especially infants and young children, is of continuing public health concern. The timing and routes of infants' exposure to tobacco smoke constituents are unique in that infants can be exposed prenatally if the mother smokes or is exposed to ETS during pregnancy; postnatal exposure may occur directly through inhalation and indirectly from ingestion of breast milk. Studies of nursing infants indicate that mother's milk contributes significantly to urinary cotinine levels in nursing infants. It is possible that other ETS constituents are also present in breast milk and ingested by the infant. Persons exposed as infants to potentially large doses (relative to their small bodyweight) of the carcinogenic constituents in ETS may face a relatively higher risk due to this early exposure. Those exposed *in utero* and in early life to the developmental toxicants found in ETS may be at higher risk for a number of negative health outcomes. With the home as the most significant ETS exposure location for these age groups, educational efforts for women who are pregnant (or plan to become pregnant) and their partners about reducing their children's ETS exposure are warranted.

The potential adverse health effects resulting from these exposures are addressed in the other chapters of this assessment.

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Developmental Toxicity I: Perinatal Manifestations

3.1 INTRODUCTION This chapter reviews the evidence on the impact of ETS exposure during pregnancy on: 1) fetal growth, including decreased birthweight, growth retardation, or prematurity; 2) fetal loss, including spontaneous abortion and perinatal mortality; and 3) congenital malformations. The review of each of these three categories of outcome begins with a brief discussion of studies which assessed the effect of active smoking by the mother during pregnancy. Although the impact of active smoking on development is not the topic of this document, it provides a context within which to consider the possible effects of ETS exposure. The brief discussion of active smoking effects is followed by detailed descriptions of epidemiologic studies relating ETS exposure to the specific outcome. Pertinent animal studies are then described. Each review concludes with a discussion of the overall evidence from animal and epidemiological studies for adverse impacts of ETS.

3.2 FETAL GROWTH By far the majority of epidemiologic studies on perinatal effects of ETS exposure have investigated fetal growth, and most of these studies have focused on birthweight. Technically, fetal growth should be measured by comparing size at a number of time intervals. However, measures at birth are commonly used as surrogates. Those measures include mean birthweight, low birthweight (LBW, <2500 grams), and intra-uterine growth retardation (IUGR), which is defined as less than the tenth percentile of weight for gestational age. The LBW category includes infants that are growth retarded or small for their gestational age, as well as infants who are not growth retarded but were born prematurely. These outcomes may result from different etiologies, therefore some investigators examine LBW (or IUGR) in term births only; pre-term births are also examined as a separate category. Examining IUGR over the range of gestational ages (22-42 weeks) provides more power than examining only LBW at term. Because a portion of the "normal" population will fall into the IUGR category, however, there is some question as to what extent this categorization measures "abnormality" (Stein and Susser, 1984).

3.2.1 Overview of Fetal Growth and Maternal Smoking During Pregnancy Smoking by the mother during pregnancy has long been considered an important independent risk factor for decreased infant birthweight. The association was first reported in 1957, and the weight of evidence indicates a causal effect (Stillman *et al.*, 1986; U.S. DHHS, 1980). Infants of active smokers typically have a mean birthweight 150-200 grams less than those of non-

smokers and are twice as likely to be of low birthweight. The reduction in birthweight does not appear to be due to more pre-term births; rather, infants are growth retarded at all gestational ages. There is evidence that other growth measures, such as length and head circumference, are also reduced in infants of smokers.

The effect of smoking may result primarily from exposure to carbon monoxide and nicotine. Carbon monoxide can cause fetal hypoxia, for which the fetus is physiologically unable to adequately compensate (Stillman *et al.*, 1986; U.S. DHHS, 1980). Nicotine leads to decreased utero-placental perfusion and also crosses the placenta to affect the fetal cardio-vascular system as well as the gastrointestinal and central nervous systems (Stillman *et al.*, 1986). Other constituents of cigarette smoke (*e.g.*, toluene, cadmium) have been shown to produce fetal growth deficits (Donald *et al.*, 1991; OEHHA, 1996). All of these compounds are also present in ETS.

3.2.2 Human Studies of Fetal Growth and ETS Exposure

Many of the early epidemiological studies of ETS exposure and fetal growth did not adjust for confounders. When examining fetal growth, a number of co-variables should be considered initially, including: maternal age, race, parity or prior reproductive history, maternal smoking, socioeconomic status, and/or access to prenatal care. Few studies have information on maternal stature or weight gain, but these are also important determinants of fetal weight, as are certain illnesses, complications of pregnancy, and gender of the infant. Gestational age at delivery is the strongest predictor of birthweight. Multiple births are much more likely to result in lower birthweights, so study populations are often limited to singleton births. Although many factors may be related to birthweight, their distribution by ETS exposure status must vary in order for them to confound an association of ETS and birthweight. A confounder in one study population is not necessarily a confounder in another.

The descriptions of the epidemiological evidence on fetal growth are presented by exposure measure (*i.e.*, home exposure, home and work exposure, biomarkers). The numerous studies on exposure to ETS in the home are presented in two different subsections, one on mean birthweight, the other on growth retardation or prematurity.

3.2.2.1 Home ETS Exposure and Mean Birthweight

All but one of the studies of the impact of ETS exposure in the home on mean birthweight found a decrement in mean birthweight, although in about half, the decrement was small (Table 3.1; Figure 3.1, top). A few early studies found little effect, but none of them controlled for confounders or performed much statistical analysis. Of the studies conducted in the last decade, seven found decrements ranging from 30 to 200 grams while four found very little association with paternal smoking, and weight decrements of less than 20 grams. Two of the four which found little association were based on selected populations (*e.g.,* offspring of twins); this may have introduced some bias and affected the generalizability of the results (Magnus *et al.* 1984; MacArthur and Knox,

Table 3.1
Studies of Birthweight and ETS Exposure Defined by Paternal Smoking Status

Authors (year) Country	Study Design	Difference in Mean Birthweight by Exposure[1]
MacMahon *et al.* (1966) U.S. (Massachusetts)	Retrospective mail questionnaire (12,192 white singletons) (5,935 maternal nonsmokers)	-22g (-57-13) females -20g (-55-15) males -28g for pipe/cigar (ns) no consistent effect by amount
Comstock & Lundin (1967) U.S. (Maryland)	Special census linked to vital records (448 births)	-42g (no statistics provided)
Underwood *et al.* (1967) Worldwide	Naval records of labor and delivery; cross-sectional (48,505 singletons with 24,674 maternal nonsmokers)	-7 to -3g, by amount smoked
Borlee *et al.* (1978) Belgium	Retrospective interview (175 normal live births, 202 malformed)	-228g (-429.0 to -26.7) crude (p = 0.06 for paternal smoking impact analysis that controlled for maternal smokers)[2]
Magnus *et al.* (1984) Norway	Retrospective interview of twins (parents of offspring studied) (3,130 families; 5,188 births)	Regression for categories of about 10 cigs/day: crude: -48g (-65 to -31) adjusted for maternal smoking[2]: -5g (-23-13)
Rubin *et al.* (1986) Denmark	Interview at delivery (500 term live births >2,000g)	Adjusted for maternal smoking: -6.1g/cig (-12 to -0.2)[2] -120g/pack
MacArthur & Knox (1987) England	Unknown (180 mothers who quit smoking in pregnancy)	-14g crude not significant in an analysis for the effect of paternal smoking

[1] *All effect measures assessed in nonsmoking mothers unless otherwise specified (e.g., "smoking adjusted"). All 95 percent confidence intervals calculated by reviewers from available data. ns = not statistically significant (p > 0.05).*
[2] *Control for at least some confounders (see text discussion of studies).*
[3] *Based on living with a household smoker, not only the spouse.*

Table 3.1 (Continued)

Authors (year) Country	Study Design	Difference in Mean Birthweight by Exposure[1]
Schwartz-Bickenbach *et al.* (1987) Germany	Interview at delivery (54 pairs-smoke and not, followed while breast-feeding)	-205g (-440-30.1), crude
Campbell *et al.* (1988) England	Interview 1 month post-delivery (518 white singles)	-113g (-216 to -8)[2] (from regression after adjusting for maternal smoking)
Brooke *et al.* (1989)[3] England (London)	Prospective interview (1,513 white births with 1,018 nonsmokers)	-18g or 0.5% reduction (p = 0.56)
Chen *et al.* (1989)[3] China (Shangai)	Retrospective mail questionnaire (1,058 births)	-11g (-81.9-64.1) paternal smoking ≤10/day -15g (-94.5-64.5) any other smokers ≥10/day adj made no difference[2] no dose effect
Saito (1991) Japan	Interview at infant care visit (3,000 couples)	Smoke any: -33.4g (-66.3 to -0.5) For 40 cigs/day: -111g (-191.0 to -31.7), crude
Mathai *et al.* (1990)[2] England (Liverpool)	Prospective interview (285 white singles)	-66g (-213.0-81.1), crude
Mathai *et al.* (1992) India (Vellore)	Interview (994 singletons)	-63g (-114g to -12)[2]
Zhang & Ratcliffe (1993) China (Shangai)	Interview post-delivery (1,785 singleton term births)	-30g (-66-7)[2] -62g for 15-19 cigs/day but +32 for ≥20/day
Martinez *et al.* (1994) U.S. (Arizona)	Interview at delivery (1,219 births, 907 nonsmokers)	-34g (-63 to -5)[2] per 10 cigarettes

[1] *All effect measures assessed in nonsmoking mothers unless otherwise specified (e.g., "smoking adjusted"). All 95 percent confidence intervals calculated by reviewers from available data. ns = not statistically significant (p > 0.05).*

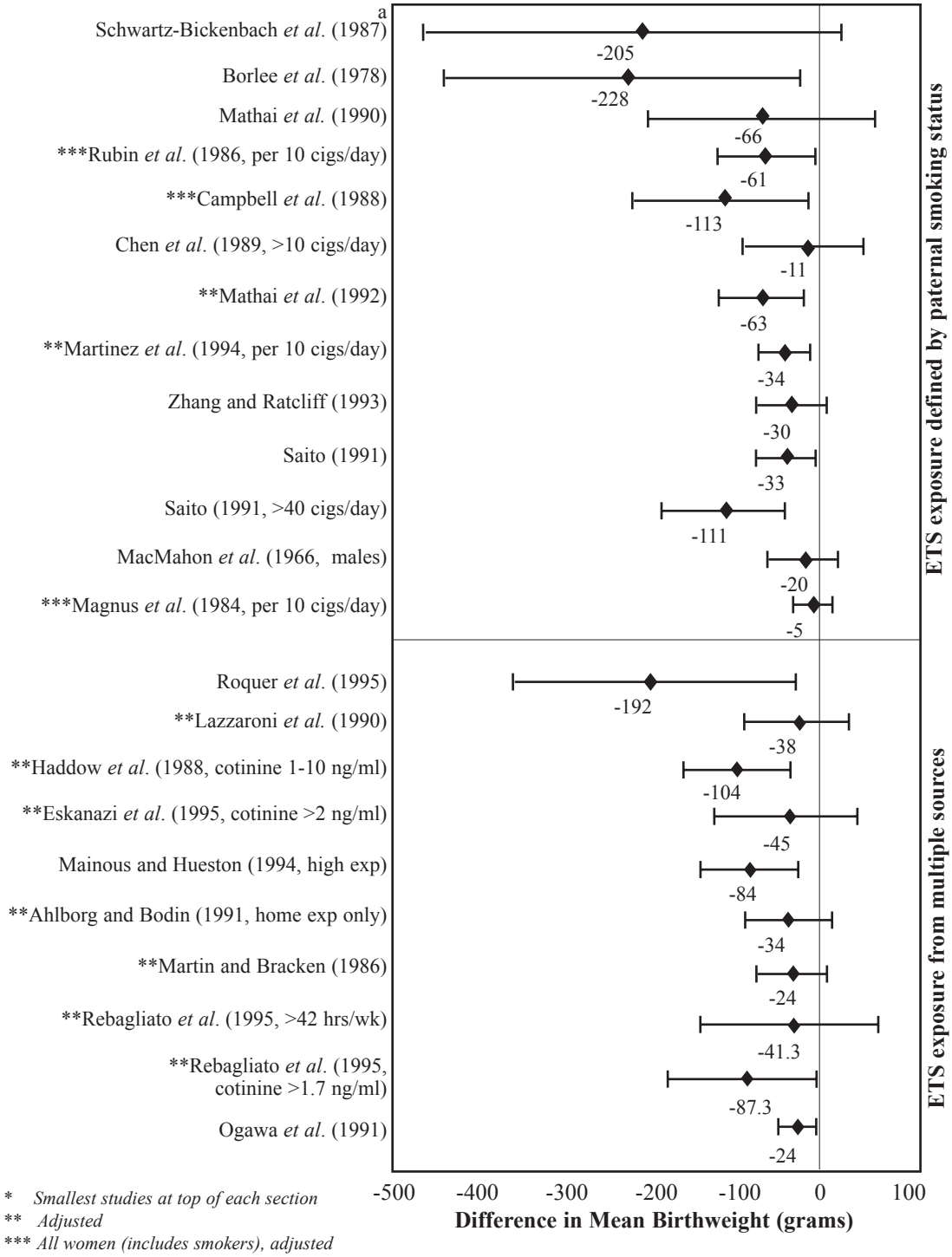
[2] *Control for at least some confounders (see text discussion of studies).*

[3] *Based on living with a household smoker, not only the spouse.*

1987). Similarly, one which found the greatest weight decrement also studied a select population (Schwartz-Bickenbach *et al.*, 1987). The studies are described in chronological order below.

MacMahon et al. (1966) MacMahon *et al.* (1966) studied a large sample of live births by sending their mothers a questionnaire to ascertain parental smoking habits during the calendar year in which the pregnancy started. Overall, the study found an 86.8-gram decrement associated with any paternal smoking for female infants, with a slightly lower decrement for male

Figure 3.1
Summary of Differences in Mean Birthweight and 95% Confidence Intervals Between ETS-Exposed and Unexposed Pregnancies by ETS Definition and Study Size*



* *Smallest studies at top of each section*
** *Adjusted*
*** *All women (includes smokers), adjusted*

infants (-78 grams). Limiting the analysis to nonsmoking mothers, a crude 22-gram decrement for female infants was associated with paternal smoking and a 20-gram decrement for males (Table 3.1). There was no evidence of a dose-response effect. Paternal pipe or cigar smoking was associated with similar decrements, on the order of 20-30 grams.

Comstock and Lundin (1967) In a study of Maryland vital records, Comstock and Lundin (1967) noted that the mean birthweight of infants with smoking fathers and nonsmoking mothers was 42 grams less than that of infants whose parents both did not smoke. In addition to a lack of statistical analysis, this study ascertained smoking status from a special census and thus was not specific to the pregnancy.

Underwood et al. (1967) Underwood *et al.* (1967) published a large study of newborns delivered in naval installations worldwide. The greatest limitation of this study is the unusual ascertainment of smoking status; it was obtained from the physician attending the birth in the various labor and delivery rooms. Examining infants whose mothers did not smoke, the authors found that mean birthweight was decreased only 3-7 grams depending on the amount smoked by the father. However, from a figure in the report it appeared that heavy (>30 cigarettes/day) paternal smoking had a greater effect on birthweight in infants born before 35 weeks (about a 100-gram decrement), although the authors did not comment on this. No confounders were considered in this analysis.

Borlee et al. (1978) Borlee *et al.* (1978) examined birthweight and body measurements of infants from a hospital-based, case-control study of congenital malformations conducted in Belgium. The authors appear to include the malformed children in most of the analyses, which may make the results less generalizable. Mean birthweight of infants born to nonsmoking mothers was decreased by 228 grams if the father smoked before conception. Among infants of smoking mothers, those with smoking fathers were heavier than those with nonsmoking fathers, but this finding is based on only 14 infants with nonsmoking fathers and smoking mothers, so is not reliable. Length and head circumference varied little by paternal smoking status. Using the entire study group for an analysis of variance with a few co-variables (malformation, prematurity, maternal tobacco use), there was an association between paternal smoking and birthweight ($p < 0.06$), but the adjusted difference was not presented. Other important potential confounders identified by the authors were not taken into account. The magnitude of effect of ETS exposure seems implausibly large, but the decrement in mean birthweight associated with active maternal smoking, among infants of nonsmoking fathers, was much greater still (*e.g.*, -561 grams, crude difference).

Magnus et al. (1984) Magnus *et al.* (1984) studied causes of variations in birthweight in offspring of adult twins in Norway. This is a select population (offspring of parents who are twins), and the generalizability of the results is unclear. The authors assumed that smoking status at interview reflected habits during childbearing years. There are few data on this topic, for fathers in par-

ticular. However, some decrease in smoking during the 10-15 years since some of the study births would be expected. Fathers who smoked during the target pregnancy but not at the later interview, would be included as nonsmokers, diluting any effect. In a bivariate regression, paternal smoking was associated with a 48-gram decrement in birthweight ($p < 0.01$). In a multiple regression analysis that included maternal smoking and some other covariates, paternal smoking was only associated with a 5-gram decrement (Table 3.1). Maternal smoking remained significantly associated with birthweight decrements.

Karakostov (1985) In a study conducted in Bulgaria, Karakostov (1985) reported an 84-gram weight decrement in infants of women exposed to ETS during pregnancy compared to infants whose parents were both nonsmokers. The measure of variability in birthweight is unclear; it is presented as the standard deviation, but because it is so small (*i.e.*, 60 to 80 grams) it appears to be the standard error. Assuming the latter, the confidence interval is wide (95% CI = -280 to 111). Mean length was decreased by about one-half centimeter. No confounders were controlled.

Rubin et al. (1986) In 1986, Rubin *et al.* reported a positive association between birthweight and paternal smoking which spurred many of the subsequent studies. Five hundred Danish women were interviewed shortly after delivery regarding smoking by fathers and other household members. Births were all greater than 2,000 grams and 35 weeks gestation, so they represent a relatively healthy group *a priori*. Maternal and paternal smoking were highly correlated; both variables were examined together in regression models. Adjusting for many co-variables (but not maternal height or weight), the independent decrement in birthweight per cigarette (or cigar or pipe bowl) smoked daily by the father was 6.1 grams ($p < 0.03$). This yields about a 120-gram decrement for smoking a pack of cigarettes each day. The association appeared to be greatest in the lower social classes, although no interaction terms were included in the regression models. The decrement seen with maternal smoking was 9.2 grams per cigarette per day (adjusted for paternal smoking and other variables).

MacArthur and Knox (1987) A second study with a highly selected sample was reported in a letter to *Lancet*. MacArthur and Knox (1987) focused on 180 women who reported that they stopped smoking during pregnancy, a group unlikely to be representative of nonsmokers. Some data related to paternal smoking were provided, but not information about the study from which the data were derived or the statistical methods used. As maternal and paternal smoking are usually correlated, it was somewhat surprising that there was no reported difference in the mean amount smoked before pregnancy by women whose partners smoked compared to women whose partners did not. The authors found only a 14-gram decrement in mean birthweight if the father smoked. They indirectly standardized the birthweight distributions of each paternal smoking group for maternal height and parity, and for sex and gestational age of the infant, and noted a 123-gram excess if the father smoked. However, both groups had an “excess” birth-

weight (100 grams among infants of nonsmoking fathers and 223 grams among those of smoking fathers) relative to an unspecified comparison group. The excess in both groups may indicate that women who stop smoking adopt other healthy behaviors that contribute to a healthier outcome, or that this group of women is not comparable to the general population.

Schwartz-Bickenbach et al. (1987) Schwartz-Bickenbach *et al.* (1987) reported on a small study in Berlin of mothers who intended to breast feed their infants; they compared infant development in pairs where one mother smoked during pregnancy and the other did not. Among the nonsmoking women (n = 54), about half had a spouse who smoked. Those infants with smoking fathers and nonsmoking mothers weighed on average 205 grams less than infants whose parents did not smoke (Table 3.1). This is a large decrement in weight, but the decrement associated with maternal smoking was on the order of 400 grams. There was no statistical comparison of these weight differences. Assuming that the variability index in the published table is the standard deviation, the p-value for a t test of the weight decrement associated with exposure to ETS would be 0.095. There was no difference in head circumference by parental smoking habits but there were slight differences in body length. The magnitude of effect of paternal smoking was about half that of maternal smoking at 1.1 cm (95% CI = -2.3-0.1). This population was highly selected, and no confounding variables were controlled.

Campbell et al. (1988) Campbell *et al.* (1988) examined the effect of ETS exposure in a population-based sample of births that occurred in Southampton, England. The mothers were interviewed one month after delivery. In infants of maternal nonsmokers, the authors found a crude weight difference of -73 grams associated with paternal smoking. In a multiple regression analysis adjusting for maternal smoking, age, alcohol consumption, and social class, current paternal smoking status was associated with a 113-gram decrement in birthweight, about one-half the effect of maternal smoking (-253 grams) in all births (Table 3.1). The greatest decrement in weight was seen when both parents smoked. This appears to be a well-conducted study, but the inclusion of maternal smokers in the regression analysis complicates its interpretation.

Brooke et al. (1989) Brooke *et al.* (1989) reported a thorough prospective study of factors influencing birthweight, which was conducted in London. Smoking habits were ascertained at registration for prenatal care and at 28 and 36 weeks gestation. The ETS exposure variable was defined as any smokers (other than the mother) in the household. Birthweight was expressed as a ratio of observed birthweight to expected mean birthweight for gestational age. That ratio was then adjusted for parity, maternal height, and infant sex. In infants of nonsmoking mothers, those with ETS exposure had a 0.5 percent reduction in the birthweight ratio; among infants of smoking mothers with ETS exposure, there was a one percent reduction. This corre-

sponded to a difference in mean birthweight (adjusted to 40 weeks) associated with ETS exposure of 18 grams in nonsmokers and 39 grams in smokers.

Chen et al. (1989) Chen *et al.* (1989) reported a retrospective study of all births occurring during a 6-month period in 1981 in an area of Shanghai, China. One advantage of this study is that none of the interviewed mothers were smokers; disentangling the correlation of spousal smoking habits is therefore not an issue. ETS exposure estimates were based on the daily cigarette consumption by the spouse and other family members. The proportion of mothers exposed to ETS (72 percent) was higher in this study than in most other studies. Mean birthweight was decreased only 9-11 grams, depending on the amount smoked by the spouse (1-9 or ≥10 cigarettes/day; $F = 0.3$, $p = 0.74$) and was decreased 4-15 grams, depending on the amount smoked by all family members ($F = 0.7$, $p = 0.92$). The authors stated that adjusting for multiple confounders (gender, parity, education, maternal age, and income) did not change the results. Two potential confounders not available were maternal height and weight, which may not be as variable in China as in the U.S.

Saito (1991) A study from Japan (Saito, 1991) examined the smoking habits of about 3,000 couples who brought their infants into a large Tokyo medical center for care during 1987. The majority of women did not smoke during their pregnancy and about half the fathers smoked. Among infants whose father smoked but whose mother did not smoke during pregnancy, there was a decrement in mean birthweight of 33.4 grams ($p < 0.05$) compared to infants of nonsmoking parents (Table 3.1). Among infants whose parents both smoked, the mean birthweight was further decreased 66 grams (or about 100 grams total). The author found a dose-response effect by amount the father smoked, with a weight decrement of 111 grams ($p < 0.01$) among infants of fathers who smoked 40 or more cigarettes per day. In this later analysis, the author appears to include couples in which the mothers also smoked. Such couples do not comprise a large portion of the sample (perhaps 8 percent), but nevertheless, a direct effect of maternal active smoking may have influenced the dose-response results. The author further found that the weight decrement was slightly greater among female (126.5 grams) than among male infants (94.3 grams) of heavily smoking fathers. This gender differential was even more striking for weight decrements seen with active maternal smoking. In addition to including smoking mothers in some analyses, this study is limited because it did not control for any confounders, despite reporting that smoking levels varied by age, education, and paternal occupation.

Mathai et al. (1990 and 1992) Mathai *et al.* (1990 and 1992) conducted two studies in different populations and obtained similar results (Table 3.1). The first study was conducted prospectively among 285 white women attending a prenatal clinic in Liverpool, England in 1987 (Mathai *et al.,* 1990). Fifty-four women (19 percent) were nonsmokers who lived with a smoker and were thus considered exposed to ETS. Their infants had a mean weight

decrement of 66 grams compared to non-exposed nonsmokers; this difference was not statistically significant, but it was based on small numbers. No confounders were controlled in the analysis. A subsequent, improved study (Mathai *et al.*, 1992), designed specifically to examine ETS exposure in a population with few women smokers, included 994 mothers of singletons born in 1990 in Vellore, India. The timing of interview was not specified, but appears to be after delivery. None of the women used tobacco, but 52 percent lived with smokers and were considered to be exposed to ETS. ETS exposure was crudely associated with a 55-gram decrement in mean birthweight. Adjusting for multiple confounders (maternal age, height, parity, social class, gestation, and infant sex), the mean decrement was 63 grams ($p = 0.015$). No information on a dose-response relationship was available.

Zhang and Ratcliffe (1993) Zhang and Ratcliffe (1993) examined the effects of paternal smoking on live births who had served as controls in a study of birth defects. Among singleton term births of nonsmoking women in Shanghai, there was a crude weight decrement of 26 grams associated with paternal smoking. Adjustment for parity, maternal age, gestational age, and mother's occupation by multiple linear regression yielded a decrement of 30 grams (95% CI = -66-7). There was a nonlinear trend by amount smoked, with greater adjusted weight decrements seen up to 19 cigarettes/day, but an increase in weight at higher levels (20 or more cigarettes/day, Table 3.1). The confidence interval at the higher level of paternal cigarette consumption overlapped with the decrements estimated at lower smoking levels. The non-monotonic trend in dose-response may be due to chance, inaccuracy in reporting of paternal amount by their spouses, or a confounding variable not taken into account. The paternal smoking ascertained appeared to reflect usual smoking status, not necessarily that during pregnancy.

Martinez et al. (1994) Martinez *et al.* (1994) studied enrollees of the Tucson Children's Respiratory Study, conducted in a large health maintenance organization in Tucson, Arizona. Information (including birthweight) was obtained by nurses while the mothers were in the hospital following the births. Each parent was given a questionnaire to answer about his or her own smoking habits, and the person's current smoking habit was used to estimate the amount smoked during pregnancy; this was possible because the current status was obtained so soon after delivery. Among the 992 nonsmoking mothers, infant birthweight significantly decreased with increasing paternal smoking; infants whose fathers smoked more than 20 cigarettes per day had a mean weight decrement of 88 grams. Maternal smoking of more than 20 cigarettes per day was associated with an average 273-gram decrement. In a multiple regression analysis adjusting for gestational age, gender, race, parity, education, and maternal age, paternal smoking was associated with a 34-gram decrement for each additional 10 cigarettes smoked per day (coded as an ordinal variable: 0 = none, 1 = one to ten, 2 = 11 to 20, 3 = greater than 20 cigarettes per day; Table 3.1). Duration of pregnancy was not affected by the smoking habits of either parent. Cotinine measured in cord blood for a subsample indicated that perhaps 1.5 percent of the women were smokers misclassified as nonsmokers. The

two women thus misclassified had nonsmoking spouses, so it is not clear that such misclassification would necessarily lead to finding a greater weight decrement with ETS exposure, which is a common criticism of studies of ETS. Detection of cord blood cotinine was reported to be strongly correlated with the number of cigarettes smoked by the father. Minor limitations of this study are the lack of information on other potential confounders such as alcohol consumption, and the use of smoking habits reported after delivery to represent smoking during pregnancy; however, it is unlikely that women who smoked during pregnancy would quit after delivery.

3.2.2.2 Home ETS Exposure and Low Birthweight, Growth Retardation or Prematurity

Several of the studies mentioned above, as well as some additional ones, examined the impact of spousal smoking status on low birthweight, growth retardation, or prematurity (Table 3.2; Figure 3.2, top). These studies are described below. Low birthweight was defined as less than 2,500 grams in all but one study. For the most part, odds ratios or similar measures indicating ETS impacts were of a magnitude of 1.5 or less; some studies found evidence of dose-response trends.

Underwood et al. (1967) In a large study of births in naval institutions (discussed above), information on parental smoking status was obtained from the attending physician (Underwood *et al.*, 1967). The authors reported little difference in rates of LBW or prematurity (<36 weeks) by amount smoked by the father, among births of nonsmoking mothers (Table 3.2). Based on the data provided, odds ratios were calculated as 0.9 for any paternal smoking and 1.05 for smoking over 30 cigarettes per day for either LBW or prematurity (Table 3.2). The reliability of the smoking information is unclear, particularly given the means of ascertainment of smoking status and the number of institutions involved. However, the finding of a dose-response relationship for maternal smoking and LBW, as expected, provides some confidence in the classification of smoking status. No confounders were controlled.

Terris and Gold (1969) A study (Terris and Gold, 1969) sometimes cited in the literature has not been included in the tables or figures. It was a case-control study of LBW among black births, with controls matched by infant sex and birth order as well as by maternal age and marital status. The main problem with the study is that no separation or control of maternal smoking was attempted in considering paternal smoking. Smoking was more frequent among mothers of LBW cases, but paternal smoking status varied little between cases and controls.

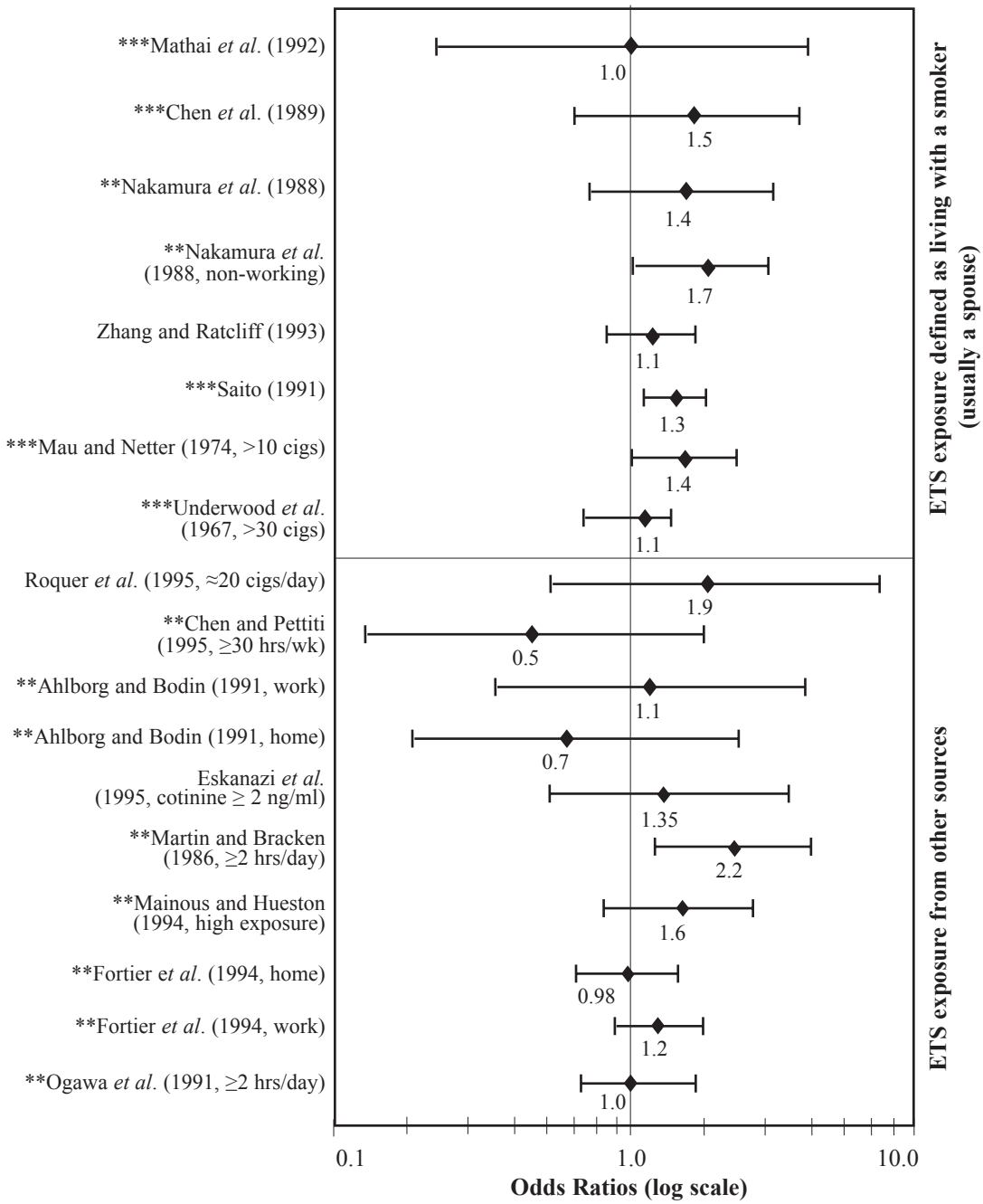
Yerulshalmy (1971) Using data from the large, prospective Child Health and Development Studies conducted among members of the Kaiser Foundation Health Plan, Yerulshalmy (1971) examined the effect of parental smoking on fetal growth. He found that the proportion of LBW infants from pregnancies in which the husband smoked was increased significantly compared to those in which the husband did not smoke. When stratified by

Table 3.2
Studies of Fetal Growth and Exposure at Home, Defined by Paternal Smoking Status

Study		Odds Ratios (with 95% CI)[4]		
Authors (year) Location	**Study Design**	**Low Birth Weight (LBW)**	**IUGR/SGA**	**Preterm**
Underwood *et al.* (1967)[1] Worldwide	Naval records of labor and delivery (24,674 nonsmoking mothers)	0.9 (0.8-1.0) any 1.05 (0.82-1.3) >30 cigs	--	0.9 (0.8-1.0) any 1.05 (0.8-1.3) >30 cigs
Yerulshalmy (1971)[1] US (N. California)	Prospective study of Kaiser members (9,793)	0.9 (n.s.) mother nonsmoker 1.4 ($p < 0.05$) mother smoker	--	--
Mau & Netter (1974)[1] Germany	Prospective interview (5,183; 3,696 nonsmokers)	1.4 (1.0-1.9) >10 cigs/day	1.2 (0.9-1.7) >10 cigs/day	1.2 (0.9-1.6) >10 cigs/day
Nakamura *et al.* (1988) Japan (Osaka)	Prospective interview (2,371 nonsmokers)	1.4 (0.9-2.2)[3] In non-working women: 1.7 (1.0-2.9)[3]	1.2 (0.8-2.0) 1.4 (0.8-2.4)	1.2 (0.8-1.8) 1.1 (0.7-1.8)
Chen *et al.* (1989)[1,2] China (Shanghai)	Retrospective, self-administered (1,163)	1.5 (0.75-3.2)	--	--
Saito (1991)[1] Japan (Osaka)	Retrospective interview (3,000 couples)	--	1.3 (1.1-1.5)	1.0 (0.8-1.3)
Mathai *et al.* (1992)[1,2] India	Interview, but timing unclear (994)	1.0 (0.4-2.3) (LBW defined as <2,000g)	--	1.6 (0.8-2.9)
Zhang & Ratcliffe (1993) China (Shanghai)	Interview post-delivery (1,785 term births of nonsmokers)	--	1.1 (0.83-1.5)	--

[1] *Odds ratio and/or confidence intervals estimated from published data, not published by original authors.*
[2] *Based on any household smoker, instead of only paternal smoker.*
[3] *Controlled for confounders.*
[4] *"n.s." indicates lack of statistical significance at $p = 0.05$*
IUGR—Intrauterine Growth Retardation; SGA—Small for Gestational Age; LBW measured at term.

Figure 3.2
Odds Ratios and 95% Confidence Intervals for the Association of Low Birthweight (or IUGR) and ETS, by ETS Definition and Study Size*



* *Smallest studies at top of each section*
** *Adjusted*
*** *OR and CI calculated from data, sometimes estimated*

maternal smoking status, this association was apparent only among pregnancies in which the mother also smoked; the highest rates of LBW occurred where both parents smoked during pregnancy. Calculating a rate ratio for LBW and paternal smoking yielded 1.4 among smoking mothers (reported $p < 0.05$) and around 1.0 among nonsmoking mothers. The raw data were not presented in this paper, nor was there any control for confounding.

Mau and Netter (1974) Mau and Netter (1974) reported data on parental smoking and a number of fetal growth parameters from a large, prospective study conducted in Germany. They examined rates of IUGR, prematurity, and LBW by amount smoked by the father among 3,696 pregnancies of nonsmoking mothers. About 44 percent of these pregnancies were exposed to paternal smoking. The investigators found slight increases in each outcome among infants of fathers who smoked more than 10 cigarettes per day, but none of the chi-square tests for the distribution of amount of paternal smoking by each pregnancy outcome was statistically significant. The authors standardized the "value of expectation" for paternal age, so it is not clear whether the rates and numbers in the tables represent raw data and can be used for confidence interval calculations (as we did in Table 3.2). Nevertheless, focusing on the fathers who smoked more heavily, the rate ratios were 1.2 for IUGR and prematurity and 1.4 for LBW (Table 3.2). No confounders other than paternal age were controlled in these analyses.

Nakamura et al. (1988) Nakamura *et al.* (1988) conducted a prospective study of pregnancies during 1984-1986 in Osaka, Japan. The authors noted that the percentage of males who smoked (67 percent) was one of the highest in the developed world, whereas few females smoked (13 percent), so the rate and intensity of ETS exposure may be greater than elsewhere. They examined the rates of LBW, LBW at term (also referred to as small for gestational age, or SGA), and prematurity. Focusing on nonsmoking mothers only, the crude rates for positive paternal smoking status were increased for LBW (OR = 1.5), and slightly for pre-term and SGA births (OR = 1.2). The investigators adjusted for a variety of potential confounders in a logistic regression model. The adjusted relative risk for LBW was 1.4 (95% CI = 0.9-2.2; Table 3.2). Because they had no information on ETS exposure at work, the investigators also performed an analysis in non-working women so that exposure would be less likely to be misclassified. The adjusted relative risk for home exposure and LBW in this group was significantly elevated: 1.7 (95% CI = 1.0-2.9). The authors noted that residence size was small in this area, which may have resulted in ETS exposures of relatively high intensity.

Chen et al. (1989) The retrospective study reported by Chen *et al.* (1989) discussed above, which was conducted in Shanghai, also reported a high prevalence of male smokers (58 percent) and no female smokers. The authors found no evidence of a dose-response relationship of amount smoked by the father or by all household members to rates of LBW, nor did consideration of a few confounders change the results (adjusted data not presented). Combining results across all categories of paternal smokers, a crude odds ratio of 1.5 (95% CI = 0.75-3.2) was calculated for LBW.

Saito (1991) In the study of Japanese couples discussed above, Saito (1991) examined the rate of "small for dates" (SFD), which was defined as a weight less than 1.5 standard deviations below an established population mean. The rates of SFD were slightly increased among infants of smoking fathers and nonsmoking mothers (calculated OR = 1.3; $p \leq 0.05$; Table 3.2). The only stratified analysis conducted was by paternal education, which appeared to confound slightly the relationship of SFD and paternal smoking. Paternal smoking of 20 or more cigarettes per day increased the rate of SFD within both categories of paternal education, by about 40 percent ($p < 0.05$), compared to infants of fathers who smoked less or not at all. The rate of prematurity did not vary by paternal smoking status.

Mathai et al. (1992) The Mathai *et al.* (1992) study of 994 East Indian births in Vellore discussed above also examined prematurity and LBW by whether the mother lived with a smoker. The authors reported that 52 percent of births were thus exposed to ETS. The outcome variable was limited to lighter (<2,000 grams) babies than the usual definition for LBW, and the authors found no difference in these rates of LBW by mother's ETS exposure (Table 3.2). The rate of prematurity was increased somewhat with ETS exposure (OR = 1.6, 95% CI = 0.82-2.9). No confounders were considered in the analysis of these outcomes.

Zhang and Ratcliffe (1993) In the Zhang and Ratcliffe study (1993) of infants of nonsmoking Chinese women discussed previously, the rates of LBW at term and IUGR were similar whether the father was a smoker or a nonsmoker (crude RRs = 1.07 and 1.11, respectively; Table 3.2). No consistent dose-response trend was seen with amount smoked. No confounders were considered in this analysis.

3.2.2.3 Home and Work ETS Exposure and Fetal Growth

Fewer studies have examined fetal growth in relation to ETS exposures defined by something other than paternal smoking status, so all outcomes are grouped together in this subsection. All of these are recent and thus tend to reflect today's higher methodologic standards. Four studies published in 1995 are reviewed as an addendum at the end of this section. Generally, these studies found associations between ETS exposure and fetal size of smaller but more consistent magnitudes than the paternal smoking studies (Table 3.3).

Martin and Bracken (1986) In 1986, Martin and Bracken published results from a widely cited prospective study of 3,891 pregnancies ending in livebirths between 1980-82 in Connecticut (Table 3.3). Passive smoking (ETS exposure) was defined as being exposed to someone else's cigarette smoke for at least 2 hours per day, either at home or at work. However, it is not clear whether this was asked as a "yes/no" question or whether data were pooled from a few questions. Among all infants of nonsmokers, ETS exposure was crudely associated with a 61-gram decrement in mean birthweight (p = 0.005) and a slightly increased rate of LBW (RR = 1.3). These associations with ETS exposure were not seen in infants of active maternal smokers. There was no association of prematurity with ETS exposure. Stratifying by

gestational age, there was a significant association in nonsmokers who had term pregnancies (OR for LBW: 2.7, weight decrement: 85 grams), which the authors interpreted as indicating an effect on growth retardation. Adjustment for confounders by multiple regression yielded a mean weight decrement of 24 grams ($p = 0.20$) and an odds ratio for LBW of 2.2 (95% CI = 1.1-4.5) among term births.

One criticism of this paper has been that the authors included only confounders that were significant at the $p = 0.1$ significance level in a step-wise regression model. This approach is now considered inappropriate because confounding should not be assessed by a significant association with the outcome variable, but by the magnitude of change in the odds ratio if that co-variate is not taken into account (Rothman, 1986). Nevertheless, the variables usually considered important were included (*i.e.*, maternal age, parity, and ethnicity). The authors also included gestational age in the models, even though they were only examining term births. The authors stated that maternal weight gain was not included because it was missing for about 25 percent of respondents. In an analysis of those for whom the information was available, this variable did not appear to confound the relationship with ETS exposure. Therefore, there is little evidence that important confounders were excluded. No association was seen with ETS exposure and prematurity in the regression analyses. The authors' interpretation that their data is indicative of an effect of ETS exposure during pregnancy leading to growth retardation rather than to preterm delivery appears justified.

Ogawa et al. (1991) Ogawa *et al.* (1991) examined ETS exposure in a study of almost 7,000 women who delivered a singleton in 1987 in Aichi Prefecture, Japan. Women were interviewed by medical staff before or soon after delivery. Each woman was asked about her smoking habits and those of her husband before and during pregnancy, as well as about the average length of ETS exposure per day during pregnancy at home, at work, or elsewhere. Overall, about 15 percent of women smoked before pregnancy, but only 6 percent of women continued to smoke during pregnancy. Among all women, 62 percent reported some ETS exposure and 65 percent had husbands who smoked. Among women who had never smoked, there was a 24-gram decrement in mean weight of term births with exposure to ETS for 2 or more hours per day. Adjusting for a number of confounders yielded a weight decrement of 10.8 grams, which was noted as non-significant. The crude and adjusted odds ratio for LBW at term did not indicate any increased risk with ETS exposure (Table 3.3). Interestingly, the adjusted weight reduction associated with active smoking of 10 cigarettes per day was only 56 grams, compared to the 200 grams found in many other studies. The data on husband-only smoking status in association with pregnancy outcome were not presented.

Lazzaroni et al. (1990) Lazzaroni *et al.* (1990) examined data from a multi-center, hospital-based study of about 1,000 pregnant women in Italy. The analysis is based on questionnaires administered to women within 5 days of delivery

of a newborn during 1989. Newborns born before 36 weeks and weighing less than 2,000 grams were excluded, so prematurity and LBW could not be examined. ETS exposure was ascertained by asking the number of hours of exposure at home and work; anyone reporting a minimum of 1 hour per day was considered exposed (about 25 percent of the respondents fell into this category). Nonsmokers with ETS exposure were compared to those without, but both categories could include women that quit smoking during pregnancy. Almost 30 percent of women were considered active smokers during pregnancy. Mean birthweight of infants of women exposed to ETS was reduced 51 grams, which was not statistically significant. Adjusting for a number of important potential confounders by multiple regression indicated a weight decrement of 16.9 grams per hour of ETS exposure ($p = 0.07$), or about 38 grams for any (versus no) exposure among nonsmoking women with term births (Table 3.3). Excluding women only exposed one hour per day yielded a greater decrement in weight of 61 grams (95% CI = -149.3-26.8), indicating that highly exposed women are at greater risk. The authors further noted that the mean birthweight of infants of women heavily exposed to ETS (≥5 hours/day) was less than that of infants of light active smokers. The adjusted overall decrease in infant length was not significant (0.26 cm, 95% CI = -0.56-0.03).

Ahlborg and Bodin (1991) Ahlborg and Bodin (1991) conducted a prospective study of 4,701 Swedish women reporting for prenatal care in 1980-1983. They examined prematurity and LBW at term among nonsmoking women exposed to ETS, which was defined as living with a smoker during pregnancy or spending most of the time at work in rooms where other people were smoking. In an attempt to separate the effects of home and work exposure, the authors further limited the sample to working women. The adjusted odds ratio for term LBW and ETS exposure only in the home was 0.7 (95% CI = 0.21-2.3) and for prematurity was 0.5 (95% CI = 0.23-1.1). These figures are based on very small numbers of affected births in the exposed group ($n = 3$ and 7, respectively).

The manner in which the question to ascertain work exposure was asked would tend to identify a fairly heavily exposed group. The adjusted relative risk for workplace ETS exposure and prematurity was 1.3 (95% CI = 0.7-2.3) and for LBW at term was 1.1 (95% CI = 0.33-3.6; Table 3.3). The women could also be exposed to ETS at home; further limiting the analysis to those with a nonsmoking partner increased the ORs (1.8 for prematurity and 1.2 for term LBW). The authors stratified the association (with any workplace exposure) by whether the work was full-time or part-time, in an attempt to examine a dose-response relationship. The adjusted relative risks among infants of full-time workers were increased somewhat for prematurity (RR = 1.5, 95% CI = 0.87-3.0) and for term LBW (RR = 1.4, 95% CI = 0.33-5.9). The authors also examined mean birth weight. Among these working women, home exposure was associated with a 34-gram decrement in mean birthweight, but workplace exposure was not associated with a birthweight reduction (Table 3.3). As noted earlier, these analyses must have been based on extremely small numbers.

Table 3.3
Studies of Fetal Growth and ETS Exposure of Maternal Nonsmokers from Multiple ETS Sources

Study		Results[2]	
Authors (year) Country (study size[1])	**ETS Level (% Exposed)**	**Difference in Mean Weight**	**IUGR/LBW[3] OR (95% CI)**
Martin & Bracken (1986) U.S.—Connecticut (*n* = 2,473) Prospective interview	≥2 hr/day at home or work (34%)	-24g adjusted (-60-13) -85g (*p* < 0.002) crude	2.2 (1.1-4.5) LBW
Ogawa *et al.* (1991) Japan (*n* = 5,336) Interview around delivery	≥2 hr/day at home, work or elsewhere (35%)	-10.8g (n.s.) -24g (-47 to -2) crude	1.0 (0.7-1.5) LBW
Lazzaroni *et al.* (1990) Italy (*n* = 648; examined births >2,000g, >37wks gestation) Interview postpartum	≥1 hr/day at home or work (25%)	-38g (-106.9-30.7) -17g/hr (-35-1.3)	--
Ahlborg & Bodin (1991) Sweden (*n* = 2,461 employed)	Home exposure only (16%)	-34g (-82-15)	0.7 (0.21-2.3) LBW (based on 3 affected infants)
Interviewed during month 2 or 3 of pregnancy	Most time at work in rooms with smokers (11%)	20g (-37-77)	1.1 (0.33-3.6) LBW 1.4 (0.33-5.9) LBW if worked full-time
Fortier *et al.* (1994)[3]	Home only (13%)		0.98 (0.67-1.44) IUGR
Canada—Quebec (*n* = 4,644 nonsmokers)	Work only (28%)		1.18 (0.90-1.56) IUGR
Interview within few months post partum	Home and Work (8%)		0.94 (0.60-1.49) IUGR

This study offers a lot of data, but there are some difficulties with its analysis of fetal growth. First, the number of pregnancies included in each analysis was unclear. There were 4,701 pregnancies that were not excluded or lost to follow-up, but information was only available about the father's smoking for 4,075 (87 percent) of these. Further reductions were made to examine only nonsmoking women and working women, although the numbers presented in the tables do not appear consistent. In addition, it is not known if mean birthweight was determined in all livebirths or only in term births, as was the case for LBW. Secondly, the proportion of non-smoking women living with a smoker seems low at about 15 percent, par-

Table 3.3 (Continued)

Study		Results[2]	
Authors (year) Country (study size[1])	**ETS Level (% Exposed)**	**Difference in Mean Weight**	**IUGR/LBW[3] OR (95% CI)**
Mainous and Hueston (1994) U.S.—nationwide (*n* = 3,253) Retrospective survey	Categorized as: never (23%) occasional (46%) often (17%) always (13%)	-84g (-150 to -18) for highest exposure, crude No decrement at lower levels	1.6 (0.92-2.7) LBW with high exposure ($p \leq 0.01$ dose-response trend)
Chen and Petitti (1995) U.S. – California (*n* = 111 cases, 124 controls, whites) Retrospective interview	Assessed in 4 locations and as average hours per week Any exposure (54%) ≥30 hours/wk (7%)	--	≥30 hrs/week: 0.5 (0.14-1.7) IUGR Work only: 1.0 (0.39-2.6) IUGR Home only: 0.5 (0.13-1.8) IUGR
Roquer *et al.* (1995) Spain (*n* = 129) Interview at delivery	"Significant" defined as exposed to ≥20 cigarettes/day	-192 (-365 to -19), crude	1.9 (0.57-6.1) 1.10 IUGR 1.11 crude
Rebagliato *et al.* (1995a) Spain (*n* = 710) Interview in 3rd trimester	Assessed hours per week from 4 sources Any exposure (88%) ≥42 hours/week (22%)	Any: -85g, crude Any ≥42 hours/wk: -41g (-144-61) Spouse ≥42hrs/wk: 31g (-103-165)	--

[1] The study size (n) presented is for term births to nonsmokers, not the total study size.
[2] Effect measure adjusted for a number of confounders, unless otherwise indicated as "crude." Abbreviations: LBW - low birth weight; IUGR - intrauterine growth retardation.
[3] The analysis adjusted for LBW in previous births. This may result in substantial underestimation of effect.

ticularly because 37 percent of women overall reported smoking in the first trimester, calling into question the validity of the reporting of paternal smoking habits. With respect to the results, a weight reduction with ETS exposure at home, but not in the workplace seems inconsistent. On the other hand, ETS exposure among full-time workers may be slightly associated with term LBW. When the authors attempted to look at possible confounders to explain this (lifting, stress, etc.), they found little change in the association. The true association may be diluted in this study by the focus on only women highly exposed at work, so that those less exposed may fall into the comparison group. The authors did note an increased risk of prematurity and term LBW with maternal smoking.

Fortier et al. (1994) A large study from Quebec, Canada also ascertained exposure at home and work (Fortier *et al.*, 1994). Women who had singleton livebirths in 1989 were interviewed by phone, on average, 6 weeks after delivery.

Questions about ETS exposure included whether the subject resided with smokers and how much they smoked in her presence, as well as hours and intensity of exposure at work. Of the over 7,000 respondents, 4,644 nonsmokers were available for analysis, of which nearly half (49 percent) were exposed to ETS at home and/or work. The crude OR for any ETS exposure and IUGR was 1.3, but decreased to 1.1 (95% CI = 0.85-1.4) with adjustment for maternal weight, parity, previous LBW, and caffeine intake (Table 3.3). ETS exposure at home only was not associated with IUGR (adjusted OR = 0.98), nor was there a dose-response trend. The risk of IUGR associated with workplace-only exposure was slightly greater (adjusted OR = 1.2) and showed evidence of a slight dose-response trend with heavier exposure, even when controlled for potential confounding by job characteristics. However, women exposed both at home and at work had IUGR rates more similar to the home-only exposed women (adjusted OR = 0.94). Adjustment for previous LBW may be over-controlling, as such LBW may have been associated with ETS exposure as well. ETS exposure at any location was not associated with pre-term birth. The authors noted that the odds ratios of IUGR in the nonsmokers most heavily exposed to ETS at work (1.30-1.36) were similar to those found in light smokers (1-5 cigarettes/day) in their study population.

Mainous and Hueston (1994) Mainous and Hueston (1994) analyzed data from the 1988 National Health Interview Survey (NHIS), a household interview conducted on a nationwide sample, examining pregnancies occurring in the past 6 years (mean was 2 years). ETS exposure was determined by asking respondents to categorize their contact with smokers (friends, coworkers or family members) as "occasional, often, always, or never" during pregnancy. There was little difference in the frequency of LBW infants among ETS exposed versus unexposed women. However, when examined by categories of increasing exposure, there was a trend towards increasing rates of LBW ($p < 0.01$). Controlling for race, parity, income, and maternal age, the adjusted odds ratio was about 1.6 for the highest exposure category (Table 3.3) and was greater among non-whites (OR = 2.3, 95% CI = 1.1-5.0). Comparing mean birthweight, women in the highest exposure category had infants that weighed on average 84 grams less than infants in the very low exposure category (Table 3.3). No dose-response trend in mean birthweight was noted for lower levels, which the authors interpreted as evidence for a threshold effect. The weight decrements were unadjusted, and information was not included about other potential confounders of the relationship with LBW. Further, this study may be subject to some recall error, as pregnancies could have occurred up to six years earlier and the measure of outcome (as well as exposure) was obtained from the women themselves. The qualitative measure of exposure used may be less subject to recall error than a more quantitative measure would have been. The main advantage of the study is its large, population-based sample.

Chen and Pettiti (1995) Chen and Pettiti conducted a case-control study of IUGR among singleton, term infants born in 1991 in Contra Costa County, California. Controls were non-growth-retarded, non-malformed infants

identified from birth certificates. ETS exposure was ascertained by first asking about location (work, home, car, other) and then the total number of hours per week exposed to ETS for each trimester. The small sample of nonsmokers is a major limitation of the study, as well as the fairly low completion rate (50-55 percent). By quintiles of average hours of exposure over all trimesters, there was no indication of an increased risk of term IUGR with greater exposure. Most women reported exposure in "other" places, but none of the locations considered showed evidence of increased risk of term IUGR. Adjusting for a variety of variables showed a decreased risk with exposure but very wide confidence intervals with home exposure or home and elsewhere (ORs about 0.5); work and car exposure had odds ratios around one. In addition to low power and a fairly high refusal rate, this study may be hampered by recall error, although subjects were interviewed fairly soon after delivery (mean was 8 months).

Roquer et al. (1995) Roquer *et al.* (1995) conducted a small study of Spanish women presenting for labor and interviewed them after delivery. ETS exposure was defined as "significant" if the woman was exposed to the smoke of 20 or more cigarettes per day at work or home; that is, exposure to one smoker who smoked a pack or more per day or two smokers who each smoked a half-pack per day. A major problem with the design is that the interviewer measured the infant within four hours after birth, so outcome determination was not blinded with respect to exposure. The mean birthweight of infants whose mothers were exposed was 192 grams less than that of infants whose mothers were unexposed, and was comparable to the weight decrement in infants of women who smoked 1 to 9 cigarettes per day. Infants of mothers who smoked heavily had weight decrements of over 450 grams. No confounders were considered, but parity and employment status were similar in ETS-exposed and unexposed women. The rate of IUGR was about doubled with ETS exposure, again similar to that seen in infants of light smokers, but was not statistically significant (Table 3.3). ETS exposure was associated with a reduction of one centimeter in length (calculated 95% CI = -1.8 to -0.2). This study is limited by its small size and lack of adjustment for confounders, as well as by the possible measurement bias (although weight is subject to less measurement error than length).

Rebagliato et al. (1995a) In the best of the new studies, Rebagliato *et al.* (1995a) conducted a prospective cohort study (also in Spain) of nonsmoking pregnant women. Subjects were interviewed in their third trimester of pregnancy, and a saliva sample was collected for cotinine analysis. The investigators asked extensive questions about exposure from four sources and on different days of the week to calculate an average weekly exposure during pregnancy. Of the 710 nonsmoking women, 88 percent reported some exposure; their infants were on average 85 grams lighter than those of unexposed nonsmokers. However, no dose-response trend was evident and results were not consistent by source, with exposure at home not resulting in a birthweight decrement. In a multiple regression model which adjusted for a number of covariates including gestational age (but not alcohol use), the highest exposure category was associated with a 41-gram decrement in

birthweight (Table 3.3), while other categories had decrements ranging from 26 to 77 grams. Because of the small numbers of subjects in these categories, none of the weight decrements were statistically significant. More women were exposed at home, and for longer periods of time, so the inconsistent results are difficult to explain. However, exposures at work may be more intense, with more smokers present.

3.2.2.4 Fetal Growth and Biomarkers of ETS

There has been an effort in the past 10-15 years to validate tobacco smoke exposures using biomarkers, and a few studies have examined biomarkers in relation to pregnancy outcome in that time, with two additional studies published in 1995 (Table 3.4). Cotinine is the preferred biomarker because of its specificity to tobacco smoke exposure and longer half-life (20-30 hours in plasma) than nicotine (see chapter on *Exposure Measurements and Prevalence*). Nevertheless, cotinine only reflects relatively recent exposures, and there is much inter-individual variation in its metabolism. Thiocyanate, a detoxification product of cyanide, has a longer half-life than cotinine (3-14 days) but is not as specific to tobacco smoke.

Hauth et al. (1984)

Hauth *et al.* (1984) looked at thiocyanate concentrations as a biomarker of ETS exposure in 163 women who had had a term pregnancy, by drawing maternal serum at the time of admission to labor and delivery. Thiocyanate (SCN) levels were compared among three groups, defined as smokers (10-40 cigarettes/day), passive smokers (live or work with a smoker), and nonsmokers. Umbilical cord blood was obtained immediately after birth. Maternal and cord blood SCN levels were significantly greater in smokers than in the other two groups, but the levels in passive smokers were only slightly greater than those in nonsmokers. There was a significant inverse relationship between umbilical cord SCN level and birthweight in infants born to smokers (published $r = 0.74$, $p < 0.001$), but not in infants of passive or nonsmokers. The authors reported that infants of passive smokers had similar birthweights to those of nonsmokers, but the data were not presented. No confounders were assessed in this analysis. Another problem is that blood obtained at the time of labor may not accurately reflect exposure earlier in pregnancy, particularly if a woman exposed to ETS at work has left her job near the end of pregnancy.

Haddow et al. (1988)

In the largest biomarker study to date, Haddow *et al.* (1988) analyzed blood sampled during the second trimester of 1,231 pregnancies of nonsmoking white women in Maine. The authors defined ETS exposure as a cotinine level between 1.1 and 9.9 ng/ml, with lower levels split into two groups: those 0.5-1.0 ng/ml and those less than 0.5 ng/ml, which was the lower limit of detection. Women who had levels of 10 ng/ml or greater ($n = 29$) were excluded. The authors found a crude decrement of weight between the highest and lowest groups of 107 grams, or 108 grams after adjustment for a number of important confounders ($p < 0.001$). Compared to the group with cotinine levels of 0.5-1.0 ng/ml, the ETS-exposed group had an adjusted weight decrement of 104 grams (95% CI = -173 to -35; Table 3.4). The authors also examined cotinine level as a continuous vari-

able and found a weight decrement of 28 grams per ng/ml of cotinine (p = 0.04). The mean level of cotinine was 2.14 ng/ml in the ETS-exposed group, which would predict about a 60-gram deficit overall. This, combined with data on active smoking, led the authors to suggest that the relationship of cotinine to birthweight may not be linear. However, the discrepancy may also be due to inter-individual variations in cotinine metabolism. The authors also mentioned that LBW was increased 29 percent in the ETS-exposed group, but no further data were provided.

Overall, this appears to be a well-conducted study. While the authors reported that in their previous work cotinine levels correlated well with self-reported exposure, data on self-reported ETS exposures unfortunately were not available for comparison to the cotinine levels. Because data were obtained from birth certificates, one variable not included in the analysis was alcohol consumption. However, nonsmokers are unlikely to be heavy drinkers, or at least not heavy enough to explain the observed results. Another variable not mentioned was gestational age—a strong predictor of weight—so it is not possible to determine whether the weight decrement seen is due to prematurity or growth retardation.

Ueda et al. (1989) A study from Japan (Ueda *et al.*, 1989) reported finding an association of ETS exposure (as well as active smoking) with lowered birthweight, based on an analysis of cotinine levels. Women attending prenatal clinics (n = 257) were interviewed, and samples of blood and urine were obtained. The authors classified women into seven categories of exposure based on their self-reported active smoking and exposure to ETS at home and elsewhere. Of the nonsmokers, most (84 percent) reported some ETS exposure. Cotinine levels in maternal urine appeared to differentiate those exposed to ETS from those not exposed. Mean cotinine levels were lowest in women who reported no exposure (3.98 ± 3.2 ng/ml), intermediate in women who reported exposure only at home (10.9 ± 39 ng/ml) or only outside the home (11.1 ± 20 ng/ml), and highest among those exposed in both places (55.5 ± 135 ng/ml). For comparison, the mean in active smokers was 228.4 ± 214.6 ng/ml. Cotinine levels in maternal serum were not well correlated with self-reported exposure.

Despite the relatively high urinary cotinine levels in exposed nonsmokers, relative birthweight did not appear to vary by self-reported ETS exposure category. Relative birthweight (RBW) was calculated by comparing the true birthweight to a national standard, by gestational age. The investigators plotted cotinine levels by RBW and found a "correlation/relation" that was significant by the chi-square test ($p < 0.01$). However, this is an unconventional statistical method for examining a correlation, and neither the magnitude of the correlation nor the slope of a regression line was provided. The authors compared the RBW in two groups of women defined by whether their urinary cotinine levels were above or below 9 ng/ml, which represented the mean ±1.5 standard deviations of the unexposed group's level. The RBW of infants of women with higher cotinine levels (n = 46) was lower (96.2 ± 12.9 percent) than that of infants of women with

Table 3.4
Studies of Fetal Growth and ETS Exposure Determined by Biomarkers

	Study		Results	
Authors (year) Location	**Design (size)**	**Biomarker Levels**	**Weight Difference**	**Low Birth Weight**
Hauth *et al.* (1984) U.S.—Texas	Maternal serum at labor Cord blood at delivery (163; 134 nonsmokers)	Mean in ETS = 26 ±2.5 µmol/L SCN vs. 23 ±1.5 in nonsmokers' cord blood (ns)	Correlation of wt. and SCN = -0.74 in smokers ($p < 0.001$) vs. $r = 0.02$ in ETS exposed, $r = 0.15$ in nonsmokers	--
Haddow *et al.* (1988) U.S.—Maine	Serum drawn early in 2nd trimester (1,231 non-smokers)	1-10 ng/ml cotinine vs. <0.5 in nonsmokers	-104 g (adj.) (-173 to -35) -28 g/ng/ml cotinine (CI = -55 to -2,)	"rate +29%" (*e.g.*, OR : 1.29) no statistics or numbers provided
Mathai *et al.* (1990) England	Urine at 16 weeks (285; 184 non-smokers)	Mean in ETS = 0.85 ±2.8 vs. 0.29 ±1.4 µg cotinine/mg creatinine in non-smokers	-25 g/µg cotinine/mg creatinine ($p < 0.001$) (includes smokers)	--
Eskenazi *et al.* (1995) U.S.—California	Serum in 2nd trimester, stored for 25 years (3,578; 2,292 non-smokers)	2-10 ng/ml cotinine versus <2 ng/ml continuous cotinine level	-45g (adj.) (-126, 36) inclding smokers: 1g per ng/ml cotinine (adj.) (-1.14 to -0.79)	1.35 (0.60, 3.0) crude
Rebagliato *et al.* (1995a) Spain	Saliva in 3rd trimester (n = 710 non-smokers)	≤0.5 = unexposed Quintiles of cotinine (Mean in ETS exposed = 1.2 ng/ml)	Any: -35g, crude. Highest quintile (>1.7ng/ml): -87g, (adj.) (-174 to -1)	--

Abbreviations: SCN—Thiocyanate; CI—Confidence Interval; OR—Odds Ratio; r—Correlation Coefficient; ns—not statistically significant

lower cotinine levels (n = 127, 102.4 ± 10.1 percent; $p < 0.001$). However, it is not clear whether active smokers were excluded. Although active smokers represent only a small proportion (6.6 percent) of the total group, they may account for a fairly large proportion of those with elevated cotinine levels. The results of this study are difficult to evaluate due to insufficient information and unusual methods. The lack of consistency between cotinine levels in maternal urine versus serum is difficult to explain.

Mathai et al. (1990) In one of the studies of Mathai *et al.* (1990) previously mentioned, the investigators obtained maternal urine to measure cotinine levels at 16 and 32 weeks of pregnancy, and at delivery. Data from 285 women were included, of which about 47 percent were nonsmokers, 19 percent were nonsmokers who lived with a smoker, and 34 percent were active smokers at study entry. Cotinine levels increased across the exposure groups, as well as slightly with increasing gestational age, although whether these differences were statistically significant was not specified. Infant birthweight was regressed against a number of co-covariates, with exposure in one model included as both the number of cigarettes smoked actively and exposed to passively at 16 weeks, as well as a separate model with cotinine levels replacing self-reported exposure. Alcohol was not included as one of the variables. There was a 25-gram decrease in birthweight with every µg cotinine/mg creatinine (creatinine is used as a measure of the concentration of the urine). The mean cotinine level of passive smokers was 0.85 µg/mg creatinine; hence only a very small weight decrement would be predicted, rather than the 66-gram decrement observed. This measure also underestimated the decrement seen with active smoking, again indicating a non-linear effect. Cotinine levels explained slightly more of the variation in birthweight than did self-reported tobacco exposure. This study would have been more valuable for assessing an association of ETS exposure (as measured by cotinine) and birthweight if smokers were excluded, particularly if there is a non-linear relationship. The fact that cotinine was detected in the urine of some of the nonsmokers who did not report living with a smoker (mean = 0.29 µg/mg creatinine) indicates that some of them are probably exposed to ETS. This confirms the problem inherent in studies that base ETS exposure status only on reported household exposure. If this misclassification of exposure is nondifferential, it tends to bias effect estimates toward the null.

Eskenazi et al. (1995) Eskenazi *et al.* (1995) used data from the Child Health and Development Studies in California (as did Yerulshalmy, 1971) to look at birthweight in relation to cotinine measured in stored serum samples. Interviews were conducted and sera were collected around the 27-28th week of pregnancies that occurred between 1964 and 1967. The infants of women who had never smoked during pregnancy experienced an average weight decrement of 45 grams (Table 3.4). This figure was similar both unadjusted and in a multiple-regression model that included women who were active smokers, as well as a number of co-variates including gestational age. The authors reported that alcohol and caffeine consumption were considered, but did not improve the model. The crude mean birthweight

of ETS-exposed infants was similar to that of infants of light smokers, but there was a 30-gram difference after adjustment. The highest cotinine level (>165 ng/ml, e.g. active smoking) was associated with a 230-gram weight decrement. Examining cotinine as a continuous variable (including smokers), there was a 1-gram weight decrement for each nanogram per milliliter increase in cotinine. This is based on a linear model, which may not be appropriate. The authors also found a slight increase in LBW associated with ETS exposure (Table 3.4), but found no effect on gestational age or prematurity (unadjusted).

The definition of ETS exposure in this population may be problematic, as the reported exposure rate of only 5 percent is so low, especially for the 1960's. Of those considered unexposed based on cotinine level, 50 percent reported having a spouse who smoked, so the reference group may have included exposed women who were not identified by the relatively high detection limit (2 ng/ml). Of reported nonsmokers with detectable cotinine levels, one-third had levels greater than 10, and were excluded. These may in fact have been nonsmokers who were more highly exposed, as there would have been fewer reasons to misreport smoking status in that time period (as the authors themselves suggest). Use of current cotinine levels to define ETS exposure (versus active smoking) may not be appropriate for these older samples and an assay that was apparently less sensitive. Another problem with exposure assessment in this study may have been the age (25 years old) of the samples.

Rebagliato et al. (1995a) As noted in Section 3.2.2.2, Rebagliato *et al.* (1995a) studied ETS exposure in 710 nonsmoking women using a questionnaire and sampling saliva for cotinine. The investigators examined birthweight by quintiles of cotinine levels less than 14 ng/ml, with subjects having cotinine levels of 0 to 0.5 ng/ml serving as the reference group. In the highest quintile (>1.7 ng/ml), there was a crude weight decrement of 98 grams, which was reduced slightly to 87 grams after adjustment for co-variates (Table 3.4). There was little evidence for a dose-response trend as subjects in the fourth quintile had a slight weight increment, but the highest category examined does not represent a particularly high ETS exposure level. For comparison to Haddow *et al.* (1988), the weight decrement associated with any cotinine level greater than 0.5 ng/ml was 35 grams. The adjusted weight decrement found with high cotinine level was greater than that found with high self-reported exposure. However, in a separate analysis of exposure measures (Rebagliato *et al.*, 1995b), the authors reported that duration of recent exposure to each source of ETS (as self-reported) and the summary measure at all locations were significantly correlated with cotinine levels (Spearman's r = 0.52 for all locations). The apparent inconsistency may be due to differences in the way women report their own exposure, so that some misclassification results.

3.2.3 Animal Studies of Fetal Growth and Tobacco Smoke Exposure

A number of studies of the effects of tobacco smoke on intrauterine growth in rodents have been reported in the literature. The majority of available studies attempted to simulate active smoking by using mainstream smoke (MS),

and some delivered the smoke in bursts or "puffs." Of 10 such studies reviewed (see Table 3.7, page 118), five reported significant group differences in intrauterine growth retardation ranging from 4 to 31 percent relative to controls. In two other studies, pup weights were lower (6-16 percent) in the groups exposed to tobacco smoke, but group differences were not significant. Pup weights were determined at the end of gestation after removal of pups by hysterotomy or after spontaneous birth. The phrase "fetal weight at term" rather than "birth weight" is used to describe the results of the animal studies. Premature delivery is rare in laboratory rodents, so that weight for gestational age is not an issue.

In addition to these studies of mainstream smoke, three recent studies in rats (see Table 3.7, page 118) which used exposures characterized as "sidestream smoke" (SS) are described below.

Leichter (1989) Leichter (1989) used a 2-hour daily exposure throughout pregnancy and found a statistically significant 9 percent reduction in mean fetal weight at term relative to controls. Fetal weights in the SS-exposed group were also significantly smaller than in a pair-fed group which was included to control for effects of sidestream smoke on food intake. The smoke was not characterized chemically in this study.

Witschi et al. (1994) Witschi *et al.* (1994) used a 6-hour exposure on days 3-10 of gestation and found identical fetal weights at term in the SS-exposed group and in controls. However, litter size was significantly lower in the sidestream smoke group. Reduced litter size can sometimes be viewed as offsetting an effect on intrauterine growth, due to a greater availability of nutrients for each fetus when there are fewer fetuses per litter (Romero *et al.*, 1992). Also, exposures in this study did not extend into the fetal period of gestation when weight gain is most rapid.

Rajini et al. (1994) Rajini *et al.* (1994), from the same research group as Witschi *et al.* (1994), used exposures on days 3, 6-10, and 13-17 of gestation and found a statistically significant 7 percent reduction in mean fetal weight at term in the SS-exposed group relative to controls. In this study there was no sidestream smoke effect on litter size; further, the exposure period extended into the fetal period of gestation. There were no group differences in maternal weight gain during pregnancy in this study.

3.2.4 Discussion and Conclusions

More than 25 epidemiologic studies of the relationship between fetal growth and ETS exposure have been reviewed. All but one of the studies that examined mean birthweight have shown a decrement with ETS exposure, although some of the weight differences were small (Figure 3.1). Only a few studies examined fetal length, and though results were in the direction of a small decrement with ETS exposure (0.25-1.1 cm), two were unadjusted, so conclusions cannot be reached. Fifteen studies have examined low birthweight or "small for gestational age" as shown in Figure 3.2. The figure indicates that the majority of studies which have examined these outcomes have shown a slightly elevated

risk with ETS exposure. The area of overlap of the confidence intervals is consistent with up to a 1.4- or 1.5-fold increased risk of small fetal size; however, it is also consistent with there being no association. Only a few of the findings were statistically significant on their own. Taken together, however, they support a slight increase in LBW or IUGR in association with ETS exposure. There was little evidence found for an association with preterm birth.

The biomarker studies, in particular Haddow *et al.* (1988), provide the most convincing evidence of an effect on growth (or weight). The Haddow *et al.* study is based on measurement of biomarkers, addressing exposure assessment issues; it has adequate control of confounders, and it has a large study population. As such, the findings of a 100-gram weight deficit must be considered strong evidence, but in need of replication. The biomarker data of Ueda *et al.* (1989) and Mathai *et al.* (1990) add some supportive evidence, but are not comparable to the Haddow study because analyses were not limited to nonsmokers. The weight decrement found by Haddow *et al.* is about half the magnitude of that seen with active smoking and is thus greater than might be expected based on cotinine levels measured in those exposed to ETS compared to active smokers. Nevertheless, this magnitude of effect relative to that of active smoking was reported in a number of other studies based on self-reported ETS exposure (Borlee *et al.*, 1978; Rubin *et al.*, 1986; Schwartz-Bickenbach *et al.*, 1987; Campbell *et al.*, 1988; Martin and Bracken, 1986; Lazzaroni *et al.*, 1990). Furthermore, the Haddow *et al.* (1988) data suggest that the association with birthweight is not linear with "dose" as measured by cotinine level. The two newer biomarker studies confirm Haddow *et al.*'s results but found lower weight differences. In Eskenazi *et al.*'s (1995) study, only a small proportion of the study subjects were found to be exposed, as defined by cotinine level, and this lack of exposure did not correspond with self-reporting; these results raise the possibility of misclassification and the dilution of an effect. Rebagliato *et al.* (1995), like Haddow *et al.* (1988), found a statistically significant effect for any ETS exposure and a similar magnitude (88-105g) of birthweight decrements with higher exposures (defined by cotinine level).

The second strongest evidence comes from studies that attempted to ascertain total ETS exposure from multiple sources, with adequate control of confounding. The four such studies published before 1994 (Table 3.3) showed small decrements in mean birthweight after adjustment (20-40 grams). Three (and perhaps four) of these studies examined term births only; weight differences in this group would be less variable than in all births and are thus not comparable to the majority of studies. In addition, the studies were not comparable in their definition of exposure, and some of the risk measures may be diluted by inclusion of less-exposed pregnancies in the reference groups, particularly in Ogawa *et al.* (1991), and Ahlborg and Bodin (1991). The studies published in 1994 and 1995 (Table 3.3) found more variable weight differences, but some of the measures presented were unadjusted or were in the highest exposure subgroup only, and thus are not entirely comparable to the earlier studies' results. Two of the

studies indicated that more highly exposed women may be more greatly affected (Lazzaroni *et al.*, 1990; Mainous and Hueston, 1994). However, Rebagliato *et al.* (1995) did not find a consistent dose-response trend with self-reported exposure; this was due in part to a finding of no effect with home exposure, only with exposure outside the home. Based on these studies, an average weight decrement of 25-50 grams appears plausible, and is closer to what might be expected based on relative cotinine levels in those exposed to ETS versus active smokers.

Among the studies which ascertained ETS exposure from multiple sources, only one found a strong association with growth retardation (Martin and Bracken, 1986). The Martin and Bracken study has been criticized (Hood, 1990) because of its low rate (2 percent) of LBW. However, the rate of LBW at term is expected to be much less than overall rates of LBW: Ogawa *et al.* (1991) found a rate of 3 percent and Ahlborg and Bodin (1991) observed a rate of only 1.5 percent. Two of the newer studies also found similarly elevated risks, although one was unadjusted and based on small numbers (Roquer *et al.*, 1995), and the other found an increased risk only with high exposure (Mainous and Hueston, 1994,Table 3.3). Two studies (Ahborg and Bodin, 1991; Fortier *et al.*, 1994) found greater associations with workplace than with home exposures; associations with work exposure increased with increasing number of hours worked. The case-control study by Chen and Pettiti (1995) also found some differences between work and home exposure, with no effect at work but a slightly protective effect at home. However, in each of these three studies which examined home and work exposure separately, the confidence intervals were wide and overlapped, so the effects of exposure at home and at work may not be truly different. Some studies have found that subjects were more likely to be exposed at work than at home (Fortier *et al.*, 1994) or that they were exposed longer at work than at home (Lazzaroni *et al.* 1990); however, this may vary by culture, as Ogawa *et al.*(1991) found more women were exposed at home. Workplace exposure may also differ from that at home due to the number of smokers contributing to ETS and to the influence of environmental conditions (*e.g.*, air exchange rates, temperature).

Overall, the weight differences observed in the studies based on exposure to spousal or household smokers vary greatly, from a decrement of 3 to over 200 grams (Table 3.1 and Figure 3.1). The studies are difficult to compare because of their many differences, including: when they were conducted (over a 25-year timespan); the location and nationality of study populations; the range of sample size and sample selection; the extent to which confounders were controlled; and the analytic methods used. Furthermore, the crude assessment of exposure in most studies allows for a great variation in the actual "amount" of exposure being compared. The two studies with the highest birthweight decrements provided only crude estimates, unadjusted for potential confounders, and neither included population-based samples.

Of these studies of mean birthweight and exposure to household smokers, the highest quality studies—based on study design, sample size, and control of confounders (Brooke *et al.*, 1989; Chen *et al.*, 1989; Rubin *et al.*, 1986; Campbell *et al.*, 1988; Mathai *et al.*, 1992; Zhang and Ratcliffe, 1993)—found weight decrements ranging from 15 to 100 grams. Martinez *et al.* (1994), the only one of the new studies in this category, found a statistically significant adjusted weight difference in the same range. Two of these studies (Campbell *et al.*, 1988; Rubin *et al.*, 1986) did not exclude active maternal smokers, but rather adjusted for them. Four of these studies reported examining the data for a dose-response relationship; such a relationship was observed by Rubin *et al.* (1986) and Martinez *et al.* (1994), while the two studies from Shanghai reported no or an inconsistent trend (Chen *et al.* 1989; Zhang and Ratcliffe, 1993). In addition to these studies, the Saito (1991) study, which was the largest but did not control for confounders, also found a mean weight decrement in the same range and demonstrated a dose-response relationship. These studies provide further evidence for a decrement in birthweight associated with ETS exposure.

The studies based on paternal or household ETS exposure tended to show slight (or no) increases in the risk of LBW or IUGR. The best, and the most recent studies (conducted in the past decade, see Table 3.2), were all from Asia and reported ORs ranging from 1.1 to 1.7. Two of these showed no indication of a dose-response trend (Chen *et al.*, 1989; Zhang and Ratcliff, 1993), whereas two others showed some evidence of a trend (Nakamura *et al.*, 1988; Saito, 1991).

In general, the results of animal studies support an effect of sidestream smoke exposure during pregnancy on intrauterine growth. In particular, the recent study by Rajini *et al.* (1994) demonstrated an effect on intrauterine growth in the absence of an effect on maternal weight gain in a situation using well-characterized sidestream smoke exposures. The extent of growth retardation in the animals studied was greater than that reported in infants of ETS-exposed women, but the exposure levels were also higher (*e.g.*, concentrations of total suspended particulates were about 10 times higher than the average exposure caused by indoor cigarette smoking).

Although it is difficult to separate out the possibility of uncontrolled confounding or misclassification in an individual study with a relative risk of 1.2-1.4, the consistency of the association found in these studies from different countries strengthens the evidence for causality, as do the corresponding effects seen in animal studies. Furthermore, there is some evidence that higher exposures may have effects approaching those expected in light smokers. Additional studies might help clarify any differences between chronic, low-level exposure and shorter, higher exposures.

Lending further support in terms of a biological basis for these findings from epidemiologic and animal studies are the well-established relationships, first, between active smoking and fetal growth retardation in

humans, and second, between constituents of tobacco smoke (e.g., nicotine, carbon monoxide, toluene, cadmium) and fetal growth retardation in animals. There appears to be sufficient evidence that ETS is associated with a decrement in birthweight (and fetal growth retardation), based on all sources of data with primary emphasis on the high quality epidemiologic studies. The effect is of a small magnitude (perhaps 25-50 grams) that may not be clinically significant for an individual infant at low risk. Yet, if the entire birthweight distribution is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants and with perinatal mortality. A meta-analysis of studies conducted up to mid-1994 was reported (Windham *et al.*, 1995a), which pooled results of the studies into a summary estimate based on a weighted average (with the weight equal to the square of the inverse of the standard error of the estimate of each study, as in Greenland, 1987). Studies which did not provide an error measurement (or confidence interval) could not be included in the summary. If study results appeared heterogeneous (p-value for homogeneity chi-square >0.10), an influence analysis was conducted by removing studies individually to see which had the greatest effect on the results. The weighted average for difference in mean birthweight was -28 grams (95% CI = -40 to -16) among studies limited to nonsmoking women (*e.g.,* with and without ETS exposure, n = 12). The summary odds ratio for low birthweight at term or IUGR studies was 1.2 (95% CI = 1.1-1.3, n = 8) and for LBW was 1.4 (95% CI = 1.1-1.8, n = 4). The latter excludes the Underwood *et al.* (1967) study, which appeared to be an outlier but had a large influence due to its high sample size, and had numerous methodological limitations as described earlier.

3.2.4.1 Risk Attributable to ETS Exposure

Low birthweight affects 6-7 percent of the births in the United States (U.S. DHHS, 1996), and thus, of the 551,226 births in California in 1995 (California Department of Finance, 1996) approximately 36,000 may have been of low birthweight. Both active smoking and ETS exposure are risk factors for low birthweight, and estimates of attributable cases due to ETS exposure are more accurate when active smoking prevalence is taken into account. From the equations used by U.S. EPA (1992) for estimating attributable lung cancer risks, attributable risk (a) for low birthweight due to ETS exposure can be estimated by using the following formula:

$$a = (1 - P_S)P_E(R_E - 1) \;/\; [(1 - P_S)P_E(R_E - 1) + P_S(R_S(P_E R_E + 1 - P_E)) + 1]$$

where P_S is the prevalence of smokers in the population, P_E the prevalence of ETS-exposed nonsmokers, R_S the relative risk of low birthweight in smokers relative to nonsmokers, and R_E the relative risk of low birthweight in ETS-exposed nonsmokers relative to non-ETS-exposed nonsmokers. The above expression assumes that there is no tobacco-related impact on birthweight among those characterized as nonexposed. In the event that this is incorrect, the expression above is biased in the direction of underestimating ETS-related attributable risk.

The prevalence of exposure can be estimated from the results of the 1993 California Tobacco Survey reported by Pierce *et al.* (1994, 1996, personal communication): 9.4 percent of women who are pregnant are active smokers; 21.2 percent of pregnant nonsmokers are exposed to ETS, based on the proportion of 18-44 year-old nonsmoking women exposed at home or work. This estimate may understate the prevalence of ETS exposure of pregnant women because those exposed in other indoor locations have not been included. To estimate the relative risk of low birthweight due to active smoking and ETS exposure, we use ORs (which we take to be approximations of the relative risk) of 2 and 1.2 to 1.4, respectively. Applying these values to the equation given above, the proportion of all low birthweight newborns in California that may be associated with ETS exposure is estimated to be 3.3 to 6.2 percent, which corresponds to 1,200 to 2,200 newborns in California in 1995 with low birthweight associated with ETS exposure.

3.3 SPONTANEOUS ABORTION AND PERINATAL MORTALITY

In this section, studies evaluating the effect of ETS on spontaneous abortion and perinatal mortality are described. For the purposes of this discussion, perinatal mortality is defined as death in the period from 20 weeks gestation to 28 days post-delivery. Perinatal mortality includes stillbirths (fetal death from 20 weeks to term) and neonatal deaths (death between birth and 28 days of life). Relatively few studies have assessed the effect of ETS exposure on perinatal mortality. Spontaneous abortion or miscarriage is currently defined as pregnancy loss in the first 20 weeks of gestation, but was defined as loss up to 28 weeks in older reports. Some authors have combined spontaneous abortions with stillbirths to look at prenatal and perinatal deaths.

Perinatal death encompasses a wide variety of causes or diagnoses (*e.g.*, *abruptio placenta*, premature rupture of membranes (PROM), severe malformation) that may result from different etiologic factors. Identification of confounders is particularly complex. As prematurity and LBW are risk factors for neonatal death, birthweight and gestational age should be considered when studying perinatal mortality. When examining spontaneous abortion, maternal age, prior history of pregnancy loss, and socioeconomic status indicators at a minimum should be considered as potential confounders.

3.3.1 Overview of Human Studies of Spontaneous Abortion and Perinatal Mortality and Maternal Smoking During Pregnancy

The literature on the association of active maternal smoking during pregnancy and fetal loss is not as definitive as it is for birthweight. Many studies have found an association with perinatal mortality (Stillman *et al.*, 1986; Kleinman *et al.*, 1988). The 1980 report of the Surgeon General states that the risk of mortality "increases directly with increasing levels of smoking during pregnancy," and that the effect is greater in women with other risk factors (U.S. DHHS, 1980). Furthermore, the increased risk appears to be related to problems of pregnancy and prematurity rather than to abnormalities of the neonate. Some of the perinatal mortality has been found to have resulted from *pla-*

centa praevia, in which the placenta separates from the uterine wall. This is consistent with the changes associated with exposure to carbon monoxide and nicotine described earlier in Section 3.2.1.

Active maternal smoking is often cited as a risk factor for spontaneous abortion in descriptive overviews (Stillman *et al.*, 1986; Pirani, 1978; Kline and Stein, 1984), but the data are not consistent. Studies which reported an association found odds or rate ratios of 1.5-2.0, particularly with heavier smoking (Kline *et al.*, 1977). Not all of these studies adjusted for confounders such as alcohol consumption. Several studies, including some discussed below (Windham *et al.*, 1992; Hemminki *et al.*, 1983), did not find substantial associations. Inconsistencies may be due to the fact that the study populations were from different backgrounds in different time periods, in which the pattern of active smoking during pregnancy may have varied. As smoking during pregnancy becomes less prevalent, fewer women are exposed and an association becomes more difficult to detect. If there is an association of perinatal mortality with active smoking, it appears more likely to occur with later fetal losses (U.S. DHHS, 1980; Kallen, 1988).

3.3.2 Human Studies of Spontaneous Abortion and Perinatal Mortality and ETS Exposure

Eight studies were reviewed. Two recent studies suggest a link between ETS and spontaneous abortion, but a third does not. Several earlier studies also suggested an increased risk of neonatal death associated with paternal smoking. Studies of stillbirth did not suggest increased risk.

Comstock and Lundin (1967) In an early study (Table 3.5), Comstock and Lundin (1967) examined stillbirth and neonatal death rates in relation to parental smoking. The sample consisted of 376 live births in Maryland between 1953 and 1963, and 476 stillbirths or neonatal deaths in the same time period. Smoking status was determined from a special population census conducted in the study area and could not be specifically related to the pregnancy under study. The authors reported "no significant differences" in the rates of stillbirth by paternal smoking status, but no data were shown. Neonatal death rates, adjusted for infant gender and paternal education, were elevated in infants with nonsmoking mothers and smoking fathers (17.2 per 1,000) compared to infants with no parental smokers (11.9 per 1,000). Neonatal death rates were highest when both parents smoked (26.5 per 1,000). There was no statistical testing of the differences in the adjusted rates. Because the adjusted rates were very similar to the crude rates, we calculated a crude odds ratio and 95 percent confidence interval for the association of neonatal death and paternal smoking (OR = 1.45, 95% CI = 0.9-2.4). The authors noted that neonatal mortality rates were also increased among a small group of infants whose mothers did not start smoking until after pregnancy. This could reflect ETS exposure of the infant. Only a few confounding factors were addressed in this study, and the possibility that birthweight could be the mediating factor in neonatal mortality was not considered.

Tokuhata (1968) Tokuhata (1968) used data from a case-control study of reproductive cancers in Tennessee to examine infertility and fetal losses in relation to the smoking experience of couples. The results showed that husbands' smoking status was unrelated to fetal loss (RR = 1.1). This study is limited in several ways. First, information about miscarriage and stillbirth was obtained from a next of kin long after the events in question had occurred. This delay makes the ascertainment of miscarriage particularly unreliable. Second, the entire reproductive period was included: some subjects had had multiple pregnancies, and the observed events were not independent. Third, lifetime smoking history was used, which may not pertain to specific pregnancies. Information on amount smoked or potential confounders was not addressed.

Yerushalmy (1971) Yerushalmy's (1971) analysis of data from the comprehensive Child Health and Development Studies conducted in 1960-1967 included an examination of neonatal mortality rates among low birthweight infants only, a select group. He found higher mortality rates among LBW births to couples in which the father was a smoker, particularly among blacks. The data presented in a figure in the study report indicate about a 10 percent increase in the rates among whites and a 35 percent increase among blacks. This pattern was seen whether the mother was a smoker or not. No raw data were presented for estimating an effect measure or confidence interval, nor were confounding variables considered.

Mau and Netter (1974) In their report of a large prospective study in Germany (see Section 3.2.2.1), Mau and Netter (1974) examined the association of paternal smoking with perinatal mortality (the definition of which was not stated). The authors found an increased rate of perinatal mortality among pregnancies where the father smoked 10 or more cigarettes per day, both for all women and for nonsmoking women ($p < 0.01$). There was not a monotonic dose-response relationship with the amount the husband smoked (there was a slightly lower mortality rate for infants of lighter paternal smokers (1-10 cigarettes per day) than for infants of nonsmokers). Calculating a crude rate ratio for the heavier smoking category yields an approximate measure of 1.5 ($p < 0.05$), (Table 3.5). Stillbirth rates were identified separately and were also included in the perinatal mortality rates. Stillbirth rates increased only slightly with heavier paternal smoking among infants of all women (RR = 1.2), with no further information provided on nonsmoking women. Mau and Netter (1974) noted that the rate of miscarriage in women whose husbands smoked more than 10 cigarettes per day was slightly higher than among those whose husbands did not smoke (9.3 percent versus 8.2 percent). This difference was not statistically significant and no further data were presented.

The small (or lack of) association of paternal smoking with either stillbirth or miscarriage indicates that the association with perinatal mortality may be due to increased neonatal mortality. The authors examined various confounding factors and judged that they had little effect on the association of paternal smoking with perinatal mortality, but the factors were not

adjusted for simultaneously. The authors apparently did not adjust for birthweight, because they did not find a significant association of low birthweight with paternal smoking in their study. They did exclude births with congenital malformations and found that the increase in perinatal mortality persisted.

Koo et al. (1988) In a small study of nonsmoking female controls (n = 136) from a lung cancer study in Hong Kong, Koo *et al.* (1988) compared life-history variables by the husband's smoking status. The authors reported that women whose husbands had ever smoked were 40 percent more likely to have had a miscarriage or abortion and twice as likely to have had a dilation and curettage (D & C) than wives of nonsmokers. The results were statistically significant ($p < 0.03$) for D & C only, and the authors claimed that most of those pregnancy losses would have been spontaneous rather than induced abortions, but that claim was not substantiated. Wives of smokers also tended to have more pregnancies, which was not accounted for in comparing the percentage of women (versus pregnancies) with one or more pregnancy losses, nor were potential confounding factors considered.

Lindbohm et al. (1991) A case-control study from Finland, designed to examine the effect of paternal lead exposure on spontaneous abortion, also reported paternal smoking habits (Lindbohm *et al.,* 1991). The crude odds ratio for spontaneous abortion associated with any paternal smoking was 1.3 (95% CI = 0.9-1.9) (Table 3.5). Maternal smoking had an OR of 1.5 (95% CI = 0.9-2.4), but was not taken into account in the association with paternal smoking. This study may not be generalizable because it targeted men who had been identified through a blood lead monitoring service.

Ahlborg and Bodin (1991) The previously described study of Ahlborg and Bodin (1991) had information about ETS exposure at home as well as in the workplace, ascertained in a prospective study of about 4,700 pregnancies in Sweden. ETS exposure (any versus none) was not found to be associated with excess risk for hospital-ascertained intrauterine deaths (spontaneous abortions plus stillbirths) among nonsmoking mothers. However, there was an excess risk among working women with workplace exposure, with an adjusted rate ratio of 1.5 (95% CI = 0.98-2.4; Table 3.5). This risk did not vary much by whether the woman worked full- or part-time, or by whether or not her partner smoked. When a distinction was made on the basis of whether the loss was early (≤12 weeks) or later in pregnancy, the association with workplace exposure appeared limited to early losses (RR = 2.2, 95% CI = 1.2-3.8) rather than later losses (RR = 1.1). Among working women, exposure only in the home was not associated with intrauterine death.

This study has several strengths, including its ascertainment of multiple sources of exposure, its use of adequate numbers of pregnancies for assessing fetal loss and its thorough control of known confounders. However, the fetal loss rate was low and first trimester losses before prenatal care began were probably under-ascertained. Several of the findings were somewhat inconsistent, such as an association only with workplace expo-

Table 3.5
ETS Exposure in Relation to Spontaneous Abortion and Perinatal Death[1]

Authors (year) Location	Design (study size)	Exposure Definition	Results	Comments
Comstock & Lundin 1967)[2] U.S.—Maryland	Sample from special census, vital records (*n* = 234 still births, 158 neonatal)	Paternal smoking (non-smoking mother)	RR = 1.45 (0.9-2.4) for NM. No effect on SB. (noted increased NM in small group where mom started smoking after pregnancy).	Adjusted for infant sex and patient education only. Exposure not specific to pregnancy. Completeness of FD records?
Mau & Netter (1974)[2] Germany	Interview in early pregnancy (*n* = 5,183)	Paternal smoking by amount (>10 cigs/day)	RR of perinatal death = 1.5 (CI = 1.1-2.3) RR for SB = 1.2 (ns) RR for SAB = 1.1 (ns)	Considered confounders, but RR not adjusted. Methods sketchy. No dose response.
Lindbohm *et al.* (1991) Finland	Case-control study of SABs in lead-monitored men and wives (*n* = 213 SABs, 300 controls)	Paternal smoking status	OR for SAB = 1.3 (0.9-1.9)	Not adjusted. Includes maternal smokers. Generalizability?
Ahlborg and Bodin (1991) Sweden	Prospective questionnaire (*n* = 4,687 pregnancies)	"Live with smoker." Most time at work with smokers (nonsmoking mother)	RR for SAB + SB and ETS at home = 1.0 at work = 1.5 (0.98-2.4) RR = 2.2 (1.2-3.8) for early SAB and work ETS.	Adjusted. Work exposure more intense.
Windham *et al.* (1992) U.S.—California	Case-control (*n* = 626 SABs, 1,300 births)	≥1 hr/day (yes/no) in first 20 weeks. Paternal smoking (non-smoking mother)	OR for SAB = 1.6 (1.2-2.1) late SAB (>12 wks) OR = 1.9 (1.4-2.7)	Adjusted. No effect of paternal smoking when adjusted.

[1] *Includes stillbirth or fetal death and neonatal mortality.*
[2] *Odds ratios and confidence intervals calculated from data, not by original authors.*
Abbreviations: SAB—Spontaneous Abortion; SB—Stillbirth; NM—Neonatal Mortality; FD—Fetal Death; RR—Rate Ratio; OR—Odds Ratio; ns—not statistically significant.

sure and not with home exposure. The question format, however, would tend to yield a more highly exposed group at work than at home (*e.g.* "Do you spend *most* of your time at work in rooms where other people are smoking?" versus "Do you live with a person who smokes inside your home?"). It might have been helpful if the authors had examined the hours of exposure at home or the amount smoked by the household smoker. Secondly, the association of ETS exposure at work with intrauterine deaths in this study is on the same order or greater than the association found for active smoking and intrauterine death. Lastly, in contrast to the ETS findings, the association with active smoking is more striking in later rather than early pregnancy losses.

Windham et al. (1992) Windham *et al.* (1992) examined ETS exposure in a large case-control study of spontaneous abortion conducted in California. Cases, which were confirmed by medical records, were compared to live-born controls frequency matched (to cases) by hospital and date of mother's last menstrual period. The ascertainment of exposure included a question on the amount smoked by the "father of the pregnancy," as well as a separate question on whether the subject was regularly exposed to cigarette smoke for an hour or more per day during the first 20 weeks of her pregnancy. The adjusted odds ratio for self-reported ETS exposure of one hour or more per day among nonsmokers was 1.6 (95% CI = 1.2-2.1), with a somewhat greater association among second trimester than first trimester losses (Table 3.5). The association varied little with the woman's employment status. For amount smoked by the father, the adjusted odds ratios were all close to unity. However, among women reporting ETS exposure, the association was slightly greater if her partner smoked (OR = 2.0) than if he did not (OR = 1.5), potentially indicating heavier ETS exposure.

This study lends some support to the findings of Ahlborg and Bodin (1991) of an increased risk of fetal death associated with ETS exposure. Of further note is that the Windham *et al.* (1992) study also found a lower association of spontaneous abortion with active smoking than with ETS exposure, even when active smokers were compared to nonsmokers with no ETS exposure (OR = 1.3). An inconsistency is that Windham *et al.* (1992) found a slightly greater association with later abortions, while Ahlborg and Bodin (1991) found a greater association with earlier spontaneous abortions. However, in the Swedish study, the late pregnancy losses also included stillbirths. Recall bias may be a concern with a retrospective study, although the questions about ETS exposure were embedded in a series of questions about other exposures and were not the main hypothesis of the Windham *et al.* study.

Windham et al. (1995b) In a recently reported prospective study (Windham *et al.* (1995b), unpublished symposium presentation), the finding of an association between ETS exposure and spontaneous abortion was not confirmed. In that study, pregnant women were interviewed in the first trimester regarding the number of hours per day of ETS exposure at home or work, from which a daily total for each woman was calculated. Among the more

than 4,000 nonsmokers in the study, there was no association with any measure of ETS exposure, including paternal smoking, nor was there any dose-response relationship (adjusted OR for any ETS = 1.0, 95% CI = 0.80-1.3). However, among women who consumed moderate amounts of alcohol (greater than or equal to three drinks per week) or caffeine (greater than 300 mg/day), there was evidence of an association with ETS (adjusted OR around 3), indicating the possibility of interaction or a more susceptible subgroup.

3.3.3 Animal Studies of Perinatal Mortality and Tobacco Smoke Exposure

Information on perinatal mortality in animals is provided by endpoints such as: numbers of resorptions, number of live and dead fetuses at term (in studies with term hysterotomy), and litter size (in studies with spontaneous birth). Studies using mainstream smoke (see Table 3.7, page 120) were not generally supportive of effects on these parameters.

In the three available studies using sidestream smoke (Table 3.7), one study (Witschi *et al.*, 1994) found statistically significant effects of SS exposure on both the number of implantation sites per litter and the number of live pups per litter; this suggests that the primary effect was on implantation. The other two studies (Leichter, 1989; Rajini *et al.*, 1994) did not find effects of SS exposure on variables related to perinatal mortality.

3.3.4 Discussion and Conclusions

Relatively few studies have examined the association of ETS exposure and perinatal death. Two early studies (Comstock and Lundin, 1967; Mau and Netter, 1974) that examined neonatal mortality rates by paternal smoking status suggested an increased risk on the order of 50 percent. A third study (Yerulshalmy, 1971) did not present enough data for satisfactory interpretation, but suggested a possible effect of paternal smoking on neonatal death rates in LBW infants. The data with respect to stillbirth are even more sparse, but are not indicative of an association.

Two more recent studies of spontaneous abortion and ETS exposure (Windham *et al.* 1992; Ahlborg and Bodin, 1991) offer better data, although the exposure assessments were still somewhat crude and were based only on questionnaire responses. Both studies reported an association of spontaneous abortion with ETS exposure, also on the order of 50 percent, although in one study the association was observed only with workplace, not home, exposure. One consideration in examining the relationship of fetal loss to paternal smoking is that it could reflect a direct effect of smoking on the sperm (if losses are due to fetal abnormalities), rather than an effect of ETS exposure to the mother and fetus. The two more recent studies of spontaneous abortion were based not only on paternal exposure, but also included other sources of ETS exposure. The finding in these two studies of a similar association of spontaneous abortion with ETS exposure as with active smoking may be difficult to reconcile with a causal association, given the lower levels of biomarkers measured in nonsmokers exposed to ETS and the fact that active smokers are also exposed to ETS. However, Remmer (1987) has suggested that enzyme induction of mono-oxygenase

systems among active smokers leads to detoxification of toxic compounds; because such enzyme induction would probably not occur with the lower exposures of those exposed only to ETS, their fetuses are less protected.

In the three animal studies of the effects of sidestream smoke on variables related to perinatal mortality, results are indicative of an effect in only one (Witschi *et al.* 1994); studies using mainstream smoke were not generally supportive of an effect on these variables. Based on this limited information, it appears that measures reflecting perinatal mortality in animals are not particularly sensitive to gestational tobacco smoke exposure.

In conclusion, there is some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion, which is consistent with some but not all studies of active smoking. More work is needed because of the few studies available and the inconsistent findings.

3.4 CONGENITAL MALFORMATIONS

Congenital malformations include a wide variety of diagnoses, such as neural tube defects (*e.g.*, anencephaly, spina bifida), cleft palate, and defects of the genitourinary and the cardiovascular systems, among others. About 2 to 3 percent of births are generally considered affected. However, this may vary across studies, because some defects are not detectable at birth and thus would not be included in studies that did not ascertain defects later in infancy. Some studies limit cases to major malformations, whereas others use a broader definition of anomaly. There is some controversy about how to categorize diagnoses, *e.g.*, by organ system or embryologic origin. Potential confounding variables are not well defined, but maternal age, prior reproductive history, and socio-economic status should be considered.

3.4.1 Overview of Human Studies of Congenital Malformations and Maternal Smoking During Pregnancy

The literature on the relationship of active maternal smoking to congenital malformations is inconsistent. Some studies have found associations with defects (Kelsey *et al.,* 1978; Himmelberger *et al.,* 1978), including tube defects (Little and Elwood, 1990) and oral clefts (Saxen, 1974; Khoury *et al.,* 1987), but others have not (Werler *et al.,* 1990; Kallen, 1989; Seidman *et al.*, 1990). The 1980 Surgeon General's report found there was insufficient data to support a judgment about whether parental smoking increases the risk of malformations (U.S. DHHS, 1980). A number of the papers cited above (and below) were published subsequent to that report, but do not present a stronger case, except perhaps for oral clefts.

3.4.2 Human Studies of Congenital Malformations and ETS Exposure

A half dozen studies have examined the potential association of prenatal ETS exposure and congenital malformations (Table 3.6); all published studies were based on paternal smoking status only. Thus, any association seen may be due to a direct effect of smoking on sperm, rather than due to ETS exposure of the mother. Some studies have suggested that active smoking might cause genetic damage to the sperm as reflected by alterations in sperm parameters (Evans *et al.,* 1981; Marshburn *et al.,* 1989). Although little

work has been done associating sperm parameters with pregnancy outcome, genetic damage could theoretically lead to a birth defect. Given the controversial nature of the data on the association of maternal active smoking and congenital malformations, we also present those results with the studies reviewed that looked at both maternal and paternal smoking.

Mau and Netter (1974) Mau and Netter (1974) looked at the incidence of malformations in their prospective study of pregnancy and child development (see Section 3.3.2). The rates of severe malformations among all newborns increased with amount smoked by the father: rates were 0.8 percent among those whose fathers did not smoke, 1.4 percent among those whose fathers smoked 1-10 cigarettes per day, and 2.1 percent among those whose fathers smoked more than 10 cigarettes per day ($p < 0.01$). A crude odds ratio of 2.6 (95% CI = 1.5-4.7) was calculated for infants of fathers smoking more than 10 cigarettes per day (Table 3.6). The authors stated that the increase in risk was similar in surviving children and independent of maternal or paternal age, socioeconomic status, and the participating clinic. No association was found with maternal smoking; deleting maternal smokers from the analysis did not change the results for paternal smoking. The increased risk was observed for specific categories of defects, namely, facial clefts (RR = 7.0), neural tube defects (RR = 1.7), and cardiac defects (RR = 1.9). These categories included very small numbers, and only the elevated risk of clefts was statistically significant. An increased risk was also observed for multiple malformations (RR = 3.3).

Holmberg and Nurminen (1980) A case-control study of central nervous system defects designed to examine occupational factors (Holmberg and Nurminen, 1980) also reported on parental smoking. Cases were identified from the Finnish Register of Congenital Malformations for the years 1976-1978, and controls comprised the live birth immediately preceding the case born in the same district. A questionnaire was administered to mothers of cases and controls within a few months of delivery. Based on a matched analysis, an odds ratio of 1.3 (95% CI = 0.74-2.5) was calculated for paternal smoking, restricted in the interview to "the time when the woman became pregnant." Maternal smoking showed a greater association (OR = 2.1, 95% CI = 1.0-4.4), but the authors reported that this association was diminished when adjusted for solvent exposure. No confounders were considered in the analysis of paternal smoking, including maternal smoking.

Hearey et al. (1984) In a very small case-control study of neural tube defects initiated to investigate an identified cluster, Hearey *et al.* (1984) examined a wide variety of possible risk factors. Both mothers ($n = 36$) and fathers ($n = 25$) were interviewed. Paternal smoking was the only variable found significantly associated with the defects. The odds ratio for paternal smoking during the 6 months before conception or the first trimester was 16.0 (95% CI = 1.1-230.7). No adjustment for other factors, including maternal smoking, was made. The authors noted that the association was not significant in the matched analysis, nor in the time period restricted to only the 6 months before conception. The latter observation may actually make a

Table 3.6
ETS Exposure and Congenital Malformations

Authors (year) Location	Design (study size)	Exposure Definition[1]	Results	Comments
Mau & Netter (1974)[2] Germany	Interview in early pregnancy (n = 5,183)	Paternal smoking by amount (>10/day)	RR for severe BD = 2.6 (1.5-4.7) RR for facial clefts = 7.0 ($p < 0.05$) Cardiac defects = 1.9 (ns) NTDs = 1.7 (ns)	Looked at some confounders, but not adjusted. Little information on methods. (Appears to include maternal smokers).
Holmberg & Nurminen (1980) Finland	Case-control, registry based (n = 120 CNS anomalies & 120 cntrls)	Paternal smoking at conception	OR = 1.3 (0.74-2.5)	Not adjusted. Includes maternal smokers.
Hearey *et al.* (1984) California	NTD cluster, case-cntrl (n = fathers of 8 cases and 17 controls) Retrospective interview	Father smoke periconceptional (father interviewed)	OR = 16.0 ($p < 0.05$) unmatched	Not adjusted. (Includes maternal smokers.) n.s. in matched analysis. Small numbers.
Seidman *et al.* (1990)[2] Israel	Interview post-partum (n = 17,152 infants)	Paternal smoking (amount)	RR = 1.45 (0.73-2.8) for >30 cigs/day[2] and major BDs. RR = 1.1 (0.85, 1.5) for minor BDs.	Multivariate adjustment (results not shown). Little dose-response.
Savitz *et al.* (1991) California	Prospective in HMO members (Child Health & Development Study) (n = 14,685 births)	Paternal smoking at prenatal interview	OR = 2.4 (ns) for hydrocephalus OR = 2.0 for VSD and urethral stenosis (ns) OR = 1.7 for CLP (ns) OR = 0.6 for NTDs (ns)	Multivariate adjustment includes smoking mothers. Multiple comparisons. Little dose response.
Zhang *et al.* (1992)[2] China	Case-control interview in hospital (n = 1,012 cases, 1,012 controls)	Paternal smoking	RR = 1.2 (1.0-1.5) for all BD. Numerous types elevated, but ns RR = 1.6 for CP RR <1.5 for hydrocephalus RR <1.0 for VSD RR = 2.0 (1.1, 3.7)[2] for NTDs	Not adjusted but low-risk subgroup. Greater association with multiple vs. single defects. No dose-response. Multiple comparisons.

[1] *Among nonsmoking women unless otherwise specified. Exposure ascertained from mother unless otherwise specified.*
[2] *Confidence interval calculated by reviewer.*
Abbreviations: BD = birth defects, NTD = neural tube defects, CNS = central nervous system, VSD = ventricular septal defect, CLP = cleft lip and/or cleft palate, CP = cleft palate, ns = not significant or p > 0.05.

stronger case for an ETS effect, because if the excess is associated with paternal smoking during pregnancy (rather than prior to conception), the possibility of an effect on sperm is precluded.

Seidman et al. (1990) Seidman *et al.* (1990) examined parental smoking and congenital malformations using data from the Jerusalem Study of Oral Contraceptive Use. Over 15,000 women who delivered between 1974 and 1976 were interviewed within a few days postpartum. Focusing on only the results for nonsmoking mothers, the authors noted nonsignificant increases in rates of minor and major malformations associated with heavy paternal smoking. The odds ratio we calculated for paternal smoking of greater than 30 cigarettes per day shows only a very slight elevation in the rates of minor malformations and a moderately elevated association with major malformations (Table 3.6). The authors reported that a multiple regression analysis revealed no significant associations with paternal smoking, but did not publish the results. In the regression analysis, maternal smoking was not associated with the incidence of either major or minor malformations. However, among older women (35 years) the malformation rates were elevated two-fold in smokers. The rates of some specific defect categories (spina bifida and genitourinary system defects) were non-significantly elevated among infants of maternal smokers, but data were not presented by defect category for paternal smoking.

Savitz et al. (1991) Savitz *et al.* (1991) analyzed data from the large Child Health and Development Studies of Kaiser Births from 1959-1966 with respect to the influence of paternal variables on the incidence of congenital anomalies. Congenital anomalies were broadly defined and were ascertained up to 5 years after birth. The association with paternal smoking was examined for over 30 categories of defects, so some were based on small numbers. Prevalence odds ratios (POR) adjusted for maternal variables were greater than 1.5 for four diagnoses: cleft lip with or without cleft palate; hydrocephalus, a nervous system defect; ventricular septal defect, a cardiovascular system defect; and urethral stenosis (Table 3.6). All of the confidence intervals were wide and included unity. A dose-response relationship for smoking one pack or more per day was suggested only for the clefts and urethral stenosis. A number of diagnoses had associations with a POR less than 0.7, including neural tube defects and patent ductus arteriosus, a cardiovascular defect. In these analyses, maternal smokers were not excluded, but this variable was controlled in the logistic regression model. Unfortunately, the number of unaffected births by exposure status was not provided, thus defects could not be grouped into broader diagnostic categories or by organ system for comparison to other studies.

Zhang et al. (1992) Zhang *et al.* (1992) examined data on paternal smoking from a case-control study of birth defects conducted in Shanghai from 1986-1987. Birth defects were ascertained within the first week of life or from pathology exams of perinatal deaths; controls were normal live births. Only two mothers reported smoking; they were excluded. Other confounders (*e.g.*, age, paternal drinking, and chemical exposures) were not adjusted because

their occurrence was rare (<5 percent). The overall odds ratio of birth defects and paternal smoking was slightly elevated with little evidence of a dose-response effect (Table 3.6). Among 25 defect categories, elevated odds ratios were seen for pigmentary anomalies of the skin (3.3, 95% CI = 0.9-1.8), diaphragmatic hernia (2.3, 95% CI = 0.7-8.4), anencephaly (2.1, 95% CI = 0.9-4.9), spina bifida (1.9, 95% CI = 0.7-5.4), and varus or valgus deformities of feet (1.8, 95% CI = 0.97-3.3). As can be seen, some confidence intervals were rather wide. The odds ratios for most other categories were greater than one. Exceptions were ventricular septal defect and other heart anomalies, polydactyly or syndactyly, hypoplasia of lung, or hypospadias; none of these were significantly below unity. For neural tube defect diagnoses (*e.g.*, anencephaly and spina bifida) alone, and in combination with other central nervous system defects (*e.g.*, hydrocephalus and microcephalus), we calculated ORs of 2.0 (95% CI = 1.1-3.7) and 1.6 (95% CI = 1.0-2.6), respectively. For some of the defects with elevated rates there was an indication of a dose-response relationship (*e.g.*, spina bifida, diaphragmatic hernia, and the pigmentary anomalies). Classifying defects as isolated or multiple (in the affected individual) revealed a slightly greater association with multiple malformations, but no dose-response effect. The authors felt that confounding or reporting bias were unlikely to explain the observed results.

Shaw and Wasserman (1993)
Wasserman et al. (1994)

A study recently reported at a scientific meeting (Shaw *et al.*, 1993) provided some data on parental smoking as well as other sources of ETS exposure. This case-control study of oral clefts found a dose-response association with amount of maternal smoking. Paternal smoking also appeared to show such an association, but not when maternal smokers were excluded. Thus, paternal smoking appeared to interact with maternal smoking. Exposure to others' smoke at work, or at places other than home, led to slightly increased risks among infants of maternal nonsmokers (OR = 1.5, 95% CI = 0.95-2.2, and OR = 1.3, 95% CI = 0.88-1.8, respectively), as well as among smokers. These data are preliminary and are not adjusted for co-covariates (and thus are not included in the tables). The findings for home (*e.g.*, paternal smoking) and workplace exposure are inconsistent, but the latter are indicative of a slight association with ETS.

A more recent presentation from the same investigators (Wasserman *et al.*, 1994) provided data on parental smoking and neural tube and conotruncal heart defects. An increase in the ORs for the heart defects was seen when both parents smoked (crude ORs ranged from 1.4 to 2.0 by amount smoked), but not when only one parent smoked. Little consistent pattern of risk with parental smoking was noted with neural tube defects, in contrast to the published studies discussed above. Information on workplace exposure was not presented.

3.4.3 Animal Studies of Congenital Malformations and Tobacco Smoke Exposure

Malformations in animals are detected in term fetuses by gross examination, soft tissue examination via dissection, and skeletal examination after staining; a complete teratology study includes all three exams. Of seven

Table 3.7
Animal Studies of Tobacco Smoke Exposure and Fetal Growth

Authors (year)	Species	Exposure Period	Fetal Weight at Term
Mainstream or Unidentified Type of Smoke			
Essenberg *et al.* (1940)	rats	mating through lactation	"2/3rds under weight" (no statistics)
Younoszai *et al.* (1969)	rats	day 3-22 gestation	-16%
Wagner *et al.* (1972)	mice	day 11-16 days gestation	-16% (not significant)
Haworth & Ford (1972)	rats	day 3-20 gestation	-19%
Reckzeh *et al.* (1975)	rats	day 1-18 gestation	-6% (not significant)
Reznik & Marquard (1980)	rats	day 0-21 gestation	-31%
Peterson *et al.* (1981)	mice	day 6-17 gestation	-4% (not significant)
Bertolini *et al.* (1982)	rats	day 1-20 gestation	-9% (not significant)
Tachi & Aoyama (1983)	rats	day 0-21 gestation	-30%
Bassi *et al.* (1984)	rats	day 5-20 gestation	-21%
Amankwah *et al.* (1985)	mice	day 0-birth	-4%
Rogers & Kuehl (1988)	baboons	"throughout pregnancy"	-17% (no statistics)
Sidestream Smoke			
Leichter (1989)	rats	day 1-20 gestation	-9%
Witschi *et al.* (1994)	rats	day 3-10 gestation	0% (not significant)
Rajini *et al.* (1994)	rats	day 3, 6-10 and 13-17 gestation	-7%
Mohtashamipur *et al.* (1987) (abstract)	rats	"1st, 2nd and 3rd week of pregnancy"	"significant losses" no statistics

studies of mainstream smoke using one or more of these techniques, four did not find any effects (Wagner and Chouroulinkov, 1972; Reznik and Marquard, 1980; Peterson, 1981; Bassi *et al.*, 1984) and three mentioned limited findings (Schoeneck, 1941; Tachi and Aoyama, 1983; Amankwah *et al.*, 1985) but did not provide enough information for evaluation or for characterization of defects.

Of the three available sidestream smoke studies, one (Witschi *et al.*, 1994) did not examine malformations. Using gross examination only, Leichter (1989) reported no effects. Rajini *et al.* (1994) reported finding no effects using gross and skeletal examinations, but did no soft tissue examination. Thus, no complete teratology study has been conducted with sidestream smoke.

3.4.4 Discussion and Conclusions Although the epidemiologic studies reviewed suggest a moderate association of severe congenital malformations with paternal smoking (with odds ratios from 1.2-2.6 for all malformations combined, or for major malformations), none presented compelling evidence that ETS

exposure causes congenital malformations. The use of paternal smoking status as a surrogate for ETS exposure means that a direct effect of active smoking on the sperm cannot be ruled out. Several studies found greater associations with specific defects, but the defects implicated differed in different studies. The most consistent association appears to be with central nervous system or neural tube defects; this association was observed in all but one study (Savitz *et al.*, 1991) of the five that provided sufficient data. Due to the limitations in assessing exposure in the existing studies, it is not possible to determine whether there is an association of ETS exposure with birth defects.

None of the studies currently published had information on ETS exposure from multiple sources (*e.g.*, home and work), nor did any include measurement of a biomarker. Thus, an association will be more difficult to detect if there is misclassified exposure such that the comparison group includes pregnancies exposed to ETS from sources other than the spouse. Given that the results of studies of active smoking have been inconsistent, a teratogenic effect of ETS is unlikely to be strong; it would be very difficult to detect a significant association of a weak teratogen which occurs at such low levels with outcomes as rare as specific birth defects. Furthermore, because of the relative dearth of information on causes of malformations, it is difficult to determine whether confounding variables have been adequately controlled. Several of the studies did not exclude maternal smokers, and only one of those adjusted for maternal smoking (Savitz *et al.*, 1991).

In animals, the three available sidestream smoke studies found no effects; however, no complete teratology study has been conducted. Results of only three of seven studies of mainstream smoke suggest an association (Shoeneck, 1941; Tachi and Aoyama, 1983; Amankwah *et al.*, 1985). Based on this limited information, measures of congenital malformations in animals do not appear to be sensitive to tobacco smoke exposure.

In conclusion, it is not possible at this time to determine whether there is an association of ETS exposure with birth defects.

3.5 CHAPTER SUMMARY AND CONCLUSIONS

More than 25 epidemiologic studies of the relationship between fetal growth and ETS exposure were reviewed. All but one of the studies that examined mean birthweight found a decrement with ETS exposure, although some of the weight differences were small. A few early studies found little effect, but none of them controlled for confounders or performed rigorous statistical analyses. The majority of studies which examined the endpoints “low birth weight” or “small for gestational age” have shown a slightly elevated risk (20-40 percent) with ETS exposure. Current epidemiologic studies, with support from animal studies and the known association with active smoking, provide sufficient evidence that ETS exposure adversely affects fetal growth. The primary effect is a reduction in birthweight that is of a small magnitude (25-50 grams) and may not be clinically significant for an individual infant at low

risk. Yet, if the entire birthweight distribution is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants and is strongly associated with perinatal mortality.

Of the relatively few studies that have examined the association of ETS exposure and perinatal death, early studies suggest an increased risk of neonatal mortality rates associated with paternal smoking. The data with respect to stillbirth are more sparse, but are not indicative of an association. Two modern studies reported an association of spontaneous abortion and ETS exposure from multiple sources, although in one study the association was observed only with workplace, not home, exposure. These, as well as two weaker studies, provide some epidemiologic evidence that ETS exposure may play a role in the etiology of spontaneous abortion, but further work is needed, particularly as a recent report did not confirm these findings.

Although the epidemiologic studies reviewed suggest a moderate association of severe congenital malformations (birth defects) with paternal smoking, none presented compelling evidence that ETS exposure causes congenital malformations. The use of paternal smoking status as a surrogate for ETS exposure means that a direct effect of active smoking on the sperm cannot be ruled out. Several studies found associations with specific defects, but the defects implicated differed in different studies. The most consistent association appears to be with central nervous system or neural tube defects; this association was observed in all but one of the five studies that provided sufficient data. Due to the limitations in assessing exposure in the existing studies, it is not possible to determine whether there is an association of ETS exposure with birth defects.

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Developmental Toxicity II: Postnatal Manifestations

4.1 INTRODUCTION In this section we examine associations between ETS exposure and three outcomes occurring after the neonatal period: Sudden Infant Death Syndrome (SIDS), neuropsychological development, and physical growth.

The discussion of each outcome begins with a brief review of studies that assessed the effect of active smoking by the mother during pregnancy. Although reviewing active smoking effects is not the purpose of this document, the review of these studies provides a context within which to consider the results of the studies of ETS exposure.

The brief review of active smoking effects is followed by detailed descriptions of epidemiologic studies of ETS exposure and their outcomes. Pertinent animal studies are then described. The section concludes with a discussion of overall evidence on the impact of ETS exposure and the endpoint.

4.1.1 Confounding in Studies of Child Development The issue of adequate control of confounding is central in attempting to identify causal factors in child development. Smokers as a group appear to differ from nonsmokers in many ways that may influence child development (Broman *et al.*, 1987). For example, smokers are more likely to be of lower socioeconomic status, to be less educated (Fiore *et al.*, 1989; Pierce *et al.*, 1989; Escobedo *et al.*, 1990), to drink alcohol (Kuzma and Kissinger, 1981), and are less likely to breast-feed their infants (Goodine and Fried, 1984) than are nonsmokers. Differences between smokers and nonsmokers with respect to personality and emotional tone have also been observed (Waal-Manning and de Hammel, 1978; Haines *et al.*, 1980; Frerichs *et al.*, 1981). Fried and Watkinson (1988) have reported that the home environments of smokers are on average less conducive to optimal child development. These associations may confound the relationship between ETS exposure and child development.

Adjustment for potential confounders must be done carefully or incomplete control may result. For example, Rantakallio (1983) discovered that within each social class stratum used in her analysis, mothers who smoked were more disadvantaged in terms of employment, family intactness, and health status than were nonsmoking mothers. Conversely, a smoking effect may be concealed through adjustment for intervening variables. For example, adjusting for birthweight could obscure an effect attributable to smoking, if smoking exerts the effect through lowered birthweight.

The above-mentioned factors make it very difficult to examine the association between ETS exposure and developmental outcomes in children. Nevertheless, postnatal ETS exposure of the child may be an important or even the most relevant route of exposure to tobacco smoke components for some outcomes. Identifying an adverse outcome associated with exposure to ETS could have significant implications for public health. Using data from the 1988 National Health Interview Study, Overpeck and Moss (1991) estimated that 49 percent of all U.S. children under 5 years of age are regularly exposed to tobacco smoke after birth by their mother or another member of their household. It is important to distinguish the effects of prenatal and postnatal exposure to tobacco smoke components because approximately two-thirds of women who quit smoking while they are pregnant restart after the birth of the child (Gillies *et al.*, 1988). Identification of any adverse developmental effects due solely to postnatal ETS exposure may help motivate women who quit smoking during pregnancy to remain nonsmokers after their babies are born.

4.2 SUDDEN INFANT DEATH SYNDROME

Sudden Infant Death Syndrome (SIDS) is generally defined as the sudden death of any infant which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death (Beckwith, 1970). The diagnosis of SIDS is usually restricted to infants aged 1 month to 1 year, but investigators sometimes expand the age-at-death criterion. In the United States and other developed countries, SIDS is the most common cause of post-neonatal death. Maternal risk factors that have been identified include young age, high parity, low socioeconomic status, cigarette smoking, and illicit drug use; risk factors in the infant include male sex, black or American Indian race, prematurity, low birthweight, a history of recent illness, having a "near-miss SIDS episode," having a sibling who died of SIDS, not breast feeding, and sleeping in the prone position; other risk factors include the winter season (Kraus and Bulterys, 1991; Guntheroth and Spiers, 1992).

4.2.1 Overview of Human Studies of SIDS and Maternal Smoking During Pregnancy

Active maternal smoking during pregnancy has been consistently found to be a significant risk factor for SIDS with odds ratios (for any versus no maternal smoking) ranging from 1.6 to 4.4. Many studies, particularly the earlier ones, did not adequately control for potential confounders (Steele and Langworth, 1966; Schrauzer *et al.*, 1975; Naeye *et al.*, 1976; Bergman and Wiesner, 1976; Lewak *et al.*, 1979); others had problems with potential selection bias (Bergman and Wiesner, 1976) or incomplete assessment of maternal smoking status (Rintahaka and Hirvonen, 1986). However, there have been two case-control studies (Hoffman *et al.*, 1987 and 1988; Mitchell *et al.*, 1991 and 1992) and two population-based cohort studies (Malloy *et al.*, 1988; Haglund and Cnattingius, 1990) that have been large and reasonably well controlled, adjusting for at least maternal age, parity, race, and socioeconomic status or maternal educational level. In these studies, maternal smoking during pregnancy remained a significant independent risk factor for SIDS with adjusted ORs ranging from 1.8 to 2.5. The effect of maternal smoking on risk of SIDS is independent of birthweight, as demonstrated by Hoffman *et al.* (1987), Malloy *et al.* (1988), Kraus *et al.* (1989), Wierenga

et al. (1990), and Li and Daling (1991). Some investigators have suggested that the residual effect of maternal smoking during pregnancy after adjusting for birthweight could represent an effect of postnatal ETS exposure to the child (Kraus *et al.*, 1989; Dwyer and Ponsonby, 1992).

Several investigators (Steele and Langworth, 1966; Naeye *et al.*, 1976; Kraus *et al.*, 1989; Bulterys *et al.*, 1990; Haglund and Cnattingius, 1990; Malloy *et al.*, 1992) have noted an increase in SIDS risk with increasing levels of maternal smoking during pregnancy. The exception (a reanalysis of the Hoffman case-control study described in Malloy *et al.* (1992)) had used maternal smoking during the first trimester as its measure of exposure. It may be that the risk of SIDS associated with maternal active smoking varies depending on the timing and duration of exposure.

4.2.2 Human Studies of SIDS and ETS Exposure

No studies were found that specifically examined the relationship of ETS exposure of the mother during pregnancy to the subsequent risk of SIDS in the infant.

4.2.2.1 ETS Exposure of the Mother During Pregnancy

4.2.2.2 Postnatal ETS Exposure

Ten studies were found that examined the relationship between SIDS and postnatal ETS exposure (Table 4.1). Some of these studies were reviewed by the U.S. Environmental Protection Agency (1992).

Bergman and Wiesner (1976) Bergman and Wiesner (1976) conducted a small case-control study of SIDS in King County, Washington. Cases and controls were matched on date of birth, sex, and race; there was no adjustment for other co-variates. Exposure was ascertained retrospectively by a mailed questionnaire. The study's case participation rate was poor (56 of 100 identified cases versus 86 of 100 identified controls) with non-responding mothers more likely to be young and to live in poor neighborhoods. This probably led to an underestimation of the proportion of smokers among the cases. The authors ascertained the level of maternal smoking both during and after pregnancy and the level of paternal smoking (timing unspecified). They found an overall crude OR for any maternal smoking during pregnancy of 2.2 (95% CI = 1.0-4.5), and for any maternal smoking after pregnancy of 2.4 (95% CI = 1.2-4.8). There was a large degree of overlap between the "smoking during" and "smoking after" groups: of the smoking mothers, the mothers of only one case and four controls did not smoke both during and after pregnancy. The effect of maternal smoking after pregnancy was independent of level of maternal education, but was present only among mothers $\leq$25 years old. Among the infants of these young mothers, there was evidence of a dose-response effect, with ORs of 3.8 (95% CI = 1.2-11.8) and 7.7 (95% CI = 1.4-52.4) for <20 cigarettes and $\geq$20 cigarettes per day, respectively. Paternal smoking had an OR of 1.5 (95% CI = 0.7-3.2). Maternal smoking was not controlled for in the analysis of paternal smoking.

McGlashan (1989) McGlashan (1989) conducted a case-control study of virtually all unexplained infant deaths in Tasmania from 1980 to 1986. Parents of the 167 cases were interviewed as part of routine grief counseling by public health nurses. Two controls were matched to each case by date of birth and

Table 4.1
Sudden Infant Death Syndrome (SIDS) Studies that Assessed some Source of Postnatal ETS Exposure

Authors (year) Location	Study Size	Exposure Group[1]	Odds Ratio (95% CI)	Comments
		Exposure Group Comparison		
Bergman & Wiesner (1976) United States (King County, Washington)	56 cases, 86 controls	• Any vs. no MS during pregnancy * Any vs. no MS after pregnancy * Any vs. no PS	2.2 (1.0-4.5) 2.4 (1.2-4.8) 1.5 (0.7-3.2)	Matched on sex, race. Poor study participation. Virtually all mothers who smoked in pregnancy also smoked afterwards.
McGlashan (1989) Tasmania	167 cases, 334 controls	• Any vs. no MS during pregnancy * Any vs. no MS in child's first year * Any vs. no PS	1.9 (1.2-2.9) 1.9 (1.2-2.9) "significantly increased"	Matched on sex; no other adjustment. ORs were calculated from table; author presented results of a matched analysis that were different. Virtually all mothers who smoked in pregnancy also smoked afterwards.
Mitchell *et al.* (1991) New Zealand	128 cases, 503 controls (subset of Mitchell *et al.* (1993))	• Any vs. no MS during pregnancy (from medical records) * Any vs. no recent MS (from interview)	2.7 (crude) 3.0 (crude) 1.8 (1.0-3.3; adj)	Controlled for many demographic and social factors, breastfeeding, season, and sleeping position. Strong dose-response noted in crude analysis. Virtually all mothers who smoked in pregnancy also smoked afterwards.
Nicholl & O'Cathain (1992) United Kingdom	242 cases, 251 controls	• Any vs. no MS during pregnancy * Any vs. no PS	2.1 (1.5-3.1) 1.6 (1.1-2.4)	Matched for date and place of birth. Controlled for spousal smoking only. Effect of PS increased as infants' ages increased.

Table 4.1 (Continued)

Authors (year) Location	Study Size	Exposure Group[1]	Odds Ratio (95% CI)		Comments
		Exposure Group Comparison			
Schoendorf & Kiely (1992) United States (U.S. National Maternal and Infant Health Survey)	435 cases, 6,000 controls	• Any vs. no MS during and after pregnancy	White 3.1 (2.3-4.2)	Black 3.1 (2.2-4.3)	Restricted to infants with birth weights ≥2,500 g. Controlled for maternal age, education, and marital status. Smokers in "during and after" category were heavier smokers than smokers in the "after only" category
		* Any vs. no MS after pregnancy only	1.8 (1.0-3.0)	2.3 (1.5-3.7)	
		* Other household smokers (vs. no other household smokers)	1.4 (1.0-1.9)	0.9 (0.7-1.3)	
Mitchell *et al.* (1993) New Zealand	485 cases, 1,800 controls	* Any vs. no recent MS	1.7 (1.2-2.3)		The first 3 ORs are adjusted for region season, breastfeeding, and bed sharing; mother's marital status, SES, age, and smoking during pregnancy; infant's age, sex, birthweight, race, and sleeping position; and where appropriate, smoking by the mother, father, and other household numbers.
		* Any vs. no PS	1.4 (1.0-1.8)		
		* Any vs. no other household smokers	1.2 (0.8-1.6)		
		* MS cigs/day:	No PS	PS	
		0	1.0 (ref)	1.0 (0.6-1.6)	
		1-19	2.6 (1.7-3.8)	4.4 (3.3-6.0)	
		≥20	3.4 (2.0-5.8)	7.4 (4.9-11.1)	

[1] *Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure.*

Table 4.1 (Continued)

Authors (year) Location	Study Size	Exposure Group[1,2]	Odds Ratio (95% CI) Unadjusted	Odds Ratio (95% CI) Adjusted	Comments
		Exposure Group Comparison			
Klonoff-Cohen *et al.* (1995) United States (Southern California)	200 cases, 200 controls	* Any MS	3.1 (1.8-5.6)	2.3 (1.0-5.0)	Adjusted ORs were controlled for birth weight, routine sleep position, medical conditions at birth, prenatal care, breast feeding, and maternal smoking during pregnancy.
		* Any same-room MS	6.2 (2.6-14.6)	4.6 (1.8-11.8)	
		* Any PS	3.5 (2.0-6.3)	3.5 (2.0-6.3)	
		* Any same-room PS	9.2 (3.7-23.2)	8.5 (3.3-21.6)	
		* Any household smoking	3.8 (2.3-6.4)	3.5 (1.8-6.8)	
		* Any same-room household smoking	6.2 (3.3-11.7)	5.0 (2.4-11.0)	
		Total number of household smokers:			
		1	3.1 (1.8-5.5)	3.0 (1.5-6.0)	
		2	5.2 (2.5-10.7)	5.3 (1.9-14.5)	
		3	8.1 (1.5-44.5)	5.1 (0.7-36.6)	
		Total cig exposure/day:			
		1-10	2.3 (1.1-4.7)	2.4 (1.1-5.4)	
		11-20	3.5 (1.7-7.1)	3.6 (1.5-8.8)	
		≥21	12.6 (4.3-37.1)	22.7 (4.8-107.2)	

Table 4.1 (Continued)

Authors (year) Location	Study Size	Exposure Group[1]	Odds Ratio (95% CI)	Comments
		Exposure Group Comparison		
Blair *et al.* (1996) United Kingdom	195 cases, 780 controls	* Any vs. no PS	2.5 (1.5-4.2)	Matching by age and region. First OR is adjusted for maternal age, marital status, SES, maternal smoking, drug and alcohol use, gestational age, sleeping position, and breast feeding.
		* PS/no MS vs. no PS or MS	3.4 (2.0-5.9)	
		* Household cigs/day:		
		0	1.0	
		1-19	2.5 (1.3-4.7)	
		20-39	4.0 (2.4-6.6)	
		≥40	7.6 (4.0-14.3)	

[1] *Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure.*

[2] *All odds ratios are for postnatal exposure and are relative to infants with no smoke exposure.*

sex. Parents of controls were interviewed much later after pregnancy than were parents of cases, introducing a potential source of recall bias. The levels of maternal smoking during pregnancy and throughout the baby's first year of life, as well as levels of paternal smoking, were ascertained. As in the Bergman and Wiesner (1976) study, there was virtually complete overlap between the women who smoked during pregnancy and who smoked during the infants' first year of life, with ORs for both forms of maternal smoking of 1.9 (95% CI = 1.2-2.9). No clear dose-response relationship was seen. The author also stated that cases were significantly more likely than controls to have a father who smoked, or to have either a mother or father who smoked, but the actual data were not presented. There was no adjustment for co-variates.

Mitchell et al. (1991) Results from the first year of a 3-year case-control study of SIDS in New Zealand were reported in Mitchell *et al.* (1991). The interim report included 128 SIDS cases and 503 controls. Cases were well-defined and study participation was over 80 percent. Information regarding all major risk factors for SIDS except for maternal illicit drug use was either obtained through an interview with the parents (conducted on average one month after the death of the case infant) or abstracted from medical records. Maternal smoking status was assessed two ways: as a yes/no variable abstracted from the obstetric record and as the average number of cigarettes smoked per day in the two weeks prior to interview. Neither of these approaches are ideal—the first method would underestimate exposure if a smoking history was not consistently obtained, and the second method might overestimate smoking among mothers of cases if they were smoking more due to the stress of recently losing a baby. Nevertheless, both methods resulted in very similar crude ORs of 2.7 and 3.0, respectively. In a multivariate analysis incorporating most known risk factors for SIDS except maternal smoking during pregnancy, any maternal smoking in the 2 weeks prior to interview had an OR of 1.8 (95% CI = 1.0-3.3). There was no data presented regarding smoking by the father or other family members.

Nicholl and O'Cathain (1992) Nicholl and O'Cathain (1992) conducted a study of 242 SIDS cases and 251 controls drawn from a larger study of post-neonatal mortality in the United Kingdom. The authors calculated independent risks of SIDS for maternal smoking during pregnancy and for smoking by the mother's partner. Smoking by the partner was associated with an OR of 1.6 (95% CI = 1.1-2.4) whereas smoking (during pregnancy) by the mother was 2.1 (95% CI = 1.5-3.1). This analysis controlled for spousal smoking but did not control for any other potential confounders. In the subset of infants whose fathers smoked and whose mothers were nonsmokers, the OR for paternal smoking was 1.4 (95% CI = 0.8-2.4). The researchers did not ascertain maternal smoking status after pregnancy, nor did they distinguish partner's smoking level during and after the pregnancy. In a secondary analysis, the infants were divided into four subgroups by age at death of the case-infant. As the infants' ages increased, the independent ORs associated with partners' smoking increased, from 1.5 at <8 weeks to 2.6 at ≥24 weeks. Conversely, the ORs associated with maternal smoking decreased (from 4.0 to 1.4) as infants' ages increased (confidence intervals were not

given). The authors suggested that this pattern implies that prenatal exposure to maternal active smoking components may be more important for younger infants, and postnatal ETS exposure more important for older infants. Their finding that maternal smoking was less important than partner's smoking in infants ≥24 weeks of age is problematic, since most mothers who smoked during pregnancy presumably also exposed their infants to ETS by continuing to smoke after delivery. However, the numbers in each age category were small and the point estimates are probably imprecise.

Schoendorf and Kiely (1992) The first study to independently examine maternal smoking during and after pregnancy was published by Schoendorf and Kiely (1992). They performed a case-control analysis of data from the 1988 National Maternal and Infant Health Survey. Within this dataset, 201 black and 234 white autopsied SIDS cases were identified from death certificates; approximately 3,000 controls for each race were used. The analysis was restricted to infants weighing ≥2,500 grams at birth. Mothers were questioned regarding their level of cigarette consumption during pregnancy and at the time of interview, and from their responses categorized as nonsmokers, smokers after pregnancy only, or smokers during and after pregnancy. After adjustment for maternal age, education, and marital status, maternal smoking only after pregnancy had an OR of 1.8 (95% CI = 1.0-3.0) for whites and 2.3 (95% CI = 1.5-3.7) for blacks. The risk of SIDS among infants of women who smoked both during and after pregnancy was 3.1 (95% CI = 2.3-4.2) and 3.1 (95% CI = 2.2-4.3) for whites and blacks respectively. The ORs for "passive" (postnatal) and "combined" (pre- and postnatal) exposure were not directly comparable, as mothers who smoked during and after pregnancy tended to smoke more cigarettes per day than mothers who smoked only after pregnancy. The authors also examined the risk of SIDS in relation to the presence of other smokers in the household. In whites, household smoking was significantly associated with SIDS (OR = 1.4, 95% CI = 1.0-1.9), but no relationship was seen in blacks (OR = 0.9, 95% CI = 0.7-1.3). This latter analysis controlled for mother's smoking status only.

Mitchell et al. (1993) Final results from the New Zealand case-control study were published in Mitchell *et al.* (1993). The study's catchment area covered 78 percent of all live births in New Zealand during the 3-year study period. Four hundred eighty-five SIDS cases were compared to 1,800 controls. Case infants were much more likely than were control infants to have mothers who had smoked in the 2 weeks prior to interview (OR = 4.1, 95% CI = 3.3-5.1). The OR decreased to 1.7 (95% CI = 1.2-2.3) but was still significant at the $p = 0.05$ level after adjusting for region, season, breastfeeding, and bed sharing; mother's marital status, socioeconomic status, age, and smoking during pregnancy; infant's age, sex, birthweight, race, and sleeping position; and smoking by the father and other household members. Although results were adjusted for maternal smoking during pregnancy, less than 10 percent of the mothers changed their smoking behavior through pregnancy and the first year of the infant's life. There was a strong dose-response relationship observed between amount smoked by the mother and risk of SIDS (these ORs were not adjusted for any co-variates). The researchers also

found a significant relationship between recent paternal smoking and SIDS, with a crude OR of 2.4 (95% CI = 1.9-3.0) and an adjusted OR of 1.4 (95% CI = 1.0-1.8; adjusted for maternal smoking as well as the other co-variates listed previously). They did not see a dose-response relationship for paternal smoking. Among infants whose mothers did not smoke (131 cases and 1,081 controls), there appeared to be no difference in SIDS risk between infants whose fathers smoked and those with non-smoking fathers (OR = 1.0, 95% CI = 0.6-1.6). However, having a smoking father appeared to substantially increase the risk of SIDS among infants whose mothers smoked. The authors speculated that non-smoking mothers may be more likely than smoking mothers to insist that fathers smoke away from the child.

Mitchell *et al.* also looked at the relationship between the number of smokers in the household and the risk of SIDS. Having any other smokers in the household—excluding the parents—resulted in a crude OR of 1.5 (95% CI = 1.2-2.0) and an adjusted OR of 1.2 (95% CI = 0.8-1.6). When parents were included, there was a strong dose-response relationship between the number of household smokers and the risk of SIDS.

Milerad et al. (1994) Milerad *et al.* (1994) published a small case-report study of autopsied SIDS cases. Sixteen consecutive cases with no other positive histological or other findings at post-mortem had pericardial fluid tested for cotinine, a nicotine metabolite often used to quantify exposure to tobacco smoke. Nine of the 16 (56.3 percent) cases had pericardial cotinine levels indicative of moderate to heavy ETS exposure (cotinine 2.2-156.9 ng/ml). Swedish national surveys report that 18 percent of Swedish women smoke after having a baby, thus more of the autopsied SIDS cases were exposed than would be expected using national data. This small descriptive study has a number of limitations, including the lack of information on the actual smoking practices of the SIDS cases' family members, and the lack of controls. However, to date this is the only study to look at a biomarker of tobacco exposure in SIDS.

Mitchell et al. (1995) Mitchell *et al.* (1995) describes a follow-up study to the New Zealand case-control SIDS study (Mitchell *et al.*, 1991) designed to examine the risk of maternal smoking by considering where the smoking took place. As location of smoking had not been determined in the original interview, a questionnaire was mailed to all participants. Mothers who smoked were asked whether they had usually, sometimes, or never smoked in various parts of their home. Non-Europeans had a poor response rate and were excluded. Of the European participants, 60.3 percent of the case parents and 76.9 percent of the control parents responded. Non-respondents were more likely than respondents to be smokers, younger, and of a lower occupational group. There was no discernible pattern in risk between locations or between smoking frequency, with ORs associated with maternal smoking ranging from 1.7 to 3.0. Mothers who smoked but claimed they never did so in the house had a higher risk of SIDS (OR = 5.1; 95% CI = 1.5-15.4) than did mothers who smoked in the house (OR = 2.2; 95% CI = 1.4-3.5), but the number of women in the group who never smoked in the house was very small (n = 18). There was no control for potential confounders. The

authors felt that the increased risk even among women who did not smoke in the home suggested that risk was primarily from *in utero* exposure. However, this conclusion was driven by a very small group of women, and there was no accounting for the smoking habits of other family members. The authors themselves cautioned that there may be societal pressures for smokers to report not smoking in the home; also, in previous analyses of their own data, they saw an effect of paternal smoking. Thus, they stated that their results should not be interpreted to mean that ETS exposure after birth is not important.

Haglund et al. (1995) Although the study by Haglund *et al.* (1995) did not measure postnatal ETS exposure, it is included here because the authors felt it had implications for the issue of pre- versus postnatal exposure. The authors linked the Swedish death register to the Medical Birth Register to create a cohort of over 800,000 infants, of whom 749 died of SIDS. Maternal smoking (yes/no) at the first prenatal visit was included in the birth registry. The authors found that the winter season and maternal smoking were both independent risk factors for SIDS, but that the excess risk due to smoking did not vary by season (*i.e.*, risks for the winter season and smoking were simply additive). The excess relative risk of smoking was approximately 3.5 for early SIDS deaths (7-90 days) and 2.5 for late SIDS deaths (91-364 days). They speculated that exposure to ETS would be likely to vary by season, and thus stated that "possibly the effect of smoking is prenatal rather than the result of passive smoking after birth." They did not have any direct information about the infants' exposure to tobacco smoke after birth, nor did they present any evidence that ETS exposure would vary significantly by season.

Klonoff-Cohen et al. (1995) Klonoff-Cohen *et al.* (1995) conducted a large case-control study (200 SIDS cases and 200 controls) that had the most extensive assessment of exposure to tobacco smoke of any SIDS study to date. The investigators assessed quantitatively the amount smoked by the mother during each trimester of pregnancy and after birth, by the father during and after pregnancy, and by other live-in adults and day-care providers;they also assessed the proximity of these individuals to the infant as they smoked. They also inquired about smoking and breastfeeding practices. Results were adjusted for several potential confounders including maternal smoking during pregnancy, birthweight, sleep position, breastfeeding, and medical conditions. Every measure of ETS exposure was associated with increased SIDS risk. The adjusted OR for postnatal maternal smoking was 2.3 (95% CI = 1.0-5.0). Paternal smoking had an adjusted OR of 3.5 (95% CI = 1.9-6.3). Although the OR for paternal smoking was higher than the OR for maternal smoking, the high correlation between maternal smoking during and after pregnancy probably resulted in an underestimate of the effect of maternal smoking after pregnancy when adjusting for smoking during pregnancy. Increased risk was also seen with increasing number of household smokers and with total cigarette exposure per day (see Table 4.1). Furthermore, the risk associated with smoking increased when the comparison was restricted to smoking in the same room as the infant. For example, the adjusted OR for postnatal maternal smoking increased from 2.3 to 4.6 (95% CI = 1.8-

11.8) when restricted to same-room exposure. Similarly, the adjusted OR for any household smoking increased from 3.5 (95% CI = 1.8-6.8) to 5.0 (95% CI = 2.4-11.0). The authors concluded, "These data suggest that exposure to tobacco smoke after birth, after adjusting for prior fetal exposure, is associated with an increased risk of SIDS."

Klonoff-Cohen *et al.* also examined the interaction between breastfeeding and maternal smoking. As expected, breastfeeding was protective for SIDS among nonsmokers (adjusted OR = 0.4, 95% CI = 0.2-0.8). No protective effect of breastfeeding was seen among the smokers, although there were only 22 women who both smoked and breastfed their infants (adjusted OR = 1.4, 95% CI = 0.2-12.0).

Blair et al. (1996) A recently published case-control study by Blair *et al.* (1996) corroborated the findings of Klonoff-Cohen *et al.* The study documented significant, dose-related increases in SIDS risk for the three main measures of household smoke that were examined: the number of smokers in the household, the hours of smoke exposure to the infant daily, and the number of cigarettes smoked daily in the household. The latter variable yielded results quite similar to those of Klonoff-Cohen *et al.*, with ORs for 1-19, 20-39, and ≥40 cigarettes per day of 2.5, 4.0, and 7.6, respectively. They also demonstrated elevated risk in families where the mother was a nonsmoker and either the father (OR = 3.4, 95% CI = 2.0-5.9) or another family member (OR not given but $p = 0.007$) smoked. These analyses were unadjusted for potential confounders. In a multivariate analysis that controlled for sleep position, breast feeding, socioeconomic status indicators, maternal smoking, and other factors, paternal smoking remained an independent risk factor (OR = 2.5, 95% CI = 1.5-4.2). The authors calculated that the population-attributable risk for SIDS associated with smoking by at least one parent was 61 percent (this included the effect of smoking by the mother during pregnancy). An interesting feature of this study was that it was conducted in England after the 1991 "Back to Sleep" campaign. This campaign, which sought to reduce the prevalence of risk factors for SIDS, particularly putting infants to sleep in the prone position, had been associated with a fall in the incidence of SIDS in the United Kingdom (Wigfield and Fleming, 1995).

4.2.3 Animal Studies of SIDS and Tobacco Smoke Exposure There is no established animal model for SIDS. However, Slotkin *et al.* (1995) proposed a rat model for SIDS based upon changes in neurochemical function and increased hypoxia-induced mortality of rat pups prenatally exposed to nicotine. According to the model, prenatal exposure to nicotine causes lasting neurochemical changes, which in turn place an infant at greater risk for cardiorespiratory failure during neonatal apneic episodes. A direct link between specific nicotine-induced neurochemical changes and the observed increase in hypoxia-induced mortality has not yet been established. However, in other studies (Milerad *et al.*, 1995), nicotine was found to attenuate the ventilatory response to hypoxia in neonatal lambs, suggesting that neurochemical effects of nicotine could alter either the sensitivity of the carotid body to carbon dioxide or the central processing of chemo-receptor input in the brain.

4.2.4 Discussion and Conclusions

Existing data indicate a causal relationship between maternal smoking in general and risk of SIDS. Numerous studies have consistently found maternal smoking to be a significant predictor of SIDS, with ORs from well-controlled studies ranging from 1.8 to 3.1. A meta-analysis performed by DiFranza and Lew (1995) on studies of SIDS among offspring of women who smoked and who did not smoke during pregnancy (regardless of smoking status after pregnancy) found a pooled OR of 2.98 (95% CI = 2.51-3.54). Several investigators (but not all) have found clear dose-response relationships between the number of cigarettes smoked per day during pregnancy and SIDS risk. Although the etiology of SIDS is not fully understood, a favored current hypothesis is that chronic fetal hypoxia impairs development of the fetal central nervous system, leading to abnormal control of cardio-respiratory activity (Harper and Frysinger, 1988). Maternal smoking during pregnancy promotes fetal hypoxia through placental insufficiency or by increasing the concentrations of carbon monoxide and carboxyhemoglobin in the fetus (U.S. DHHS, 1980). In support of this hypothesis is the finding by Bulterys *et al.* (1990) that low hematocrit during pregnancy becomes an important predictor of SIDS as the level of maternal smoking increases. Exposure to nicotine may also alter an infant's catecholamine metabolism and response to hypoxia (Milerad and Sundell, 1993), an effect recently demonstrated in rats (Slotkin *et al.*, 1995).

Ten epidemiologic studies have attempted to specifically examine the relationship between ETS exposure and SIDS. These studies have looked at smoking by the mother after pregnancy, paternal smoking, household smoking, and smoking during different seasons. In three studies that looked at maternal postnatal smoking (Bergman and Wiesner, 1976; McGlashan, 1989; Mitchell *et al.*, 1991), extensive overlapping between women smoking during and after pregnancy precluded any attempt to identify an independent relationship to ETS exposure. Haglund *et al.* (1995) speculated that because the risk associated with maternal smoking did not rise in the winter, when indoor ventilation might be poorer, prenatal tobacco exposure might be more important than postnatal exposure. They did not, however, measure postnatal maternal smoking, nor did they provide evidence that ETS exposure is greater in the winter. In Mitchell *et al.* (1993), a significant association between postnatal maternal smoking and SIDS remained after adjustment for smoking during pregnancy and other co-variates. However, the number of smokers who had not smoked during pregnancy was very small. Mitchell *et al.* later attempted to refine their assessment of maternal smoking by reinterviewing their subjects about location of smoking (Mitchell *et al.* 1995). Although the authors interpreted their finding that never smoking inside the home did not reduce the risk of SIDS as implying that prenatal exposure is more important than postnatal exposure, the numbers in this group were very small. In addition, they did not link location of smoking to the location of the infant. Schoendorf and Kiely (1992) took advantage of the recent trend for women who are smokers to quit smoking during pregnancy by comparing infants of women who smoked primarily only after pregnancy with infants of non-smoking mothers. Their adjusted OR (1.8) was quite similar to the adjusted OR (1.7) calculated by Mitchell *et al.* (1993). Bulterys (1993) pointed out that most

of the women who smoked "after pregnancy only" also smoked during the first few weeks of pregnancy; thus, it was possible, though not likely, that the increased risk was due to ETS exposure or to maternal active smoking early in pregnancy. Klonoff-Cohen *et al.* (1995), in a fairly large study with detailed exposure assessment and good control of potential confounding, reported an adjusted OR for postnatal maternal smoking of 2.3. This value is also consistent with the ORs seen in Mitchell *et al.* (1993) and Schoendorf and Kiely (1992). In addition, Klonoff-Cohen *et al.* (1995) found that the risk associated with maternal smoking increased when the exposed group was restricted to those women who smoked in the same room as their infant, implying that more concentrated exposure increased risk.

Six papers examined the association between paternal smoking and SIDS. Two (Bergman and Wiesner, 1976; McGlashan, 1989) found that crude ORs for paternal smoking were slightly elevated, but no adjustment for maternal smoking had been made. The third paper to examine paternal smoking (Nicholl and O'Cathain, 1992) found a significantly elevated risk of SIDS independent of maternal smoking. The risk associated with paternal smoking increased with the age of the infant, suggesting that passive exposure of the infant was important. They also found an increased risk of SIDS in families where the father but not the mother smoked, although the confidence interval included unity (OR = 1.4, 95% CI = 0.8-2.4). Lack of control for potential confounders somewhat reduces confidence in their findings. Mitchell *et al.* (1993) looked extensively at smoking among fathers. Overall, paternal smoking remained associated with SIDS even after controlling for maternal smoking and a number of other co-variates. However, the risk did not vary with the amount smoked by the father, and in families where the mother did not smoke, the presence of a smoking father did not appear to increase SIDS risk. The authors presented a plausible explanation for this pattern of results, namely that in families where the mother does not smoke, the father may be less likely to smoke near the infant; however, this speculation remains to be confirmed. Klonoff-Cohen *et al.* (1995) found an increased risk of SIDS associated with paternal smoking independent of maternal smoking. Their OR (3.5) was somewhat higher than Nicholl and O'Cathain and Mitchell *et al.* (1.6 and 1.4 respectively), but this difference could have been due to differences in the time fathers spent with their children. Klonoff-Cohen *et al.* found some evidence of a dose-response in that the risk increased substantially when the analysis was restricted to those fathers who smoked in the same room as their infant. Blair *et al.* (1996) was able to demonstrate significantly increased SIDS risk in families where the father smoked but the mother was a nonsmoker (OR = 3.4, compared to families were neither parent smoked). In a fully adjusted model, any paternal smoking conferred an OR of 2.5, which was between the ORs reported by Mitchell *et al.* and Klonoff-Cohen *et al.*

Four studies looked at household smoke exposure and SIDS. Schoendorf and Kiely (1992) found that among white infants there was an increased risk of SIDS associated with the presence of smokers other than the mother in the household; no such association was seen among black infants. With the information available to them, Schoendorf and Kiely (1992) were not able to explain why no association was seen among blacks.

Mitchell *et al.* (1993) found a dose-response relationship (unadjusted) between the number of smokers in a household and the risk of SIDS. The adjusted OR for the presence of any smokers other than the parents in the household was small (1.2) and the confidence interval included unity. These non-parental smokers might have spent less time with the infant, however. Klonoff-Cohen *et al.* (1995) looked extensively at household smoke exposure, measuring it as total number of household smokers, and as total cigarette exposure per day. A dose-response relationship between ETS and SIDS was seen with both these measures: adjusted ORs for 1-10, 11-20, and ≥21 cigarettes/day were 2.4, 3.6, and 22.7, respectively. Blair *et al.* (1996) found very similar dose-related risks for household cigarette exposure, although their results were unadjusted for possible confounding.

One study in Sweden, Milerad *et al.* (1994), examined cotinine levels in the pericardial fluid of a small number of consecutively autopsied SIDS cases. They found cotinine levels indicating ETS exposure in over half of the cases, a proportion approximately three times higher than would be expected given the percentage of Swedish women who report smoking postnatally. Although limited, this study provides further corroboration of the association between ETS and SIDS seen in other studies.

There is some evidence that suggests a relationship between ETS and SIDS is biologically plausible. Hoppenbrouwers *et al.* (1981) found an association between air pollution levels and incidence of SIDS, suggesting that airborne contaminants may play a role in the etiology of SIDS. Since tobacco smoke is a major contributor to indoor air pollution, ETS could influence SIDS risk through mechanisms similar to those of other air pollutants. ETS may impair respiratory control through chronic carbon monoxide (Watkins and Strope, 1986) and nicotine exposure (Milerad and Sundell, 1993), and ETS can directly affect lung function (U.S. DHHS, 1986). Finally, exposure to ETS increases the likelihood of respiratory tract infections in infants (as discussed in the chapter *Respiratory Health Effects*) which in turn may increase the risk of SIDS. These hypotheses remain to be confirmed.

In conclusion, the strength of the Klonoff-Cohen *et al.* and Blair *et al.* studies, their consistency with two earlier well-conducted studies (Mitchell *et al.*, 1993; and Schoendorf and Kiely, 1992), and the identification of dose-response relationships provide sufficient evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS.

4.2.4.1 Risk Attributable to ETS Exposure

In a large epidemiological study that addressed several potential confounders (Klonoff-Cohen *et al.*, 1995), an OR of 3.5 (1.8-6.8) was found for ETS exposure resulting from any household smoking. Pierce *et al.* (1994) estimated that, in 1993, 17.3 percent of children under the age of five were exposed to ETS in California households. Following DiFranza and Lew (1996), from the proportion exposed to ETS (p) and relative risk (R, which is approximated by the OR), the proportion of cases attributable (a) to ETS exposure can be estimated:

$$a = p(R - 1) / (p(R - 1) + 1)$$

Thus, of the 398 cases of SIDS in California occurring in 1995, 30 percent—or 120 cases—may be attributed to ETS exposure. Nationally, 40-55 percent of children may live in households with ETS exposure (Pirkle *et al.*, 1996; Overpeck and Moss, 1991; Greenberg *et al.*, 1989), and 4,669 cases of SIDS occurred in 1993 (U.S. Bureau of the Census, 1996). Thus, 50-58 percent of SIDS cases nationally (1,868-2,708 deaths in 1993) may be attributed to ETS exposure.

4.3 COGNITION AND BEHAVIOR IN CHILDREN

The determinants of cognitive ability and behavior in children are extremely complex. A wide array of genetic, social, and environmental factors are thought to influence neuropsychological development, including parental intellectual and emotional make-up, socioeconomic status, nutritional status, quality of the home environment, number and spacing of siblings, birth order, sex, and maternal intake of alcohol during pregnancy. Many of these factors do not act independently of each other, but instead create a web of influence that can be very difficult to untangle.

4.3.1 Cognition and Behavior in Children whose Mothers Smoked During Pregnancy

4.3.1.1 Studies of Children whose Mothers Smoked During Pregnancy

A number of epidemiological studies have examined the association between active maternal smoking during pregnancy and cognition and behavior in children. These have been reviewed in Rush and Callahan (1989), Rush (1992), and Tong and McMichael (1992). In the following summary of the literature, studies of cognition in infants, pre-schoolers, and older children are discussed, followed by a review of behavioral studies.

Infant neuropsychological development is often assessed using the Bayley Scales of Infant Development, an administered test that includes mental, psychomotor, and behavioral components (Bayley, 1969). Garn *et al.* (1980) examined the Bayley scores of over 43,500 infants enrolled in the National Collaborative Perinatal Project and found that the proportion with low mental and motor scores increased as maternal cigarette consumption increased. The association was very small until maternal consumption exceeded 20 cigarettes per day; there was no control for potential confounders. Streissguth *et al.* (1980) failed to find significant relationships between maternal smoking (converted to a nicotine score) and Bayley scores after adjusting for gestational age and maternal education, parity, alcohol and caffeine intake. Whether non-significant relationships existed could not be determined from the data presented. Gusella and Fried (1984) found modest negative correlations between nicotine consumption and psychomotor, verbal comprehension, and fine motor indices (the range of Pearson correlation coefficients (r) was -0.11 to -0.22), controlling only for father's education. Only the relationship with verbal comprehension was significant (exact p-values were not calculable from data presented).

Fried and Watkinson (1988) studied a larger sample from the same cohort studied by Gusella and Fried (1984), weighted so that children with heavier exposure to prenatal tobacco and alcohol would be over-represented. They found that after adjustment for the quality of the home environment (assessed by the Home Observation for Measurement of the

Environment (HOME) test), maternal alcohol use, and various demographic factors, differences between 2-year-old children of smokers and nonsmokers diminished to nearly nil (the HOME test measures a variety of characteristics of the home environment and maternal-child interaction and is strongly correlated with many measures of child development (Siegel, 1982)). Thus, this study suggests that most, if not all, of the negative association between maternal smoking during pregnancy and scores on the Bayley exam can be explained by confounding by other variables.

Two studies have evaluated pre-school children using the McCarthy Scales of Children's Abilities. The McCarthy is an administered test with verbal, perceptual, quantitative, general cognitive, memory, and motor subscales, and is a good predictor of school performance (Kaufman and Kaufman, 1977). Fried and Watkinson (1990) found negative correlations between nicotine consumption during pregnancy and all subscales, particularly the verbal subscale (approximate 10 percent decrement among children of heavy smokers). These differences were adjusted for HOME score only. The investigators also found comparable decreases in Peabody Picture Vocabulary Test scores (a test of receptive vocabulary) and the expressive language component of the Reynell Developmental Language Scales. Sexton *et al.* (1990) compared children born to women who quit smoking during pregnancy with children of persistent smokers. One-third of the mothers were "quitters" and two-thirds of the mothers had smoked throughout pregnancy. Children of persistent smokers had adjusted scores that were 2 to 4 percent lower than scores of children of quitters; the effect was most pronounced in the verbal and general cognitive indices. Control variables included a variety of demographic factors, family characteristics, maternal use of alcohol during pregnancy, maternal smoking after pregnancy, and the child's birthweight, gestational age, and health status. Similar results were seen using the Minnesota Child Development Inventory. Thus, in both studies of pre-schoolers there was a pattern of decreased McCarthy scores, especially in the verbal subscale.

Conversely, two studies that used data from the Kaiser Permanente Child Health and Development Studies, Bauman *et al.* (1991) and Eskenazi and Trupin (1995), failed to find an association between smoking during pregnancy and lowered scores on the Peabody Picture Vocabulary Test and the Raven Colored Progressive Matrices Test. Bauman *et al.* defined smoking status using interview data, whereas Eskenazi and Trupin used serum cotinine levels measured in mid-pregnancy. These studies were large (over 1,500 subjects) and well-controlled, including adjustment for postnatal smoke exposure.

The association between maternal smoking during pregnancy and impairments of cognition and school achievement in older children are generally consistent, although the decrements are small and not always statistically significant. A longitudinal study of 17,000 British children found modest but statistically significant dose-related delays in reading, math, and general ability at 7, 11, and 16 years, and a lower level of educational attainment at age 23 (Davie *et al.*, 1972; Butler and Goldstein, 1973; Fogelman, 1980; Fogelman and Manor, 1988). The decrements were

approximately halved after adjusting for a variety of demographic factors and birthweight. In studies derived from the National Collaborative Perinatal Project, Hardy and Mellits (1972) and Naeye and Peters (1984) found adjusted decrements of two to four percent among children of smokers on the spelling and reading sections of the Wide Ranging Achievement Test; Naeye and Peters (1984) also found an increasing effect with number of cigarettes smoked. Nichols and Chen (1981) found a 25 percent increased risk (unadjusted) of learning difficulties among children of heavy smokers (≥20 cigarettes per day). In their crude analysis, risk varied with dose; however, the association between maternal smoking and learning difficulties diminished to non-significance in the final multivariate model. In an uncontrolled analysis, Dunn *et al.* (1977) found that children of mothers who smoked during pregnancy scored approximately 3 percent lower on the Wechsler Intelligence Scale than did children of nonsmokers.

None of these studies of older children controlled for maternal alcohol intake during pregnancy, parental intelligence, quality of the home environment, or current smoking status of the child or family members. In an attempt to control for unassessed genetic and environmental factors, Naeye and Peters (1984) also conducted a sibling pair comparison, balanced for birth order, in which the mother smoked during one pregnancy and not the other. This study again found achievement test scores 2-5 percent lower among children of smoking mothers. Changes in marital status or outside employment did not explain the association.

Behavioral problems such as hyperactivity have been inconsistently reported in studies of children with prenatal exposure to maternal active smoking. Dunn *et al.* (1977) found that male children of mothers who smoked during pregnancy were judged by their teachers to have more problems with behavior, social development, and temperament (uncontrolled analysis; proportions were not given). In their work with the large National Collaborative Perinatal Project, Nichols and Chen (1981) found that school-aged children of women who smoked more than 20 cigarettes per day during pregnancy had a 28 percent increased risk of hyperkinetic-impulsive behavior. Naeye and Peters (1984) found that children's attention span decreased and level of activity increased as the number of cigarettes smoked per day by the mother during pregnancy increased, even after adjustment for demographic factors, gestational age, and breast feeding. Similar results were found in the sibling pair comparison.

The findings of Landesman-Dwyer *et al.* (1981) did not support an association between maternal active smoking during pregnancy and hyperactive behavior. They scored 4-year-olds on a large number of behaviors during a 3-hour observation period in the children's homes. There were no differences noted between children of smokers and children of nonsmokers after adjustment for sex, birth order, maternal alcohol use, and HOME score. However, smoking mothers rated their children as "intense", "persistent", and "willing to approach strangers" more often than did nonsmoking mothers. Similarly, in a large, well-controlled study, Eskenazi and Trupin (1995) failed to find an association between smoking during pregnancy and "active" behavior as reported by the mother. Unlike the other

studies, this study also adjusted for the child's exposure to tobacco smoke after birth. Thus, of all the studies described in this section, their results are the only ones likely to represent the effect of prenatal exposure alone.

Three groups of investigators have used computer-controlled "vigilance tasks" to evaluate attention, impulsivity, and reaction time in children. Poor vigilance performance is related to childhood hyperactivity (Porrino *et al.*, 1983). Streissguth *et al.* (1984), controlling for birth order and maternal education, nutrition, and caffeine and alcohol intake, found that maternal nicotine consumption in pregnancy was significantly associated in a dose-related manner with poorer attention span. Kristjansson *et al.* (1989) found that increased activity levels were more common in children of mothers who smoked during pregnancy, even after adjustment for age, sex, income, maternal education, alcohol and marijuana use, and postnatal smoke exposure. In a larger sample drawn from the same cohort as Kristjansson *et al.* (1989), Fried *et al.* (1992) found that vigilance parameters reflecting impulsiveness and attention, as well as the McCarthy memory subscale, significantly discriminated between children whose mothers were non-, light, and heavy smokers in a discriminant function analysis. Smoking mothers were also more likely to report impulsive and hyperactive behavior in their children, but the difference was not significant ($p > 0.10$). No adjustments for co-variates were made, as the authors stated that no potentially confounding variables were associated with both smoking and the outcome variables.

4.3.1.2 Discussion of Evidence from Studies in Children whose Mothers Smoked During Pregnancy

Most studies of cognitive development demonstrated small decrements, especially in language skills, in children whose mothers smoked during pregnancy. Where data were presented to make the calculation possible, differences associated with maternal smoking ranged from about 2 to 5 percent (Sexton *et al.*, 1990; Hardy and Mellits, 1972; Naeye and Peters, 1984; Rantakallio, 1983). In most studies that found an association, dose-response relationships were also noted. Studies of infants tended not to show effects after adjustment for co-variates, whereas studies of older children tended to show significant effects. The relative lack of association seen in studies of infants may reflect the fact that studies of infants tended to be better controlled than studies of older children. This hypothesis is supported by the results of Baghurst *et al.* (1992), Bauman *et al.* (1991), and Eskenazi and Trupin (1995), all well-controlled negative studies of older children. Alternatively, effects of active maternal smoking during pregnancy may become more "measurable" as children mature, and their intellectual functions become more complex.

Eight of ten studies of behavior and active maternal smoking during pregnancy have shown increased activity level and decreased attention span in children of smokers. Of the four studies with good control of potential confounders (Landesman-Dwyer *et al.*, 1981; Weitzman *et al.*, 1992; Naeye and Peters, 1984; Eskenazi and Trupin, 1995), Weitzman *et al.* (1992) and Naeye and Peters (1984) found significant behavioral impairments in children of smokers. However, Weitzman's outcome measure was based on mothers' reports, making it possible that the effect of smoking was due to

differences in mothers' interpretations of their children's behavior, rather than differences in the actual behavior of the children. This possibility is supported by Landesman-Dwyer *et al.* (1981) who reported no differences in objective measures of children's behavior related to maternal smoking during pregnancy, but found smoking-related differences in mothers' assessments of their children's behavior.

It is biologically plausible that smoking during pregnancy could eventually lead to neuropsychological deficits. One hypothesis is that chronic hypoxia impairs fetal brain development. There are several mechanisms by which maternal smoking can make the fetus hypoxic. Maternal smoking exposes the fetus to both nicotine and carbon monoxide. Nicotine reduces uteroplacental blood flow and carbon monoxide produces carboxyhemoglobin, both of which reduce oxygen delivery to fetal tissues (Lehtovirta and Forss, 1978; Cole *et al.*, 1972). Supporting this hypothesis is the finding by Naeye and Peters (1984) that among children of smoking mothers, those with behavioral abnormalities had had significantly higher neonatal hemoglobin levels (a sign of chronic fetal hypoxia) than had children with normal behavior. Furthermore, nicotine has been shown to have direct adverse effects on the developing brain (Lichtensteiger *et al.*, 1988). Although the few animal studies of exposure to mainstream or sidestream smoke that have been reported do not provide supportive data, the large literature on the effects on animals of prenatal exposure to carbon monoxide and nicotine do suggest that adverse impacts of these agents on postnatal neurobehavior is biologically plausible.

In summary, there is some evidence from reasonably well-controlled studies that maternal smoking during pregnancy is adversely associated with measures of cognition and behavior in children. Dose-response relationships were demonstrated in several studies, and an adverse effect is biologically plausible. However, most of the studies that found significant relationships failed to control for smoke exposure after birth, thus it is difficult to determine if the findings are truly related to smoking during pregnancy, or are in fact related to smoking after pregnancy. Studies that did control for postnatal smoke exposure tended to find no association between prenatal smoke exposure and cognition or behavior. Furthermore, smoking is also known to be strongly associated with many social and environmental characteristics that adversely influence neuropsychological development (Overpeck and Moss, 1991; Fried and Watkinson, 1988). That fact, along with the small size of the associations seen between maternal smoking and neuropsychological outcomes, makes it particularly difficult to rule out the possibility of a spurious effect due to undercontrolled confounding.

4.3.2 Cognition and Behavior in Children whose Mothers were Exposed to ETS During Pregnancy

Two papers that addressed ETS exposure of the mother during pregnancy were identified.

Makin et al. (1991)

Makin *et al.* (1991) administered an extensive neuropsychological test battery to children of women who were active smokers, exposed to ETS, and not exposed to ETS during pregnancy. Assessment of exposure to ETS was prospective but imprecise, as it was ascertained by ask-

ing subjects during pregnancy "Are you regularly exposed to a smoke-filled environment?" There were less than 35 children in each exposure group. Measures of language, intelligence, and attention were outcomes that significantly distinguished non-exposed, ETS-exposed, and active-smoking mothers in a discriminant function analysis. Scores of children of ETS-exposed mothers tended to fall between scores of children of non-exposed and active-smoking mothers. No adjustment was made for potential confounders, as the authors stated that none were related to both tobacco smoke exposure and outcome.

Eskenazi and Trupin (1995) The Child Health and Development Studies were conducted from 1959 to 1967 among women and children who received their health care at the Kaiser Permanente Medical Center of Oakland, California. Pregnant women were interviewed and gave serum samples, which were stored. The children of these pregnancies were administered various neurobehavioral tests at ages 5, 9-11, and 15-17 years. Eskenazi and Trupin (1995) measured cotinine, a nicotine metabolite, in the stored serum samples and examined the results in relation to the 5-year neurobehavioral scores. There were a total of 2,124 mother/child pairs included in this analysis, of whom 1,348 were considered to have no tobacco exposure during pregnancy (nonsmokers with cotinine levels <2 ng/ml) and 68 were classified as having ETS exposure during pregnancy (nonsmokers with cotinine levels from 2-10 ng/ml). The remainder were classified as either active smoking during pregnancy only, active smoking after pregnancy only, or active smoking during and after pregnancy. Forty-three women were excluded because of cotinine levels that did not correspond to their self-reported smoking status. There have been some questions raised about the validity of the definition of ETS exposure used in this study (see discussion of Eskenazi *et al.*, 1995 in Section 3.2.2.4). The neurobehavioral tests examined in this study included the Peabody Picture Vocabulary Test (PPVT), the Raven Colored Progressive Matrices Test (tests of vocabulary and nonverbal reasoning, respectively), and the child's activity level as rated by the mother. Children whose mothers were exposed to ETS during pregnancy did not have Raven or PPVT scores that differed significantly from the scores of children with no smoking exposure, even after adjustment for race, birth order, preschool attendance, parents' education, socioeconomic status, and other factors. The OR for "active" behavior among children whose mothers were exposed to ETS during pregnancy was somewhat elevated (adjusted OR = 1.5), but the confidence interval included unity (95% CI = 0.7-3.1).

4.3.3 Cognition and Behavior in Children Exposed to ETS Postnatally

Of seven studies of neuropsychological development that have assessed effects of some measure of postnatal ETS exposure, four focused on cognitive ability and two focused on behavioral outcomes. One examined both. These seven studies are reviewed below and summarized in Table 4-2.

4.3.3.1 Studies of Cognition and Postnatal ETS Exposure

Rantakallio (1983) Rantakallio (1983) conducted a nested exposure-control study within the Finnish Cohort Study. Women who had smoked through the second month of pregnancy (n = 1,819) were matched on age, parity, marital status, and residence to nonsmoking pregnant women. When their off-

spring were 14 years of age, information regarding the children's health and school performance and the fathers' smoking status was obtained by a mailed questionnaire. As an outcome measure Rantakallio devised a six-point score based on school performance in "theoretical subjects." The method by which this score was derived was not explained. The magnitude of the association seen with maternal smoking during pregnancy was comparable to other studies of prenatal exposure, with an adjusted difference in mean performance score between children of heavy smokers and nonsmokers of approximately 2.5 percent (this is an estimate from a figure, data were not presented). In a regression analysis that included social class, family size, maternal age and education, and sex of the child as co-variates, both maternal and paternal smoking were significant predictors of the school performance score. Paternal smoking was a slightly stronger predictor of score (standardized coefficient = -0.068) than maternal smoking during pregnancy (standardized coefficient = -0.049). It was unclear if paternal smoking represented current smoking status or smoking at the time of the pregnancy. The smoking status of the mother after the second month of pregnancy, and the current smoking status of the child or other family members were not ascertained.

Bauman et al. (1989) Bauman and coworkers conducted two studies that looked at current smoking by the parents and other family members. The first study (Bauman *et al.*, 1989) was a re-analysis of data collected in 1980 to investigate social and psychological determinants of smoking among eighth-graders in one North Carolina school district. The students had been interviewed regarding their own smoking behavior, and their mothers had been given a questionnaire which ascertained the total number of cigarettes smoked per day by all family members. Smoking status of the students and mothers was validated by analysis of breath samples for carbon monoxide. For this study, the analysis was restricted to the 973 students who denied being smokers themselves and who had alveolar carbon monoxide levels of <9 ppm. The students were later routinely administered the California Achievement Test (CAT) by their school. In the crude analysis, scores for the total battery and each of the four subtest scores (math, language, reading, and spelling) decreased as family smoking increased over four categories (zero, 1-19, 20-39, and ≥40 cigarettes per day). The differences by smoking level were all statistically significant ($p < 0.001$). After adjustment for eight co-variates, including age, sex, race, and parents' educational level, generally consistent inverse relationships between family smoking and test scores remained. However, the associations between the math and reading subscores were no longer significant at the $p = 0.05$ level. The magnitude of difference in scores was not large. For example, the mean adjusted total CAT score was 618.8 for children of nonsmoking families and 602.9 for children in the heaviest family smoking category—a difference of about 3 percent of the range for these test scores. The language subscores also differed by approximately 3 percent, whereas the spelling subscores differed by about 6 percent. There was no adjustment for maternal smoking status during pregnancy.

Bauman et al. (1991) The second study (Bauman *et al.*, 1991) was done using data from the examinations of children at ages 5, 9-11, and 15-17 years (referred

to as the 5, 10, and 16-year examinations) enrolled in the Kaiser Permanente Child Health and Development Studies. This dataset allowed the authors to control for maternal smoking during pregnancy, as well as a number of other pertinent co-variates. Sample sizes for each of the examinations ranged from 2,020 (the 16-year exam) to 4,939 (the 5-year exam). Parental smoking status was obtained by periodic interviews with the mothers, but fathers' smoking had to be interpolated for the 5- and 16-year examinations. Twelve to thirty percent of the children had missing parental smoking information and were excluded from the analysis. Cognitive tests performed at the 5-year exam included the Peabody Picture Vocabulary Test (PPVT), the Raven Colored Progressive Matrices Test (a test of reasoning ability), the Quick Test (another test of receptive vocabulary), and the Goodenough-Harris Draw-A-Man test of intellectual maturity. Ten-year-olds were administered the PPVT and Raven test, and the 16-year-olds were administered the PPVT only.

The authors first examined mean test scores by mother's prenatal smoking (yes/no) and current smoking (yes/no). For all Raven and PPVT exams, mean scores were 3-10 percent lower in children of current smokers, independent of maternal smoking status during pregnancy ($p < 0.001$). Conversely, there was little difference in mean scores by prenatal smoking status after stratification by current parental smoking (No difference by smoking status was seen in the Quick Test or Draw-A-Man, and the authors did not consider these tests further). The investigators then examined the effect of current parental smoking after adjustment for multiple confounders, including mothers' smoking during pregnancy, age, sex, race, low birthweight, and parents' education, occupation, and income. For the 16-year exam, active smoking by the child was also included in the regression. Again, current parental smoking had a negative effect on PPVT and Raven scores whereas the mother's smoking during pregnancy had a negligible effect.

The results were significant only at the 10-year examination, where a 3-5 percent decrement in test scores was seen. The authors speculated that the loss of significance at the 5- and 16-year exams may have been related to their method of interpolating smoking status, which would have biased results toward the null. The adjusted scores for the 10-year PPVT and Raven examinations displayed a dose-response relationship over four categories of parental smoking ($p < 0.01$ for linear trend).

Baghurst et al. (1992) Baghurst *et al.* (1992) conducted a longitudinal study that examined maternal smoking during and after pregnancy. Their study cohort had been assembled for the primary purpose of assessing the effect of lead exposure upon cognition. Of the 723 infants enrolled in the study at birth, 548 were still enrolled at the age of 4 years. Each child was administered the Bayley exam at age 2 and the McCarthy exam at age 4. One hundred and sixty children had been exposed to prenatal maternal smoking, and 232 were exposed postnatally to ETS (most of these were also exposed prenatally). In the crude analysis, both prenatal and postnatal maternal smoking were associated with lower scores on all Bayley and McCarthy subscales. The decrements in scores seen with postnatal smoking

Table 4.2
Cognition in Children: Studies that Assessed some Source of Postnatal ETS Exposure

Authors (year) Location	Design (*n*) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison[1,2] Exposure Group	Results	Comments
Rantakallio (1983) Finland	Prospective (1,763 prenatally exposed, 1,781 controls) 14 year olds	School ability in theoretical subjects	• MS during pregnancy: <10 cig/day vs. 0 ≥10 cig/day vs. 0 * Any vs. no PS	Change in score: -1.8% -2.5% ^^^ Inverse association	MS adjusted for sex, maternal age, parental height, SES, and family size. PS also adjusted for prenatal exposure and maternal education.
Bauman *et al.* (1989) United States (North Carolina)	Prospective (973) 8th graders	California Achievement Test	* Cig/day smoked by family: 0 1-19 20-39 >40	Mean total score: 618.8 610.0 606.8 602.9 ^	Nonsmoking children only (confirmed by breath CO). Adjusted for age, sex, parental education, some psych characteristics. No control for SES, prenatal exposure.
Bauman *et al.* (1991) United States (California)	Prospective (1,500-2,800) 5,10,16 year olds	PPVT RAVEN	* Any vs. no parental smoking at age: 5 10 16	Score difference: PPVT / RAVEN -0.06 / -0.14 -1.55^^^ / -0.89^ -0.92	Up to 30% had missing values for parental smoking. Father's smoking interpolated at ages 5 and 16. Adjusted for age, sex, race, birth weight, SES, income, parental education, prenatal exposure, and (in 16-year-olds) active smoking. Dose-response seen with PPVT scores in 10-year-olds.

Table 4.2 (Continued)

Authors (year) Location	Design (*n*) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison[1,2] Exposure Group	Results	Comments
Baghurst *et al.* (1992) Port Pirie, Australia	Prospective (548) 2 and 4 year olds	Bayley (at 2 years) McCarthy (at 4 years)	* Any vs. no maternal postnatal smoking	Score difference: Bayley MDI -0.55 McCarthy GCI -0.45 verbal -0.17 perceptual -0.67 quantitative -0.21	Adjusted for SES, maternal IQ, and HOME score. No control for prenatal exposure. Adjustment caused score differences to drop 65-90% and lose statistical significance.
Eskenazi and Trupin (1995) California	Prospective (2,124) 5 year olds	PPVT RAVEN		Mean score: PPVT / RAVEN	Adusted for parents' education, socioeconomic status, race, birth order, preschool attendance, and other factors.
			• No smoke exposure	50.7 / 10.7	
			* Maternal ETS during pregnancy	51.9 / 10.8	
			• MS during pregnancy	52.5^ / 11.3^	
			* MS after pregnancy	49.9 / 10.4	
			* MS both during and after pregnancy	50.8 / 10.6	
			* Current cig/day smoked by mother:	Score difference from children of nonsmoking mothers PPVT / RAVEN	Adjusted for above factors as well as prenatal exposure
			1-9	-1.5^ / -0.5^	
			10-19	-1.3 / -0.3	
			≥20	-1.3 / -0.6^	

[1] *Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (o) denotes on-ETS exposure; PPVT-Peabody Picture Vocabulary Test; RAVEN-Raven Colored Progressive Matrices Test,; MDI-Mental Development Index of the Bayley Scales of Infant Development; GCI-General Cognitive Index of the McCarthy Scales of Children's Abilities; HOME-Home Observation for Measurement of the Environment.*

[2] *ns = not significant (p>0.05), ^p<0.05, ^^p<0.01, ^^^p<0.001, n = study size.*

were consistent with other studies (ranging from 2.4-4.1 percent) and were generally statistically significant. In contrast, differences associated with prenatal maternal smoking were smaller and not statistically significant. A dose-response relationship was seen between level of maternal smoking after pregnancy and the Mental Development Index of the Bayley exam. There was no attempt to calculate the effect of postnatal maternal smoking independent of prenatal maternal smoking. When the analysis of postnatal smoking was adjusted for socioeconomic status, HOME score, and the mother's intelligence quotient, test score differences dropped by 65-90 percent to near nil and lost statistical significance. In the final regression model (which also included sex, birthweight, number of siblings, and breast- versus bottle-feeding), neither maternal nor paternal smoking was associated with any subscale score.

Eskenazi and Trupin (1995) Similar to Bauman *et al.* (1991), Eskenazi and Trupin (1995) also conducted a re-analysis of data from the Child Health and Development Studies to examine the relationship between cognition and postnatal ETS exposure. Although Eskenazi and Trupin used serum cotinine levels during pregnancy to determine ETS exposure of the mother (see section 4.3.2), interview information was used to classify smoking status at the child's 5-year examination. In addition to categorizing children as being exposed to active maternal smoking during pregnancy only (prenatal exposure), after pregnancy only (postnatal exposure), or during and after pregnancy, the number of cigarettes smoked by the mother per day at the time of the 5-year examination was evaluated. Unlike Bauman *et al.*, paternal smoking was not considered, and results from the 10- and 16-year examinations were not included. Raven and PPVT scores for children with prenatal or postnatal exposure only were not significantly lower than scores for children with no smoking exposure. In contrast, Raven and PPVT scores for children with both pre- and postnatal exposure were lower ($p < 0.05$) than those for children with no exposure; however, the differences in mean scores disappeared after adjustment for parent's education, socioeconomic status, race, birth order, preschool attendance, and other factors. When the number of maternal cigarettes smoked per day was examined, mean scores on both the Raven and the PPVT among children of smoking mothers were generally lower than the mean scores among children of nonsmoking mothers; this was true whether the model was unadjusted, adjusted for prenatal exposure only, or adjusted for prenatal exposure and a variety of other co-variates. However, no clear dose-response relationship was seen in any of the models (see Table 4.2). Because of the lack of a dose-response relationship, the authors felt that the effect seen in children of smoking mothers could potentially be explained by uncontrolled social and environmental factors.

4.3.3.2 Studies of Behavior and Postnatal ETS Exposure

Denson et al. (1975) Denson *et al.* (1975) conducted a small case-control study comparing 20 hyperkinetic children with dyslexic and normal controls, matched for sex, age, and social class (Table 4.3). Parental cigarette consumption at the time of interview and during pregnancy was ascertained by interview with the mother. The mean number of cigarettes smoked per day during pregnancy was greater in mothers of cases than in mothers of normal controls

(14.3 vs. 6.3 cigarettes/day, $p < 0.05$). The difference was more pronounced when consumption at the time of interview was compared (23.3 vs. 8.2 cigarettes/day, $p < 0.001$). Sixteen of the twenty case mothers smoked during pregnancy (80 percent), but the number of control mothers who smoked was not given (thus ORs cannot be calculated). The fathers of cases smoked slightly more than fathers of controls, both during pregnancy (22.2 vs. 18.5 cigarettes/day) and at interview (21.3 vs. 20.7 cigarettes/day), but the differences were not significant. There was no control for confounding other than matching, and there was no attempt to separate pre- and postnatal exposure.

Weitzman et al. (1992) Weitzman *et al.* (1992) attempted to examine the separate contributions of pre- and postnatal exposure. The investigators examined children of women who had been enrolled in the National Longitudinal Survey of Youth in 1979. A total of 2,256 children aged 4 to 11 years were studied. Maternal smoking was categorized as none, only during pregnancy (there were only 132 children in this group), only after pregnancy, and during and after pregnancy. Since the smoking categories were derived from the mother's smoking status during pregnancy and in 1984, exposure misclassification among the smokers probably occurred. Thus, some mothers in the "only during pregnancy" group may have smoked in pregnancy and for several years afterwards as long as they quit before 1984. Mothers completed a Behavior Problem Index (BPI) survey regarding their children's activities and social relationships. A large number of potential confounders were included in the analysis, including demographic factors, birthweight, current health status of mother and child, HOME score, and maternal education, intelligence, use of alcohol during pregnancy, self-esteem, and employment. Paternal or family smoking was not assessed.

The investigators found that smoking was associated with BPI score in a dose-related manner in two groups of children with mothers who smoked: children whose mothers smoked after pregnancy only, and children whose mothers smoked both during and after pregnancy. In the small group of children whose mothers smoked during pregnancy only, smoking 1-20 cigarettes per day was also associated with higher BPI scores, but not significantly so ($p = 0.13$). The adjusted differences in BPI score were fairly comparable across the three categories of exposure. A similar pattern of results was seen when odds ratios for extreme scores on the BPI were calculated. Since the outcome measure was assessed by the mother, differences in BPI may have reflected different perceptions of behavior by smoking mothers rather than altered behavior of the child.

Eskenazi and Trupin (1995) In addition to examining the effects of tobacco smoke during and after pregnancy on cognition, Eskenazi and Trupin (1995) used data from the Child Health and Development Studies to examine the relationship between behavior and postnatal ETS exposure. Their measure for "active" behavior was based on three questions from a 42-item behavioral inventory completed by the mother at her child's 5-year examination. If the mother felt that her child had more energy than most, hated to sit still, and disliked playing quietly, the child was rated as "active." Overall, 17.3 percent of the children were rated as active by their mothers. Analyses

Table 4.3
Behavior in Children: Studies that Assessed some Source of Potential ETS Exposure

Authors (year) Location	Design (*n*) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison[1]	Results	Comments[1]
Denson *et al.* (1975) Saskatchewan	Retrospective (20 cases, 40 controls) 5-15 year olds	Hyperactivity	• MS during pregnancy * PS during pregnancy * Current MS * Current PS	Parents of cases smoked more cig/day than parents of controls. $p < 0.05$ only for MS.	Matched by age,sex, and minimally by SES, no other adjustment for potential confounders. ORs could not be calculated from data presented.
Weitzman *et al.* (1992) US National Longitudinal Survey of Youth	Prospective (2,256) 4-11 year olds	Behavior Problem Index >14 (rating by mother)	MS in cig/day: • Pregnancy only: <20 vs. 0 ≥20 vs. 0 * Post-preg only: <20 vs. 0 ≥20 vs. 0 * Both: <20 vs. 0 ≥20 vs. 0	OR (95% CI): 1.6 (1.0-2.5) 0.4 (0.1-1.6) 1.2 (0.9-1.7) 2.0 (1.3-3.1) 1.4 (1.1-1.8) 1.5 (1.1-2.2)	Only 19 women in high-dose pregnancy-only category thus estimate unstable. Adjusted for age, sex, race, birth weight, health, HOME, income, and maternal education, intelligence, self-esteem, marital status, alcohol use in pregnancy, employment.

Table 4.3 (Continued)

Authors (year) Location	Design (*n*) Age at Follow-up	Outcome Assessment	Tobacco Exposure Comparison[1]	Results OR (95% CI)		Comments[1]
Eskenazi and Trupin (1995) California	Prospective (2,124) Five year olds	Rated "active" by mother		Unadjusted	Adjusted	Adjusted for parents' education, socioeconomic status, race, birth order, preschool attendance, and other factors.
			• No smoke exposure	1.0	1.0	
			* Maternal ETS during pregnancy	1.6 (0.7-3.3)	1.5 (0.7-3.1)	
			• MS during pregnancy only	1.1 (0.6-2.0)	1.0 (0.5-1.9)	
			* MS after pregnancy only	1.4 (0.8-2.7)	1.2 (0.6-2.2)	
			* MS during and after pregnancy	1.6 (1.2-2.1)	1.2 (0.9-1.7)	
			* Current cig/day smoked by mother:	Unadjusted	Adjusted	Adjusted for above factors as well as prenatal exposure
			1-9	1.2 (0.7-1.9)	1.0 (0.6-1.7)	
			10-19	1.5 (0.9-2.3)	1.1 (0.8-2.0)	
			≥20	1.8 (1.2-2.6)	1.6 (0.9-2.8)	

[1] *Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure; HOME-Home Observation for Measurement of the Environment-Short Form, n-study size.*

analogous to those described in the previous section on cognition were performed. The OR for active behavior was somewhat elevated among children with postnatal exposure only, and with prenatal and postnatal exposure, although the effect diminished with adjustment for co-variates (unadjusted OR for pre- and postnatal exposure = 1.6, 95% CI = 1.2-2.1; adjusted OR = 1.2, 95% CI = 0.9-1.7). When maternal cigarettes/day were examined, the ORs for active behavior increased with increasing exposure. This dose-response relationship was seen whether the model was unadjusted, adjusted for prenatal exposure only, or adjusted for prenatal exposure and a variety of other co-variates. However, the effect diminished and lost statistical significance in the full model (see Table 4.3). Despite the presence of a modest dose-response relationship, the authors felt they could not rule out uncontrolled confounding as an explanation for their findings.

4.3.4 Animal Studies of Cognition and Behavior and Tobacco Smoke Exposure

Behavioral teratology studies in animals examine postnatal behavioral function after developmental exposures to toxicants. Bertolini *et al.* (1982) reported an enhanced rate of learning of an active avoidance task in offspring of rats exposed to mainstream tobacco smoke daily during gestation. Studies using sidestream smoke have been reported only in abstract form (Lindsay *et al.*, 1985; Mactutus *et al.*, 1993) and do not present enough information for evaluation. There is a large literature concerning the effects of prenatal exposure to nicotine and carbon monoxide on postnatal behavior; these data are discussed in a recent review (Mactutus, 1989).

4.3.5 Discussion and Conclusions

The evidence that ETS exposure of a nonsmoking pregnant woman can result in neuropsychologic deficits in the child, though very limited, is inconclusive. One small study (Makin *et al.*, 1991) found an association between ETS exposure of nonsmoking mothers during pregnancy and decrements in their offspring's test scores. However, a much larger study that used a biomarker to ascertain ETS exposure (Eskenazi and Trupin, 1995) failed to find any associations between ETS exposure during pregnancy and three measures of cognition and behavior.

The five studies that have looked at postnatal ETS exposure and cognitive endpoints in children have shown inconsistent results. Four of the studies (Rantakallio, 1983; Bauman *et al.*, 1989 and 1991; Eskenazi and Trupin, 1995) found modest decrements in performance by ETS-exposed children, even after adjustment for a variety of other factors. Dose-response relationships were reported in the two Bauman *et al.* studies, but were not seen in Eskenazi and Trupin. The findings of Bauman *et al.* (1991) were internally inconsistent in that associations were not seen at all ages, and results differed for two tests of receptive language (the PPVT and the Quick Test). None of these studies adjusted for parental intelligence or characteristics of the home environment. In the fourth study, Baghurst *et al.* (1992), in their crude analysis, also found decrements in test scores associated with maternal smoking after pregnancy. However, these decrements disappeared after adjustment for several powerful confounders, including socioeconomic status, HOME score, and maternal IQ.

Of the three studies that examined postnatal ETS exposure and children's behavior, Denson *et al.* (1975) was too small and poorly conducted to

allow any conclusions to be drawn. On the other hand, Weitzman *et al.* (1992) conducted a large, well-controlled study that enabled prenatal exposure to maternal active smoking and postnatal ETS exposure to be examined independently. They found significant, dose-related associations between most categories of postnatal maternal smoking and a behavior problem index. Eskenazi and Trupin (1995) also found modest, dose-related asociations between postnatal ETS exposure and "active" behavior. Both studies used a mother-reported outcome; thus, they were unable to determine if maternal smoking was associated with differences in the children's behavior or in the mothers' perceptions.

Proposed mechanisms through which ETS could affect a child's neuropsychological development include a direct effect of nicotine (a stimulant) upon the central nervous system, and adverse impacts of chronic exposure to carbon monoxide. Exposure to ETS increases concentrations of carboxyhemoglobin in the blood (Huch *et al.*, 1980; Jarvis *et al.*, 1983), and increased ambient carbon monoxide levels adversely affect mental functioning in humans (National Research Council, 1977; World Health Organization, 1979). As noted above, the large literature on the effects on animals of prenatal exposure to carbon monoxide and nicotine suggest that adverse impacts of these agents on postnatal neurobehavior is biologically plausible.

In conclusion, there are very few studies that have examined the relationship of neuropsychological development to postnatal ETS exposure of the child, independent of prenatal exposure to maternal active smoking. Two studies of behavior (Weitzman *et al.*, 1992; Eskenazi and Trupin, 1995) did a reasonably good job of separating postnatal from *in utero* exposure and also controlled for other pertinent co-variates. These studies found adverse relationships associated with childhood ETS exposure. With respect to cognitive development, one well-controlled study showed no association with ETS, but four other fairly well controlled studies showed modest decrements associated with ETS. No conclusions regarding causality can be made on the basis of these studies, but they do provide suggestive evidence that ETS exposure may pose a neuropsychological developmental hazard.

4.4 POSTNATAL PHYSICAL DEVELOPMENT

When evaluating studies of postnatal physical development, it should be kept in mind that growth varies not only with genetic influences (*e.g.*, sex and parental height) and nutrition, but also with social factors such as socioeconomic status, birth order, and family size (Goldstein, 1971).

4.4.1 Postnatal Physical Development of Children whose Mothers Smoked During Pregnancy

4.4.1.1 Studies of Children whose Mothers Smoked During Pregnancy

Active maternal smoking during pregnancy can cause significant decreases in birthweight (U.S. DHHS, 1980). There is also evidence that body length at birth is affected by smoking during pregnancy (Persson *et al.*, 1978). Birthweight, which is also a significant predictor of physical development, may be an intervening variable between prenatal exposure to tobacco smoke and growth. There may also be an effect of prenatal exposure to tobacco smoke independent of birthweight. A review of the topic is contained in Rush and Callahan (1989).

Several studies, some involving thousands of children, have examined the relationship between maternal smoking during pregnancy and height, and have found that children of smokers are slightly shorter than children of nonsmokers. The largest height decrements were seen in studies by Dunn *et al.* (1976) and Naeye (1981). Dunn *et al.* (1976), in an uncontrolled study, reported differences of 1.6-2.0 cm for normal birthweight children aged 4-6.5 years. Naeye (1981), in a sibling pair comparison, found the offspring of smoke-exposed pregnancies were 1.7 cm shorter than their non-exposed siblings. Among studies of pre-pubertal children that controlled for a variety of social factors, height decrements for offspring of maternal heavy smokers (at least 10 cigarettes per day) ranged from 0.7-1.0 cm (Hardy and Mellits, 1972; Goldstein, 1971; Butler and Goldstein, 1973; Wingerd and Schoen, 1974; Eskenazi and Bergmann, 1995). The last four papers reported mean heights of children whose mothers were moderate smokers to be intermediate between those of children whose mothers were heavy smokers and nonsmokers.

Fox *et al.* (1990) compared 3-year-old children of women who smoked throughout pregnancy with children of women who had quit and also found an adjusted height difference of 1.0 cm. Studies of the British National Child Development Study cohort at 16 and 23 years of age have shown that the effect of maternal smoking during pregnancy appears to persist beyond puberty, although the size of the effect is not consistent (Fogelman, 1980; Fogelman and Manor, 1988). The sole exception to this pattern was reported by Fried and O'Connell (1987), who failed to find a significant negative correlation between children's height and mothers' smoking status during pregnancy. The point estimate was not presented, so the direction of the association is not known. However, a subsequent larger study taken from the same cohort found children of heavy smokers to be significantly shorter than children of nonsmokers (Fried and Watkinson, 1988). The presentation of data did not allow a specific height difference to be identified.

The effect of adjusting height differences for birthweight has been explored in four study populations. Goldstein (1971), and Fogelman and Manor (1988), using data from the National Child Development Study, found that adjusting for birthweight reduced height differences by 30-60 percent. Fox *et al.* (1990) corroborated this finding, calculating a 50 percent reduction of effect. The studies by Hardy and Mellits (1972) and Eskenazi and Bergmann (1995) reported that differences in height were virtually eliminated when birthweight was taken into account.

Hardy and Mellits (1972), Dunn *et al.* (1976), Naeye (1981), Fried and Watkinson (1988) and Fox *et al.* (1990) also examined prenatal exposure to maternal smoking and children's weight. All five studies found small negative associations with maternal smoking, but the effect was significant only in Naeye's sibling pair comparison. Both Fox *et al.* (1990) and Hardy and Mellits (1972) reported that the effect disappeared when birthweight was controlled.

4.4.1.2 Discussion of Evidence from Studies on Physical Development in Children whose Mothers Smoked During Pregnancy

Investigators have consistently observed a height decrement of 0.7-1.0 cm among children of women who smoked at least 10 cigarettes per day during pregnancy. Fox *et al.* (1990) demonstrated a similar effect when comparing children of quitters and persistent smokers. Dose-response relationships have also been consistently observed. Although very small, the effect appears to be independent of sex, parental height, socioeconomic status, birth order, and family size. One study (Eskenazi and Bergmann, 1995) also controlled for postnatal exposure to ETS. This, together with the lack of evidence associating ETS exposure with height growth (see below) and Berkey *et al.*'s (1984) finding that ETS exposure was not related to rate of growth, suggests that the effect is specifically associated with *in utero* exposure to maternal active smoking.

Half or more of the effect on height appears to be related to reductions in birthweight among offspring of smokers. As maternal smoking is known to cause reductions in birthweight, and as birthweight is a predictor of height (Goldstein, 1971), it is plausible that *in utero* exposure to maternal active smoking could result in small reductions in height growth.

Five poorly controlled studies have found small inverse relationships between maternal smoking during pregnancy and children's postnatal weight growth. More work is required before any conclusions can be drawn regarding the effect of active smoking during pregnancy and children's weight.

In summary, the evidence suggests that the relationship between active maternal smoking during pregnancy and impaired height growth of approximately one centimeter in the pre-adolescent child may be causal. Dose-response relationships have been repeatedly demonstrated, and there are plausible mechanisms to explain the association.

4.4.2 Postnatal Physical Development of Children Exposed to ETS

One study was found that examined the relationship of ETS exposure of the mother to the height of the child at 5 years of age.

4.4.2.1 ETS Exposure of the Mother During Pregnancy

Eskenazi and Bergmann (1995)

Eskenazi and Bergmann (1995) reanalyzed data from the Kaiser Permanente Child Health and Development Studies that were conducted in Oakland, California from 1959 to 1966. The authors measured cotinine, a nicotine metabolite, in stored serum samples taken from women in mid-pregnancy. Of the 2,622 women included in this study, 1,610 were considered to have no tobacco exposure during pregnancy (nonsmokers with cotinine levels <2 ng/ml) and 77 were classified as having ETS exposure during pregnancy (nonsmokers with cotinine levels from 2-10 ng/ml). The children's heights were measured within 6 months of their fifth birthday; the measurements were then extrapolated using linear regression to their height at exactly 5 years. Children of ETS-exposed pregnancies were on average 0.4 cm higher than non-smoke-exposed children (95% CI = -0.5-1.4) after adjustment for birth weight, gestational age, race, sex, birth order, and maternal height, body mass index, education, and age.

4.4.2.2 Postnatal ETS Exposure

Six studies have evaluated the association between some indicator of postnatal ETS exposure and height (Table 4.4). No studies were found of ETS exposure and children's postnatal weight growth.

Rona et al. (1981 and 1985)
Chinn and Rona (1991)

Three studies have been conducted by Rona and colleagues using cross-sectional data from the ongoing British National Study of Health and Growth. In their initial study of 4,961 primary school children in England and Scotland, Rona *et al.* (1981) found an inverse association between the number of people smoking more than five cigarettes per day at home and the standardized height of the child. Height differences could not be calculated from the data presented. Results remained significant after adjustment for birthweight, age, sex, social class, and parental height. Prenatal exposure to tobacco smoke was not assessed.

Rona *et al.* (1985) refined their exposure assessment by ascertaining the total number of cigarettes per day smoked at home by both parents. Forty-three percent of fathers, and 34 percent of mothers smoked in this sample. After adjusting for prenatal exposure to maternal smoking, parental height, infant birthweight, age, sex, degree of overcrowding, and number of siblings, children of smokers were still slightly but significantly shorter than non-exposed children ($p < 0.01$). The adjusted height decrement was small—approximately 0.2 cm for every 10 cigarettes smoked at home. Father's smoking, mother's current smoking, and smoking during pregnancy were all independently associated with height.

In Chinn and Rona (1991), the study was varied by using an even larger cohort of over 11,000 school children and including more co-variates in the analysis, including social class, ethnicity, and receiving school meals. No association was seen between number of cigarettes smoked at home and height. The investigators then repeated the analysis using their 1985 database and found that the height difference, although still negative, diminished by a third and was no longer statistically significant. They concluded that postnatal ETS exposure has no effect on children's height.

Rantakallio (1983)

Rantakallio (1983) studied over 2,800 Finnish 14-year-olds, evenly divided as to prenatal exposure status. The adjusted height decrement associated with maternal smoking during pregnancy was approximately -0.9 cm (estimated from a figure), consistent with estimates calculated by other investigators. In a regression analysis that included demographic and socioeconomic factors, prenatal exposure status, and maternal height, paternal smoking status was negatively related to children's height ($p = 0.07$). The size of the standardized coefficients for maternal smoking during pregnancy and paternal smoking were roughly equivalent. There was no adjustment for birthweight.

Berkey et al. (1984)

Berkey *et al.* (1984) examined height and height growth rate in a longitudinal study of 9,273 children aged 6-11 years (the same study is also described in Ferris *et al.*, 1985). The study's main intent was to examine the health effects of air pollution. The authors found a very significant dose-related decrease in height with increasing current maternal cigarette consumption. Children of mothers who smoked $\geq$10 cigarettes per day were 0.7 cm shorter than children of nonsmokers, after adjusting for age, sex,

parent's education, and use of gas for cooking in the home. There was no adjustment for prenatal exposure to maternal smoking or birthweight, thus it is likely that the effect associated with current maternal smoking actually reflected the effect of smoking during pregnancy. The similarity of the height decrement to decrements seen in studies of maternal smoking during pregnancy supports this interpretation. A nonsignificant association was seen with paternal smoking, with an adjusted height decrement of 0.1 cm among children of fathers smoking ≥10 cigarettes per day. Over an average of 4 years of observation per child, there was no association of either mother's or father's smoking with the child's rate of growth, which led the authors to suggest that the height differences were due to *in utero* or early life exposure.

Eskenazi and Bergmann (1995) As described in the previous section, Eskenazi and Bergmann (1995) used data from the Child Health and Development Studies to examine the relationship between maternal smoking and height of the child at age 5 years. They used information from interviews with the mothers during pregnancy and at their child's 5-year examination to categorize smoke exposure as prenatal only, postnatal only, and pre- and postnatal. Children with prenatal exposure only, and those with pre- and postnatal exposure were 0.3 cm and 0.5 cm shorter than children of nonsmokers, respectively (prenatal exposure, 95% CI = -1.1-0.5; pre- and postnatal exposure, 95% CI = -0.9 to -0.1; adjusted for race, sex, birth order, and maternal education, age, height, and body mass index). These differences diminished to -0.01 and -0.02 cm after also controlling for birthweight and gestational age. In contrast, children with postnatal exposure only were on average 0.5 cm taller than children of nonsmokers, though this difference was not statistically significant (95% CI = -0.3-1.3). The authors concluded that any height decrements seen in children of smokers were probably related to *in utero* exposure rather than postnatal exposure.

4.4.3 Animal Studies of Postnatal Physical Development and Tobacco Smoke Exposure

No studies on this topic that used mainstream smoke were located. One study (Tachi and Aoyama, 1988b) purports to deal with the effects of "sidestream" tobacco smoke on postnatal growth in rats. Exposures began at weaning (21 days postnatal) and continued through adulthood (54 days of age). Rats mature sexually at 35-45 days of age. Reduced growth rates in smoke-exposed animals were reported within a few days of initiation of the exposure. Growth was determined by daily weighing during the study and determination of organ weights at the conclusion of the study. A control group was exposed to carbon monoxide levels comparable to those experienced by the group exposed to tobacco smoke. However, no pair-fed controls were included. Pair-fed controls are important in establishing that the exposure protocols did not lead to reduced food intake due to disruption of normal feeding routines or general malaise.

4.4.4 Discussion and Conclusions

Using paternal smoking as a proxy for postnatal ETS exposure, Rantakallio (1983) and Berkey *et al.* (1984) found very small, nonsignificant negative correlations with height after adjusting for maternal smoking. Berkey *et al.* (1984) found no association between current maternal or paternal smoking and the rate of growth, suggesting that

Table 4.4
Height Growth in Children: Studies that Assessed some Source of Postnatal ETS Exposure

Authors (year) Location	Design (*n*) Ages at Follow-up	Source/Amount of Tobacco Exposure[1]	Height Difference in cm	Comments
Rona *et al.* (1981) United Kingdom	Cross-section (4,961) 5-11 year olds	*Number of people smoking >5 cig/day at home	Inverse association ($p < 0.05$)	Adjusted for age, sex, parental heights, # sibs, SES, birth weight. No control for prenatal exposure.
Rona *et al.* (1985) United Kingdom	Cross-section (5,903) 5-11 year olds	*Every 10 cig/day smoked at home by parents	-0.2 ($p < 0.01$)	Adjusted for age, sex, location, parental heights, # sibs, prenatal exposure, birth weight.
Chinn & Rona (1991) United Kingdom	Cross-section (11,224) 5-11 year olds	*Total cig/day smoked at home by parents	No significant association	Adjusted for same covariates as above, plus SES, ethnicity, school meals.
Rantakallio (1983) Finland	(1,763 prenatally exposed, 1,781 controls) 14 year olds	•MS during pregnancy: <10 cig/day vs. 0 ≥10 cig/day vs. 0 *Any vs. no PS	 -0.6 -0.9 ($p < 0.05$) Inverse association (ns)	MS adjusted for sex, maternal age, parental height, SES, and family size. PS also adjusted for prenatal exposure and maternal education.
Berkey *et al.*(1984); Ferris *et al.* (1985) United States	Longitudinal cohort (9,273) 6-11 year olds	Current cig/day: •MS <10 vs. 0 ≥10 vs. 0 •PS ≥10 vs. 0 ≥10 vs. 0	 -0.5 -0.7 ($p < 0.001$) -0.04 -0.1 (ns) No association between MS or PS and rate of growth	Adjusted for age, sex, location, parental education, gas cooking. No control for parental height, prenatal exposure, birth weight.

Table 4.4 (Continued)

Authors (year) Location	Design (*n*) Ages at Follow-up	Source/Amount of Tobacco Exposure[1]	Height Difference in cm		Comments
			Model I	Model II	
Eskenazi and Trupin (1995) California	Prospective (2,622) 5 year olds	*Maternal ETS during pregnancy	0.5 (-0.5-1.4)	0.4 (-0.5-1.3)	Model I adjusted for race, sex, birth order, and maternal education, age, height, and body mass index.
		•MS during pregnancy only	-0.3 (-1.1-0.5)	-0.01 (-0.8-0.8)	
		*MS after pregnancy only	0.5 (-0.3-1.3)	0.5 (-0.3-1.3)	Model II adjusted for the above factors and birth weight and gestational age.
		*MS during and after pregnancy	-0.5 (-0.9 to -0.1)	-0.02 (-0.4-0.4)	

[1] *Abbreviations: MS-maternal smoking; PS-paternal smoking; asterisk (*) denotes proxy measurement for ETS exposure; bullet (•) denotes non-ETS exposure; n-study size.*

height decrements seen in children of smokers reflect differences that exist at birth. In corroboration of this interpretation, Eskenazi and Bergmann (1995) found no height decrement among children with postnatal ETS exposure only; they also found that the height decrement seen among children whose mothers smoked during and after pregnancy disappeared after controlling for birth weight and gestational age.

In Rona *et al.* (1985) and Chinn and Rona (1991), a reasonably good measure of ETS exposure was obtained (number of cigarettes smoked at home by parents), and analyses were controlled for prenatal exposure to maternal active smoking. These studies found an extremely small ETS effect (-0.2 cm) and no effect, respectively. When the 1985 data were reanalyzed using the same methods employed for the 1991 data, the height decrement diminished by a third and lost statistical significance. These results imply that if any effect of ETS exposure on height exists, it is vanishingly small.

Although there are plausible mechanisms through which ETS exposure could impact postnatal height growth (*e.g.*, impairment of appetite, increased frequency of illness), there is little to no epidemiological evidence that ETS exposure has a significant effect on height growth of children. A single animal study of postnatal sidestream smoke exposure did find reduced growth rates in exposed animals; however, the lack of pair-fed controls in this study limits the conclusions which can be drawn from its results.

4.5 RESPIRATORY DEVELOPMENT AND FUNCTION

The impact of ETS exposure on the respiratory tract has been reviewed by a number of authoritative bodies (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992). Several acute and chronic non-cancer respiratory health effects of ETS have been observed, including exacerbation of childhood asthma, acute lower respiratory tract illness, middle ear infection, and chronic respiratory symptoms in children. Also, while the results from all studies are not wholly consistent, there is substantial evidence that childhood exposure to ETS affects lung growth and development, as measured by small but statistically significant decrements in pulmonary function tests. Drawing on the above-mentioned reviews, as well as more recent literature, these impacts are discussed at length in the Chapter entitled *Respiratory Health Effects of Exposure to Environmental Tobacco Smoke*.

4.6 CHAPTER SUMMARY AND CONCLUSIONS

Interest in Sudden Infant Death Syndrome (SIDS) stems from numerous studies demonstrating that infants of smoking mothers have an increased risk of SIDS. There is adequate epidemiological evidence of a causal relationship between maternal smoking in general and risk of SIDS. In most of the studies examining the relationship between ETS exposure and SIDS, it was not possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent findings of elevated risk of SIDS associated with postnatal ETS exposure independent of maternal smoking in reasonably well controlled epidemiological studies provide compelling evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS.

Although studies have shown fairly consistently that maternal smoking during pregnancy is adversely associated with measures of cognition and behavior in children, very few studies have examined these effects in relation to children's postnatal ETS exposure. One study of behavior which did a reasonably good job of separating postnatal from *in utero* exposure and controlled for other pertinent co-variates found significant adverse relationships associated with childhood ETS exposure. With respect to cognitive development, the best controlled study showed no association with postnatal ETS exposure, but three other fairly well-controlled studies showed modest decrements associated with postnatal ETS exposure. A single small study of nonsmoking pregnant women found an association of ETS exposure during pregnancy with decrements in their offspring's test scores. While conclusions regarding causality cannot be made on the basis of these studies, they do suggest that ETS exposure may pose a neuropsychological developmental hazard.

While small but consistent effects of active maternal smoking during pregnancy on physical growth of offspring have been demonstrated in a number of studies, there is no epidemiological evidence that postnatal ETS exposure has a significant effect on the height growth of children after controlling for prenatal exposure to maternal active smoking. Although a relatively small number of studies have addressed this issue, to date there is no evidence that postnatal ETS exposure is an independent and significant hazard to height growth in humans.

Further evidence of developmental toxicity of ETS exposure on respiratory outcomes is provided in Chapter 6, which presents substantial evidence that childhood exposure to ETS affects lung growth and development, exacerbates childhood asthma, and causes acute lower respiratory tract illness, middle ear infection and chronic respiratory symptoms in children.

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Reproductive Effects

5.1 INTRODUCTION The study of reproductive toxicity includes measures of female fertility and fecundability; other female reproductive effects, such as lowered age at menopause and menstrual disorders; and male reproductive effects, including altered sperm parameters, which may influence a couple's fertility and/or fecundability. Very few studies have investigated the effects of ETS exposure on male and female reproductive function (Tables 5.1 and 5.2). Of these, most have examined delay to conception in women who eventually achieve pregnancy, as an indication of subfecundability. Many of these studies were designed to look at the woman's active smoking, not ETS exposure, but they also reported the husband's smoking status, a surrogate for ETS exposure used in studies of other outcomes. Three of the studies reviewed examined the possibility of an effect on women's fertility occurring earlier in development by trying to ascertain childhood and *in utero* exposure to ETS.

The discussion below of the potential impact of ETS on each outcome begins with a brief review of epidemiological studies that assessed the effect of active smoking. Although reviewing active smoking effects is not the purpose of this document, the review of these studies will provide a context within which to consider the results of the studies of ETS exposure. Epidemiologic studies of ETS exposure are discussed in more detail, followed by a description of pertinent animal studies. Studies are then discussed as a group, and conclusions are presented.

5.2 FEMALE FERTILITY AND FECUNDABILITY In epidemiological studies, measurement of female fertility (ability to reproduce) and fecundability (the probability of conceiving in a given menstrual cycle) generally relies on reported failure to conceive or delay to conception following a time period of unprotected sexual intercourse. Infertility is commonly defined as not becoming pregnant within a year of unprotected intercourse; of course, some couples may go on to conceive later. Fecundability may be measured by determining the number of cycles needed to conceive and calculating the conception rate in each cycle. The probabilities (or rates) of conception can then be compared between two groups—exposed and unexposed—in the form of a ratio. When such a "fecundability ratio" (FR) is less than one, it indicates that the exposed group has lower or "sub"-fecundability than the comparison group. When examining fertility and fecundability, covariates related to sexual practices are important to consider, including frequency of coitus, contraceptive use, and history of sexually transmitted diseases, as well as maternal age, socioeconomic status, and reproductive history. In animal studies, measures of female fertility derived from the standard

Table 5.1
ETS Exposure and Infertility or Fecundability: Adult Exposure

Authors (yr) Location	Design (study size)	Exposure Definition	Results[1]	Comments
Tokuhata (1968) United States (Memphis)	Questionnaire to next-of-kin. Case-control study of cancer (*n* = 2,016)	Husband smoked	Had lowest risk of never having been pregnant. OR = 0.67 (0.46-0.98)	Not adjusted. Crude measure of infertility. Lifetime history.
Baird & Wilcox (1985) United States (Minnesota)	Retrospective interview of pregnant volunteers (*n* = 678)	Husband smoking	No association with delay to conception after adjustment for active smoking and confounders.	Thorough questions about delay. Not a representative sample (high SES). Data not shown.
Suonio *et al.* (1990) Finland	Retrospective interview at prenatal care clinics, population-based (*n* = 2,198)	Husband smoking	Adjusted OR of delayed conception (6-12 mo): = 1.3 (1.2-1.4), potentiated by age.	No data on intercourse or contraception. Included smokers.
Olsen (1991) Denmark	Retrospective questionnaire to pregnant women (*n* = 10,886)	Husband smoking	OR = 1.3 (1.0-1.8) for ≥20 cig/day and delay of >6 mos. In maternal non-smokers. OR in smokers = 1.6 (1.3-2.1)	No data on intercourse. Spouse smoking during pregnancy (vs. before).
Florack *et al.* (1994) The Netherlands	Interview of women planning pregnancy, follow 12 months (*n* = 259) Prospective	Partner smoking	FR: = 2.1 (1.2-3.5) for 1-10 cig/day FR: = 1.0 (0.7-1.6) for >10 cig/day	Not adjusted. Includes female smokers.

[1] *OR = odds ratio; SES = socioeconomic status; FR = fecundability ratio; Fecundability ratio (FR) indicates probability of conception at each cycle. FR > 1 indicates improved fecundability, whereas FR < 1 indicates sub-fecundability, when comparing 2 groups.*

Table 5.2
ETS Exposure and Infertility or Fecundability: Childhood Exposure

Authors (yr) Location	Design (study size)	Exposure Definition	Results	Comments
Wilcox *et al.* (1989) Minnesota	Re-interview women who had pregnancy (n = 631)	Parental smoking (childhood ETS and *in utero* exposure)[2]	FR[1] = 1.3 (1.1-1.6) for 1 or 2 household smokers, 1.6 (1.1-2.2) for more	Biologic plausibility? *In utero* exposure FR = 0.9. Other characteristics of moms not ascertained.
Weinberg *et al.* (1989) North Carolina	Prospective study after stopping birth control (n = 230)	Childhood exposure to smokers. *In utero* exposure[2]	FR = 1.0 crude FR = 1.6 (1.0-2.4) if exposed to 2 smokers, adjusted for *in utero* exposure and other variables.	Selected group. *In utero* exposure FR = 0.5 (0.4-0.8). Exposure prior to attempt to conceive.
Schwingl (1992) California	Prospective exposure (of mother) and cross-sectional (n = 318)	Childhood exposure *In utero* exposure[2]	FR = 1.1 for 1 smoker FR = 1.2 for 2 smokers (p > 0.2) FR = 1.2 (0.9-1.4), no dose-response.	Exposure from mother herself. Adjusted. No association of FR with active smoking.

[1] *Fecundability ratio (FR) indicates probability of conception at each cycle. FR > 1 indicates improved fecundability, whereas FR < 1 indicates sub-fecundability, when comparing 2 groups.*
[2] *In utero exposure indicates that the mother of the target participant smoked during her pregnancy.*

multigeneration study in rodents are the fertility index, the fecundity index, the mating index, and the parturition index; however, multigeneration studies have not been conducted with tobacco smoke. Reproductive organ weights and histology, ovulation, estrus cycles, mating behavior, implantation and resorption may be directly determined from other study designs, and effects on these parameters are considered relevant to female fertility.

5.2.1 Overview of Human Studies of Female Fertility and Fecundability and Active Smoking

Active smoking by women has been found to be associated with decreased fertility in a number of studies (reviewed in Stillman *et al.*, 1986; Westhoff, 1990; and Spira *et al.*, 1987). Associations have been found between smoking and both delay to conception and infertility, particularly related to tubal factors. Delay to conception has been measured in different time intervals, but studies have found increased risks of 40-80 percent among smokers (*e.g.*, odds ratios of 1.4-1.8; Howe *et al.*, 1985). The studies that found an association with tubal infertility reported odds ratios of 1.6-3.3 (Daling *et al.*, 1986; Stillman *et al.*, 1986). Many of the studies have found a dose-response effect. The 1980 Surgeon General's report (U.S.

DHHS, 1980) stated that "cigarette smoking appears to exert an adverse effect on fertility," and many of the important studies were conducted since that report was published. In the ETS studies reviewed below, associations reported for active smoking and fertility are presented along with the ETS findings.

5.2.2 Human Studies of Female Fertility and Fecundability and ETS Exposure

The human studies are presented below in two groups, based on when exposure to ETS occurred: first, studies are described in which exposure occurred during adulthood, usually from a smoking spouse (Table 5.1); second, studies are described in which exposure occurred during childhood from smoking parents (as well as *in utero*, or exposure as a fetus, due to maternal active smoking; Table 5.2).

5.2.2.1 Exposure During Adulthood

Tokuhata (1968)

In the single study of infertility conducted to date, Tokuhata (1968) obtained information from the next-of-kin of 1,095 cancer cases and 921 controls about the lifetime reproductive history and smoking history of the subjects and their spouses. Infertility was defined as never having been pregnant. The crude odds ratio for fertility among couples in which the wife did not smoke and the husband did smoke was calculated as 0.67 (Table 5.1). There did appear to be an association with the wife's active smoking (OR = 1.5) which was diminished when only couples with nonsmoking husbands were examined (OR = 1.3).

This study has a number of problems. Many of the couples (about 400) were excluded because of lack of data on husband's smoking status. The reporting by next-of-kin about pregnancies that ended in fetal loss is probably not accurate, so some women may be misclassified as infertile. There was no information available on any confounders, nor on contraceptive practices. Neither was there any detailed information on exposure to tobacco smoke during specific reproductive periods.

Baird and Wilcox (1985) Baird and Wilcox (1985) conducted a study in Minnesota to investigate the effect of smoking on fertility. Reduced fertility was determined retrospectively as time to conception in 678 pregnant women who had stopped using birth control in order to become pregnant, and who had subsequently conceived within two years. A strength of the study is that the authors made some attempt to exclude cycles "not at risk" for conception, *e.g.*, those during which women reported being sexually abstinent or using birth control. The authors found that women who were smokers had reduced fertility, with a dose-response effect. They stated that husband's smoking status did not affect fertility after adjusting for the woman's smoking status and other potential risk factors ($p = 0.95$). However, no data were presented. These results may not be generalizable because the study was conducted in a population of volunteers from a group with high socioeconomic status who had planned their pregnancies.

Suonio et al. (1990) A study in Finland (Suonio *et al.*, 1990) examined data from interviews conducted with 2,198 women during their 20th week of pregnancy. Fecundability—or specifically, delay to conception—was analyzed by

husband's smoking status. Limiting the analysis to women who conceived within 12 months, the risk of not conceiving by 6 months was 1.3 (95% CI = 1.2-1.4) if the husband smoked and 1.5 (95% CI = 1.3-1.8) if the pregnant woman herself smoked. Both effects were potentiated by increasing age. This effect was not seen when the entire dataset was analyzed (*i.e.*, not truncated at 12 months). The odds ratios were adjusted for some factors, but many that are related to time to conception were not available, including contraceptive practices and coital frequency. This study also did not appear to have data for determining cycles at risk of pregnancy and may thus have some misclassification bias. Furthermore, the association was examined in all pregnancies, including those of women who were active smokers as well as those of nonsmokers, and it is not clear whether maternal and paternal smoking were entered in the regression models simultaneously. If not, the results are not adjusted for smoking by the partner.

Olsen (1991) Olsen (1991) examined fecundability in a large study of almost 11,000 Danish women who completed a questionnaire in their last month of pregnancy. The question about time to conception was pre-coded with broad categories of 0-6 months, 7-12 months, and greater than 12 months. Women treated for infertility were excluded. Current smoking by the woman's partner was associated with a delay to conception in the pregnancies of both smoking and nonsmoking women; a dose-response effect was more apparent in pregnancies of women who were smokers. Among nonsmoking women, the adjusted risk of not conceiving within 6 months was 1.1 if their partner smoked 1-9 cigarettes per day and 1.3 for those whose partner smoked ten or more per day (10-19 cigarettes/day, 95% CI = 1.1-1.6; 20 cigarettes/day, 95% CI = 0.96-1.8). The risk for not conceiving within 12 months for these nonsmoking women with spouses who smoked was also elevated, but did not show any dose-response effect. Contraceptive practices and coital frequency were not assessed. This analysis included women who became pregnant while using contraception, but Olsen stated that excluding these women did not change the results. The measurement of time to conception was rather crude in this study.

Florack et al. (1994) A recent study examined cigarette smoking, alcohol consumption, and caffeine intake of both partners in relation to time to conception in Dutch non-medical hospital workers. Current habits were recorded and rates of conception were followed for the next twelve months to estimate fecundability ratios. A major problem with the approach used by these investigators is that more than half the study population had been trying to conceive for greater than one year prior to the beginning of the study. Not taking this attempt time into account can bias results, particularly if those having difficulty conceiving had changed habits such as smoking. The univariate analysis by proportionate hazard models showed slightly increased fecundability if either partner smoked moderately (Table 5.1). Heavier smoking by spouses made no difference in time to conception, while heavier smoking by females was associated with a slight decrement in fecundability. No data on per-cycle conception rates were reported. Adjusted odds ratios were not presented, although they were reported to change little. No data on confounders such as frequency or timing of intercourse

were available. The association of fecundability with spousal smoking was not examined separately for female nonsmokers, so the possible effects of ETS exposure cannot be estimated.

5.2.2.2 Exposure *In Utero* or During Childhood

Wilcox et al. (1989)

In the Wilcox *et al.* (1989) study, women who participated in the Minnesota study described above (Baird and Wilcox, 1985) were re-interviewed about the smoking status of their mother when she was pregnant with them, as well as about household smokers during their childhood. The authors found that women exposed to ETS as children became pregnant faster than unexposed women. In other words, their probability of conceiving in a given menstrual cycle (fecundability) was higher than in the unexposed women. This association was present irrespective of who the household smoker was, and was slightly stronger with more smokers in the household. The adjusted fecundability ratio (FR) was 1.3 for one or two household smokers and 1.4 for more smokers. Controlling for exposure due to the woman's mother smoking during pregnancy (*in utero* exposure) in the regression model made these associations slightly stronger, with an FR of 1.6 (95% CI = 1.1-2.2) for three or more household smokers. *In utero* exposure to maternal smoking showed a weak association with reduced fecundability (FR = 0.9, 95% CI = 0.7-1.1). Women who were exposed to tobacco smoke during childhood but not *in utero* had an FR of 2.0 (95% CI = 1.3-2.9) compared to unexposed women. Age at menarche was not altered by ETS exposure in childhood. Several covariates that may confound the association were not controlled, particularly socioeconomic variables relating to the women's parents. The authors speculated on possible biological mechanisms to explain this unexpected finding, including earlier maturation and accelerated growth of oocytes in exposed females, or induction of liver enzymes in ways that change adult patterns of hormone metabolism.

Weinberg et al. (1989)

The second study with data on the issue of fecundability and childhood ETS exposure was conducted in North Carolina to examine rates of very early fetal loss (Weinberg *et al.*, 1989). The study participants (*n* = 230), who were enrolled at the time they discontinued contraception, collected urine for 6 months and were then re-contacted at 12 and 24 months if they had not yet conceived. Time to conception was truncated at 13 months so that treatment for infertility would not effect the analysis.

According to the authors, when adjustment was made for *in utero* tobacco smoke exposure and other variables (*e.g.*, age, frequency of intercourse, age at menarche, and current smoking status) in a proportional hazards model, there was an association of childhood exposure with increased fecundability; without adjustment, there was no association. The adjusted FR was 1.3 (95% CI = 0.9-1.8) for one household smoker and 1.6 (95% CI = 1.0-2.4) for two smokers. The authors also reported that *in utero* exposure reduced fecundability (adjusted FR = 0.5, 95% CI = 0.4-0.8). This study did not consider the spouse's smoking status or other sources of ETS exposure in adulthood. These results support the findings of the Minnesota study with respect to childhood exposure, but indicate a much stronger association of reduced fecundability with *in utero* exposure. The authors concen-

trated their discussion on this reduced fecundability and did not comment on the childhood ETS findings. No other information about the mothers of these women was available for analysis.

Schwingl (1992) A recent study available as a dissertation (Schwingl, 1992) was conducted in association with researchers Baird and Weinberg, who conducted studies described above. In this study, daughters of women who had participated in the Child Health and Human Development studies of the 1960's were followed into adolescence and recontacted when they were of reproductive age. Thus, prospectively collected data were available on prenatal (or *in utero*) exposure of women who were now approximately 30 years old. These women completed questionnaires about their most recent non-contracepting interval (NCI) of sexual activity to determine "attempt" times or time to conception. Women never at risk of pregnancy were excluded, but unlike the two previous studies, not all NCIs ended in pregnancy. The crude FR for *in utero* smoke exposure varied only slightly with adjustment for various confounders, and the final model yielded an FR of 1.2 (95% CI = 0.9-1.4). Adding childhood exposure to the model reduced the *in utero* FR slightly to 1.1. Childhood ETS exposure (one or two parents smoking) was associated with FRs of 1.1-1.2. Current smoking by the daughters was also not associated with fecundability (FR = 1.0-1.1 by amount smoked).

These findings do not support the findings of the two earlier studies with respect to increased fecundability among women exposed to ETS as children. The finding of little association with *in utero* smoke exposure is similar to the Wilcox *et al.* (1989) study, but not that of Weinberg *et al.* (1989). The finding of no association of reduced fecundability with active smoking is inconsistent with most of the studies discussed above and in the literature. The sample for this study was highly selected, as it included only women who had remained in a longitudinal study during their childhoods and who were still traceable; these women tended to come from families of higher socioeconomic status than the original study population and were mostly white. However, the mothers of the sample women had smoking habits very similar to those of the original study population.

5.2.3 Animal Studies of Female Fertility and Fecundability and Tobacco Smoke Exposure

The standard study design for evaluating male and female reproductive toxicity, the multi-generation breeding study, has apparently not been conducted with tobacco smoke. One abstract using such a design was located (Mays *et al.*, 1987), but a report of the full study was not found in the literature.

Two studies of ovarian cyclicity in female rats using mainstream smoke have been reported. Tachi and Aoyama (1983, 1988) found disrupted estrus cycles but no effect on ovulation (number of corpora lutea produced once estrus occurred) or mating behavior (once estrus occurred) with inhalation exposure to mainstream smoke. McLean *et al.* (1977) found that mainstream smoke exposure in rats delayed the luteinizing hormone surge associated with ovulation. In this study, the incidence of ovulation was

reduced in rats exposed to smoke from a high (but not a low) nicotine cigarette. No studies of ovarian cyclicity using sidestream smoke have been reported.

An early study described ovarian atrophy in young mice after 2-3 months of exposure to mainstream smoke (Essenberg *et al.*, 1951). A study demonstrating oocyte destruction after exposure to cigarette condensates has also been conducted (Mattison *et al.*, 1989), but a full report of these data was not located in the literature. No studies of ovarian pathology using sidestream smoke were located.

Studies using sidestream smoke exposure during pregnancy (discussed in Section 3.2.3) also contain information on female reproductive toxicity, such as implantation and resorption rates and litter size. Of the three studies using sidestream smoke, one (Witschi *et al.*, 1994) reported a reduced number of uterine implantation sites and a smaller number of live pups at the end of gestation in rats, while the other two (Leichter, 1989; Rajini *et al.*, 1994) did not. The discrepancy between the Witschi *et al.* study and the Rajini *et al.* studies, which used identical sidestream smoke exposure methodology, may be due to the timing of the exposures. In the Rajini *et al.* study, rats were not exposed on gestation days 4 and 5, the days immediately preceding implantation (on day 6), while Witschi *et al.* exposed their animals continuously from days 3 through 10 gestation.

5.2.4 Discussion and Conclusions

By its association with various adverse reproductive outcomes as well as certain chronic diseases, cigarette smoking appears to be anti-estrogenic (Baron *et al.*, 1990). Several studies have reported finding altered levels of hormones or their metabolites in smokers as compared to nonsmokers. Both the steroids estrogen and progesterone, as well as homeostatic hormones (from the adrenal or pituitary glands) may be affected (MacMahon *et al.,* 1982; Michnovicz *et al.*, 1986; Seyler *et al.*, 1986; Barrett-Connor, 1990; Canick and Barbieri 1990; Stillman *et al.*, 1986). Nicotine has been suggested as the primary constituent in tobacco smoke that produces these effects (Stillman *et al.*, 1986).

The study of infertility (and fecundability) is complicated by the fact that it includes a number of components that may have different causes. Successful reproduction is a multi-step process that includes gametogenesis, ovulation, fertilization, tubal transport, implantation, and early placentation, any of which might be affected by tobacco smoke exposure. The entire process is mediated by hormones, so an alteration in their production or metabolism caused by constituents of tobacco smoke could impair fertility. The processes most affected by such alterations would likely be ovulation and perhaps implantation.

Other mechanisms have been suggested to explain an association between smoking and reduced fertility (Stillman *et al.*, 1986). Some human and animal studies have suggested an effect of tobacco smoke or nicotine on tubal physiologic features leading to altered tubal transport, which supports the findings of an association of smoking with tubal infertility. Animal data suggest that exposure to tobacco smoke, or its nicotine and

PAH constituents, results in oocyte/follicle destruction, which could lead to reduced fertility.

In summary, the mechanism by which smoking may affect fertility has not been definitively identified, but such an effect appears plausible; the epidemiologic literature on active smoking and fertility is supportive of an effect. If active smoking leads to reduced fertility, ETS exposure might also be associated with reduced fertility. The epidemiologic data on this topic are not extensive and show mixed results. Three studies examined conception delays (in women who ultimately became pregnant) with respect to spousal smoking habits. Two of the studies (Suonio *et al.,* 1990; Olsen 1991), both conducted in Scandinavia, found slightly (about 30 percent) but significantly increased risks of conception delays (of 6 to 12 months). This is only slightly lower than the magnitude of association seen with active smoking. A study in the United States did not find such an association (Baird and Wilcox, 1985), nor did a study of time to conception in Dutch women (Florack *et al.*, 1994). With the data provided, it is not possible to compare the different studies in terms of smoking rates or proportions of conceptions delayed, but exposures may well be more intense in Scandinavia where smoking is generally more accepted and prevalent. On the other hand, the U.S. study had more information about sexual practices and evaluated delay to conception in a more rigorous fashion than did either of the "positive" Scandinavian studies. In addition, because ETS exposure is defined as spousal smoking in these studies, the association seen may be due to direct effects on male reproductive parameters. Thus, it is not possible to determine from the studies conducted to date whether ETS exposure as an adult is associated with female fertility.

Three studies examined childhood ETS exposure and fecundability (Wilcox *et al.*, 1989; Weinberg *et al.*, 1989; Schwingl, 1992). Two of them, conducted by the same investigators but in different populations, found that childhood exposure tended to increase the fecundability ratio, or likelihood of conceiving; the third study did not confirm this finding. Potential problems with the studies of childhood exposure include the reliability of exposures reported with a longer period of recall and the lack of ascertainment of other covariates associated with childhood exposure. No mechanism to explain this increased fecundability has been suggested by the data collected to date. An inconsistency in these data is that *in utero* exposure to tobacco smoke (from maternal active smoking) was not associated with a similar pattern of increased fecundability. Such exposure occurs at another time in development (and is not considered to be ETS exposure for the purpose of examining reproductive and developmental effects in this document).

Animal studies have demonstrated effects of tobacco smoke exposure on ovarian cycles and implantation that are compatible with reduced fertility. However, multigeneration studies that would provide a more complete evaluation of effects of chronic exposure on production of offspring have not been conducted.

In conclusion, the data are inadequate to determine whether there is an association of ETS exposure with effects on fertility or fecundability.

5.3 OTHER FEMALE REPRODUCTIVE EFFECTS

In addition to studies of fertility and fecundability, investigators have examined the role of exposure to tobacco smoke on earlier age at menopause and on rates of menstrual disorders.

5.3.1 Overview of Human Studies of Other Female Reproductive Effects and Active Smoking

Substantial data exist to document that smokers have earlier age at menopause (U.S. DHHS, 1980; Midgette and Baron, 1990; Tajtakova *et al.*, 1990). The mean age at menopause in smokers is on average 2 years less than that of nonsmokers. Some studies have also suggested increases in menstrual disorders associated with cigarette smoking (Brown *et al.*, 1988; Sloss and Frerichs, 1983). Furthermore, as discussed above (Section 5.2.4), cigarette smoke appears to be anti-estrogenic and may affect homeostatic hormones as well.

5.3.2 Human Studies of Other Female Reproductive Effects and ETS Exposure

Everson et al. (1986)

Everson *et al.* (1986) reported an association of ETS exposure and lower age at menopause. Data were obtained from 261 women who had been controls in a case-control study of cancer in North Carolina. The mean age at menopause was reduced by 2 years among nonsmoking women whose spouses smoked, compared to those whose spouses did not smoke. The risk of early menopause was elevated in nonsmokers exposed to ETS ("passive smokers") compared to those not exposed (OR = 1.9, 95% CI = 1.0-3.9). Adjustment for some confounders (age, race, education, and alcohol intake) increased the odds ratio to 2.1 (95% CI = 1.0-4.5). Both these measures were similar to the association observed for active smoking and earlier age at menopause in this study. The authors found that childhood exposure to paternal smoking was not associated with early menopause. Only four subjects had mothers who smoked and these subjects' age at menopause was reduced about 2 years. These findings were reported in a brief format, so details of the study design and analysis were not available. For example, the definition of early menopause was not specified, nor was it clear if the term "passive smokers" included those exposed to a parent or only to a spouse who smoked. Whether the decrease of 2 years in the age at menopause of passive smokers was statistically significant is not discussed. The finding of an association with maternal, but not paternal, smoking during the subject's childhood appears inconsistent. However, the estimate (OR) of the maternal association is based on very small numbers and is probably imprecise. On the other hand, children may be more exposed to their mothers' smoking habits than to their fathers', and children of mothers who smoke may also have been exposed *in utero*.

Tajtakova et al. (1990)

One additional study (Tajtakova *et al.*, 1990) provided data on age at menopause and exposure to ETS, but it was published in Slovak and therefore could not be thoroughly evaluated. According to the English abstract, women who were smokers had a mean age at menopause 1.7 years younger than that of nonsmokers; the dose-response relationship was such

that the mean age at menopause was up to 2.4 years earlier in heavier smokers, consistent with other studies. Those exposed to ETS had a mean age at menopause that was slightly younger than nonexposed nonsmokers, but the difference was not statistically significant. We calculated a difference of -0.7 years (95% CI = -1.9-0.51) from data presented in a table. These differences are unadjusted for confounders.

5.3.3 Animal Studies of Other Female Reproductive Effects and Tobacco Smoke Exposure

No material was located which used an animal model for menopause.

5.3.4 Discussion and Conclusions

Two studies found indications of early menopause associated with ETS exposure, which is consistent with findings of early menopause among active smokers. The possible mechanisms described in relation to infertility (Section 5.2.4), such as hormone perturbations or oocyte destruction, might also influence age at menopause. The magnitude of the effect of ETS exposure on age at menopause, because it is similar to that of active smoking, seems large in one of the studies. However, studies of the effect in active smokers generally compare smokers to all nonsmokers, including those exposed to ETS. If there is an association with ETS exposure as well, studies of active smokers should exclude ETS-exposed women from the comparison group, which should then strengthen the association seen with active smoking. Everson *et al.* (1986) demonstrated such a phenomenon in their data. More studies are needed to confirm this finding of decreased age at menopause with exposure to ETS. While human studies have examined the effects of active smoking on menstrual disturbances and hormonal status, none were found that examined these in relation to ETS exposure.

In conclusion, there is a paucity of data on the association of ETS exposure and lowered age at menopause or other measures of menstrual cycle dysfunction, and conclusions regarding causal associations cannot be reached.

5.4 MALE REPRODUCTIVE TOXICITY

Male reproductive toxicity includes altered sperm parameters, such as lower density, decreased motility or abnormal morphology, and effects on fertility.

5.4.1 Overview of Human Studies of Male Reproductive Toxicity and Active Smoking

Several studies have shown an association between active smoking and altered sperm parameters, including abnormally shaped sperm (Evans *et al.*, 1981), decreased seminal fluid and decreased sperm motility (Marshburn *et al.*, 1989). Authors of a recent meta-analysis of the literature on sperm density and smoking (Vine *et al.*, 1994) concluded that smokers' sperm density is on average 13-17 percent lower than that of nonsmokers. The 1980 Surgeon General's Report (U.S. DHHS, 1980) states that "spermatogenesis, sperm morphology, sperm motility and androgen secretion appear to be altered in men who smoke." These outcomes could result from some of the same mechanisms proposed to explain the effects of smoking on female

reproductive functions, namely alterations in hormone regulation and gamete production.

5.4.2 Human Studies of Male Reproductive Toxicity and Exposure to ETS

No published studies were found that were designed to examine the association between ETS exposure of males and altered sperm parameters or fertility. The report by Wilcox *et al.* (1989) of their Minnesota study (described above in Section 5.2.2.2) briefly states that childhood ETS or *in utero* exposure of the husband was not related to the couple's fecundability (*i.e.*, time to pregnancy). Another study (Ratcliffe *et al.*, 1992) examined the effects of early exposure to maternal smoking on fertility in adult males using data from clinical trials of diethylstilbesterol treatment (DES). This study could not separate *in utero* exposures (due to maternal active smoking) from postnatal ETS exposure. The authors reported no significant effects on sperm quality, hormone levels or perceived infertility in the sample of 229 men in the follow-up study. However, among the subgroup of men not exposed to DES, there was a significant decrease in sperm motility and a significant increase in oligospermia (deficiency in the number of spermatozoa in the semen); this subgroup is probably more representative of the general population than those who were exposed to DES. Confounders other than adult smoking status of the subjects were not assessed. Compared to nonsmokers, men who smoked as adults had a significantly lower percentage of sperm with normal morphology, after adjustment for maternal smoking and DES exposure.

5.4.3 Animal Studies of Male Reproductive Toxicity and Exposure to Tobacco Smoke

No animal studies specifically examining male fertility and exposure to mainstream or sidestream smoke were located. There are some limited data on testicular pathology from chronic toxicity studies using mainstream smoke. Viczian (1968) reported disruption of the sperm cycle in male rats exposed for 15 minutes 8 times daily for 6 weeks. Dontenwill *et al.* (1973a & b) reported a higher incidence of testicular atrophy in hamsters exposed for 6 to 80 months. This effect occurred only with certain cigarettes and particular daily exposure durations. The functional implications of these results are unclear. No studies of testicular pathology using sidestream smoke were located.

5.4.4 Discussion and Conclusions

No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. A study that examined the effects of early exposure to maternal smoking (both *in utero* and postnatal ETS exposure) found significant differences in sperm motility and oligosperma in the subgroup of subjects not exposed to DES. Associations have been seen in human studies of active smoking and sperm parameters. Therefore, the findings of subfecundability in women exposed to ETS sby husbands who smoke may in fact be due to direct effects of active smoking on male reproductive capacity rather than to the effects of ETS exposure of the women.

In conclusion, due to the paucity of data it is not possible to determine whether there is a causal association between ETS exposure and male reproductive dysfunction.

5.5 CHAPTER SUMMARY AND CONCLUSIONS

Though active smoking by women has been found to be associated with decreased fertility in a number of studies, and tobacco smoke appears to be anti-estrogenic, the epidemiologic data on ETS exposure and fertility are not extensive and show mixed results. A well-controlled study in the U.S. found no association of conception delays with spousal smoking habits, contrary to the results of two Scandinavian studies which found slight increases in conception delays but were potentially more biased studies. A recent Dutch study also did not find an association, but included maternal smokers. When ETS exposure is defined as spousal smoking (as in all these studies), any association seen may be due to direct effects of active paternal smoking on male reproductive parameters. Two studies have found an association between ETS exposure during childhood and increased fecundability (in adulthood); a third study did not confirm these findings. All three studies are constrained by lack of information on potential confounders related to childhood ETS exposure. Thus, it is not possible to determine from the conflicting epidemiologic studies conducted to date whether or not ETS exposure is associated with changes in female fertility or fecundability.

One study found a strong association of early menopause with ETS exposure, which is consistent with findings of early menopause among active smokers. Another study reported a slight, non-significant decrease in age at menopause. Because the analytic methods of these two studies could not be thoroughly evaluated, more studies are needed to confirm this finding. While the effect is biologically plausible, at present there is not firm evidence that ETS exposure lowers the age at menopause or affects other measures of female reproductive dysfunction.

No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. Associations have been seen in human studies of active smoking and sperm parameters. At present, there is inadequate evidence to draw conclusions regarding the effect of ETS exposure on male reproductive dysfunction.

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Respiratory Health Effects

6.0 INTRODUCTION The relationship between ETS exposure and a variety of nonmalignant respiratory tract health endpoints has been examined extensively in the epidemiologic and experimental literature. Among children, the most common outcomes studied include asthma induction and exacerbation, alterations in lung development, and otitis media and chronic middle ear effusions in children. Among adults, endpoints of interest have included lower respiratory tract symptoms, reduced lung function, and acute irritative symptoms of the upper respiratory tract. Each of the lower respiratory tract endpoints, as well as otitis media, were reviewed in reports by the Surgeon General's Office (U.S. DHHS, 1986), the National Research Council (NRC, 1986), and most recently by the U.S. Environmental Protection Agency (U.S. EPA, 1992); upper respiratory tract irritation and sensory annoyance were reviewed in the Surgeon General's and NRC reports only. This chapter synthesizes the data considered in these prior literature reviews with results from more recent studies in order to assess the possible relationship between ETS exposure and each of the above-mentioned health endpoints.

6.1 ACUTE HEALTH EFFECTS

6.1.1 Asthma (exacerbation) Asthma is a chronic respiratory condition characterized by airway inflammation and episodic airflow limitation. Depending on the clinical definition used, about 2-3 percent of adults and up to 10 percent of children may be affected (Evans *et al.*, 1987b; Schwartz *et al.*, 1990; Gergen and Weiss, 1990; Gerstman *et al.*, 1989). Asthma is the most common chronic condition of childhood and in 1990 accounted for approximately $6.2 billion in health care expenditures nationally (CDC, 1992). No similar cost estimate is available for California; however, in the state in 1993, there were approximately 43,000 admissions to hospitals with a primary diagnosis of asthma, about 18,600 of which were for children under age 18 (personal communication: Dr. Marvin Bohnstedt, California Department of Health Services). Typical symptoms of asthma include cough, chest tightness, difficulty breathing, and wheezing. One of the hallmarks of asthma is airway hyperresponsiveness, an exaggerated tendency of the airways to constrict in response to chemical agents, such as methacholine or histamine, or to physical stimuli, such as cold, dry air.

In its recent review, the U.S. EPA (1992) concluded that, "There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children

Table 6.1
Studies Cited by U.S. EPA (1993) as Evidence Supporting a Causal Relation Between ETS Exposure and Increased Episodes and Severity of Asthma in Children

Authors	Population Studied	ETS Exposure Assessment	Outcome Variable	Results	Observations
Evans *et al.* (1987b)	191 children, aged 4 to 17 yrs. in New York, New York	Parental questionnaire	Emergency room visits and hospitalizations for asthma (from medical records)	3.1± 0.4 vs. 1.8 ± 0.3* ($p = 0.008$) emergency room visits per year in children of smoking and nonsmoking parents *mean ± standard error	No distinction made between maternal and paternal smoking; independent of race and parental employment status
O'Connor *et al.* (1987)	292 subjects aged 6 to 21 yrs. in Boston, Massachusetts	Parental questionnaire	Bronchial response to cold air	Significantly increased response in asthmatic subjects whose mothers smoked	No increase in non-asthmatic subjects whose mothers smoked
Murray and Morrison (1989)	415 children aged 1 to 17 yrs. with asthma in Vancouver, Canada	Parental questionnaire	Asthma symptom score for severity of asthma	Higher scores ($p < 0.01$) in children of smoking mothers	Stronger effect in boys and older children
Oldigs *et al.* (1991)	11 asthmatic children	Direct exposure to ETS for 1 hour	Changes in lung function	No effect	No assessment of effect of chronic exposure
Ehrlich *et al.* (1992)	228 children: 72 with acute asthma, 35 with nonacute asthma, and 121 controls	Cotinine levels in urine of children; smoking by maternal caregiver	Emergency room and asthma clinic visits	Higher levels of cotinine in asthmatic children OR = 1.9 (95% CI = 1.0-3.4)	Similar cotinine levels in acute and nonacute asthmatic children

Source: Adapted from U.S. EPA (1993), Table 7-7

who already have the disease" (p. 248). This conclusion appears to have been based on a review of several studies summarized in Table 6.1. These and additional relevant studies are described in the following pages.

6.1.1.1 Epidemiologic Evidence

Evans *et al.* (1987b) analyzed data on 276 children from low-income families receiving care for asthma at outpatient clinics of several New York City hospitals. Information on ETS exposure was obtained during interviews of the parent or guardian and the child. Data on emergency room (ER) visits and hospitalizations were obtained by reviewing records for a 1-year period; data on lung function were obtained during a random clinic visit occurring within 1 year after the interviews. Eight children who admitted to active smoking were excluded from the analysis, as were 77 other children with incomplete data. The relationships between the child's ETS exposure (as reported by the parent or guardian) and the outcome variables were analyzed by multiple-regression techniques in which the influence of up to 34 potential confounders and effect modifiers were considered, including age, gender, ethnicity, several indicators of socioeconomic status, indices of medical management, and an index of residential allergen and irritant exposure, among others. Evans *et al.* reported that ER visits were positively associated with reported ETS exposure ($p < 0.01$). The mean annual frequency of ER visits among the children exposed to ETS in the home was 3.09 ± 0.40, while that for children not exposed was 1.83 ± 0.29. Thirty-nine percent of children from nonsmoking homes made no ER visits, compared with 29 percent of children from households with smokers. In addition, 13 percent of children from nonsmoking homes made four or more ER visits, compared with 32 percent of children from smoking households.

Evans *et al.* also reported, however, that ETS exposure was not associated with either hospitalizations or with percentage of predicted lung function. While ostensibly inconsistent with the ER results, there were relatively few hospitalizations during the period of observation (191 children x 0.20 (mean) hospitalizations/child/yr ≈ 38), resulting in a low power to detect an effect. Furthermore, to the extent that nondifferential misclassification of exposure occurred (or that some smokers may have reported that they were nonsmokers), the analysis could be biased against finding an effect. Either of these types of misclassification of exposure would also tend to diminish the reported relationship between ETS exposure and ER visits. The report does not provide enough information to evaluate the lack of association of ETS exposure and lung function. The protocol for pulmonary function test (PFT) administration is not well described; for example, it is not clear whether any children were experiencing an asthma flare when tested. Here also, misclassification of exposure status could also create a bias against finding an association.

More recently, Chilmonczyk *et al.* (1993) undertook a study of similar design to that of Evans *et al.*(1987b), using more sensitive indicators of asthma exacerbations (review of medical records at a large allergy/asthma clinic) and of ETS exposure (measurement of urinary cotinine at enrollment in addition to parental questionnaire). Cotinine is the major metabolite of

nicotine and is a good integrated indicator of recent ETS exposure (1-2 days; see chapter on *Exposure Measurements and Prevalence*). Review of medical records was done by observers blinded to the children's ETS exposure status. Of the 199 children (aged 8 months to 13 years, mean ≈ 7.5 years) enrolled in the study, 145 were old enough to undergo pulmonary function testing. Whether assessed by urinary cotinine or by parental reporting, ETS exposure was found to be associated with increased frequency of asthma exacerbations in a dose-dependent manner. Using multiple-regression techniques that adjusted for the child's age, gender, daycare attendance, and the mother's age and educational level, the investigators reported relative risks for the highest versus the lowest exposure categories of 1.7 (95% CI = 1.4-2.1) for exposure assessed by cotinine and 1.8 (95% CI = 1.4-2.2) for parent-reported exposure. Pulmonary function tests reported as percent predicted FEV_1 (forced expiratory volume in 1 second—a measure of lung volume and central airway caliber) and FEF_{25-75} (expiratory flow during the middle half of a forced vital capacity (FVC) maneuver—an indicator of the caliber of the more peripheral, mid-sized to smaller airways) were decreased with increased ETS exposure in a dose-dependent manner, with urinary cotinine as the exposure indicator.

In this investigation, parental reports of no ETS exposure were consistent with the cotinine results 86 percent of the time, while the concordance of reported exposure and cotinine measurements was 77 percent. Henderson *et al.* (1989) have previously shown that cotinine levels in preschool children tend to be stable over at least a 4-week period, presumably due to regular daily patterns of ETS exposure. Ogborn *et al.* (1994) reported similar findings in children aged 3 to 11 (see below). To the extent that the single urinary cotinine measurement in the study by Chilmonczyk *et al.* was an accurate reflection of longer-term exposure, this study suggests an exposure-related chronic effect on exacerbations of pediatric asthma and on indices of lung function.

Murray and Morrison (1989) examined 419 children aged 1 to 17 attending an allergy clinic in Vancouver, British Columbia. At the initial visit, a trained interviewer administered a standardized questionnaire to the parent and the patient containing questions regarding the child's asthma history, symptoms and medication use, other respiratory illnesses, and a variety of potential residential exposures (ETS from one or both parents, whether a woodstove was used for home heating or a gas stove for cooking, the presence of cats or dogs). The children were asked privately if they were themselves active smokers: the four that admitted to this were excluded from the analysis. The investigators created an asthma severity score based on questionnaire responses. In addition, the patients had allergy testing (by skin prick), spirometry (for those ≥ 6 years old), and an examination of bronchial reactivity to histamine (in children ≥ 7 years old). Children of smoking mothers (n = 92) had more severe asthma than children of nonsmoking mothers (n = 322), as evidenced by an increased asthma score, and greater airway reactivity, as well as decreased FEV_1 and FEF_{25-75} (for all these differences, $p < 0.01$). These results were driven by the effects observed in boys; for girls, only the asthma severity score was significantly increased with smoking versus nonsmoking mothers.

Murray and Morrison found that differences between asthmatic children of smoking versus nonsmoking mothers became more pronounced with increasing age (or duration of exposure). In multivariate regressions of these indices of severity on several independent variables (recent respiratory infection, recent bronchodilator use, positive skin prick test, presence of gas stove or wood stove, and the number of cigarettes smoked at home by either parent), stratified on age and/or gender, maternal smoking repeatedly emerged as one of the two strongest predictors of asthma severity. Paternal smoking was generally without effect.

The results of this study were consistent with earlier publications by the same investigators using subsets of this study population (Murray and Morrison, 1986 and 1988). In an analysis of 240 subjects for whom data were collected as described above (for the 1989 publication), Murray and Morrison found a highly significant association between indices of increased asthma severity (here limited to airway reactivity, FEV_1, and FEF_{25-75}) and maternal smoking, with no such associations observed for paternal smoking. Hypothesizing that the children's asthma would be exacerbated during the colder, wetter months (when homes would be kept more tightly closed and children would spend more time indoors, thereby increasing the intensity of ETS exposure), they stratified the analysis by season (October through May versus June through September). They observed no differences in any of the above indices between children of smoking and nonsmoking mothers during the dry season, but found highly significant differences in FEV_1, FEV_{25-75}, and airway reactivity during the wetter months. Moreover, during the wet, but not the dry, season there was evidence of an exposure-response relationship between the number of cigarettes smoked by the mother in the home with each of these indices. These relationships were corroborated by multiple regressions of FEV_1, FEF_{25-75}, and airway reactivity on age, duration of asthma, gender, recent respiratory infection, recent medication use, positive skin allergy test, family history of asthma, presence of pets, heating type, presence of a gas range, number of siblings, and parental smoking.

More recently, Murray and Morrison (1993) expanded their analysis to include 807 nonsmoking asthmatic children and adolescents meeting the same eligibility requirements and for whom similar data were collected as in these authors' prior reports. In this analysis, they compared indices of asthma severity in children first attending the asthma clinic before July 1986 with those attending afterward. They reported that, among children with at least one smoking parent, reported daily exposures to cigarettes smoked in the same room were markedly lower after 1986 (3.4 after versus 6.6 before for smoking mothers ($p = 0.005$) and 2.0 after versus 4.6 before for fathers ($p = 0.001$)). Concomitant with this apparent decline in exposure, children of smoking parents entering the study after July 1986 had asthma that was less severe than those entering earlier, as manifested by significant improvements in the asthma score, FEV_1 and FEF_{25-75}. Among children of nonsmoking parents who enrolled after July 1986, the asthma severity score was not significantly different, but both FEV_1 and FEF_{25-75} were increased, though less so than among the children of smoking par-

ents. Improvements in pulmonary function test values occurred regardless of the smoking status of either parent; however, a significant difference in the asthma severity score was observed only among the children of smoking mothers. Modeling the spirometric indices as a function of numbers of cigarettes smoked in the same rooms as the child(ren), controlling for several relevant covariates (age, gender, age of asthma onset), Murray and Morrison found that the differences among smokers' children across the time periods decreased, which would be expected if exposure to parents' smoking is one of the etiologic factors underlying the difference. Airway reactivity showed no marked differences in before/after comparisons within either group of children. In light of the significant improvement in the other indicators of asthma severity, the lack of a significant change in airway reactivity was unexpected; the authors had no ready explanation for this anomaly other than that the persistent hyperresponsiveness of these asthmatics' airways might not have been affected by recent decreases in exposure to parental ETS.

O'Connor *et al.* (1987) examined the relationship between parental smoking and airway reactivity in 286 children, aged 6 to 21years (mean ≈ 13), in East Boston. Airway responsiveness was assessed by measuring FEV_1 before and after challenge with subfreezing air. Of the 21 asthmatic study subjects, those with smoking mothers showed a greater reduction in FEV_1 in response to cold air challenge than did those with nonsmoking mothers (24 ± 3.3 percent versus 11.9 ± 4.8 percent, respectively; $p = 0.07$). In multiple linear regression models examining cold air-induced change in FEV_1 as the dependent variable in relation to nine putative independent variables, maternal smoking emerged as a significant ($p = 0.02$) predictor of ΔFEV_1, after adjusting for predicted FEV_1. In a stepwise multiple linear regression, maternal smoking and predicted FEV_1 were the only two variables to enter the model. Paternal smoking was unrelated to bronchial responsiveness in any analysis. The small sample size of the asthmatic children and adolescents in this study limits both the statistical significance and the generalizability of the findings. Nevertheless, the trend observed in this investigation is consistent with the results reported by Murray and Morrison (1989).

Strachan and Carey (1995) reported the results of a case-control study of residential environmental determinants of severe asthma among 763 children, aged 11-16, in Sheffield, England. To be eligible, the child must have had 12 or more episodes of wheezing or at least one speech-limiting attack of wheezing (during which the child could say only one or two words between breaths). Controls who had no history of asthma or wheeze at any age were frequency matched on age and school class. ETS exposure was assessed by parental questionnaire. The analysis focused on factors in the home environment that contributed to status as a case, which was defined as having had at least 12 episodes of wheezing, one or more speech-limiting attacks, or both. The only ETS-related data pertained to three current parental smoking categories: none, 1-10, or >10 cigarettes/day. While paternal smoking was unrelated to the outcomes examined, maternal smoking of >10 cigarettes/day was significantly related to the combined category of frequent wheezing plus speech-limiting attacks (crude odds ratio

2.28, $p < 0.05$). However, in models adjusting for numerous other household factors (e.g., current and past pet ownership, type of pillow and bedding used, age of mattress, and so forth), the odds ratio for maternal current smoking was still elevated (1.49) but no longer significant. It is not clear from this report whether the investigators examined the "healthy passive smoker effect,"—*i.e.*, whether the parents of children most severely affected stopped smoking because of the children's asthma. This study examines risk factors for having severe asthma versus not having asthma at all; it does not address whether exposure to ETS or other factors influence the severity of asthma among children who already have the disease.

Household ETS exposure may affect severity of asthma in adults as well as children. Jindal *et al*. (1994) investigated several measures of respiratory morbidity in 200 never-smoking adult asthmatics, aged 15 to 50, attending an outpatient chest clinic in India. Information on ETS exposure and on various indices of asthma control during the preceding year were obtained by questionnaire during a clinic visit. ETS-exposed participants (n = 100) were defined as those who reported a minimum of 1 hour exposure/day, or 7 hours/week, for at least 1 year. Indices of asthma control included lung function measurements, the use and number of maintenance bronchodilator medications, requirement for corticosteroids (presumably orally administered, though this is not clear from the article), number of visits to the emergency department, admissions to the hospital, number of acute episodes, and number of times that the patients used parenterally administered (*i.e.*, via injection) asthma medications at home (reportedly a common practice in the study area). Pulmonary function testing was done within 24 hours of the clinic visit at which the questionnaire was administered. In comparison with a nonexposed group of 100 patients, the ETS-exposed group showed significantly lower forced expiratory lung function indices (FEV_1, FEV_1/FVC, and FEF_{25-75}). In addition, though the numbers of patients in the two groups did not differ with respect to most of the morbidity measures, the ETS-exposed group included significantly more patients on maintenance bronchodilator therapy and corticosteroids required to control symptoms. When expressed on a per-patient-per-year basis, however, all the indices in the ETS-exposed group were significantly higher, except for the numbers of hospital admissions and weeks of bronchodilator use per patient. Although not conducted or analyzed as meticulously as the investigation by Chilmonczyk *et al.* (1993, above), this report suggests that regular ETS exposure may affect control and severity of asthma in adults as well as children.

Bailey *et al.* (1990) report a primarily descriptive examination of patients served by the Comprehensive Asthma Program of the University of Alabama at Birmingham. Though the investigators apparently examined the prevalence of passive smoking among the 263 of 479 patients served by this clinic program, there were no data on ETS exposure assessment or prevalence or on the relationship of ETS exposure to asthma severity provided in the report, other than that the investigators "found no relationship between asthma severity and … passive smoking," and that "exposure at work was more common (for those who worked) than exposure at

home." This report analyzed numerous asthma co-morbidities and potential determinants of severity and asthma management, but, unlike the Jindal study, provides no information about ETS exposure assessment, and hence is difficult to evaluate.

Hong *et al.* (1994) examined the influence of numerous lifestyle and behavioral influences on indices of asthma morbidity in 787 of 1,352 eligible adult patients, aged 21-54, attending government-run asthma outpatient clinics in Singapore. Asthma morbidity was assessed by questionnaire and the dichotomous outcome variable of "increased morbidity" was designated to include, during the year preceding administration of the questionnaire, ≥1 "attack"/week (in the day or at night), ≥4 urgent care visits for asthma, ≥1 hospital admission, or ≥7 days of sick leave. Unlike the Jindal study, which undertook a quantitative assessment of the relationship between ETS exposure and a variety of indices of asthma severity, Hong *et al.* apparently collapsed their indices of severity into a single dichotomous variable, thereby decreasing substantially the likelihood of detecting any effect of ETS exposure. In addition, this study provides no detail about exposure assessment, other than that it was ascertained by questionnaire and that it was treated as a dichotomous variable. Dichotomizing ETS exposure as well would tend to bias the analysis towards the null hypothesis of no effect. These limitations, in addition to potential selection bias (fewer than 65 percent of eligible patients were included in the analysis) all limit the interpretability and generalizability of this study.

The above reports support the existence of an association of chronic or repeated ETS exposure with severity of asthma measured by a variety of indices. In several epidemiologic studies, ETS has been implicated as a risk factor for exacerbation of asthma, measured as an increase in symptoms, medication use, and clinic or emergency room visits (Evans *et al.*, 1987a; Chilmoncyzk *et al.,* 1993; Jindal *et al.,* 1994; Ostro *et al.,* 1994 (see below)). Airway responsiveness, one indicator of asthma severity, tends to be increased in asthmatic children whose mothers smoked in comparison with those with nonsmoking mothers (O'Connor *et al.*, 1987; Murray and Morrison, 1989). The results of one controlled-chamber investigation suggest that even single exposures of adult asthmatics to ETS can elicit prolonged airway hyperresponsiveness (AHR), which could provide experimental support for the epidemiological observations (Menon *et al.,* 1992). Increased airway responsiveness facilitates bronchoconstriction (and the concomitant symptoms of chest tightness, wheeze, and difficulty breathing) in response to respiratory irritants, such as ETS (NRC, 1986). The above findings support the assessment articulated by the U.S. EPA that there is sufficient evidence to support the inference of a causal relationship between ETS exposure and "additional episodes and increased severity of asthma in children who already have the disease."

Whether acute ETS exposure can precipitate a specific asthma flare is not so clear-cut, however. Ehrlich *et al.* (1992) undertook a case-control study of 72 children visiting the emergency room (ER) for their asthma, 35 children attending an asthma clinic who were not acutely ill, and 121

nonasthmatic control children. ETS exposure was assessed by questionnaire and by urinary cotinine/creatinine ratios (CCR). Using a cut-point of 30 ng cotinine/mg creatinine to distinguish exposed versus unexposed children, they found no difference in recent ETS exposure between asthmatics recruited from the ER and those from the clinic. In contrast, the ETS exposure odds ratio for all asthmatics versus controls was 1.9 (95% CI = 1.04-3.35). The mean CCR in the acute asthmatics (46.2 ± 98.3) was greater than that in the nonacute asthmatics (38.5 ± 74.1), but this difference was not statistically significant. From the questionnaire responses, there was no significant difference between acute and nonacute asthmatics in relation to maternal smoking, whereas the exposure odds ratio for asthmatics versus controls was 2.0 (95% CI = 1.1-3.4). This investigation suggests that ETS exposure is a risk factor for clinical asthma but, in this study population, may not have been a significant precipitant of asthma flares serious enough to warrant a visit to the ER. However, the investigation by Ehrlich *et al.* cannot adequately address the latter issue because of limited statistical power (<50 percent probability of detecting a two-fold exposure difference between acute and nonacute asthma), coupled with the likelihood that the children recruited from the clinic had more severe asthma (with 80 percent on daily asthma medication versus 36 percent of the ER patients).

Ogborn *et al.* (1994) also investigated whether there was an association between exacerbations of asthma and acute exposure to ETS. Data consisted of parental responses to detailed ETS exposure questionnaires and measurements of urinary cotinine obtained from children, aged 3 to 11, who were seen during a visit to the ER or primary-care clinic during an acute asthma flare and at a follow-up clinic visit after the flare had subsided. The investigators found no significant difference between mean urinary cotinine values (± standard deviation) at the acute versus the well visit (81 ± 62 ng/ml and 77 ± 57 ng/ml, respectively). Similarly, the mean CCRs at the acute versus the well visits were 93 ± 109 ng/ml and 97 ± 87 ng/ml, respectively. (Note that the mean CCR values in this study are at least twice as great as those reported in the Ehrlich *et al.* (1992) study, suggesting heavy ETS exposure.) In this population, the prevalence of household smoking was remarkably high (77 percent overall, and 63 percent among the children's mothers). However, this investigation is also limited by low power—the sample size of 56 had a power of 0.80 ($\alpha = 0.05$) to detect the change in CCR expected to result from a 20-cigarette per day change in ETS exposure. In other words, this study would have the power to detect a difference equivalent to household smokers' (or other sources of ETS exposure) reducing their consumption of cigarettes by one pack a day, over a several-week interval, with no concerted smoking cessation intervention. Thus, this underpowered study cannot address the issue of whether acute ETS exposure can provoke an exacerbation of asthma.

However, the study by Ogborn *et al.* does provide additional interesting information about the stability of CCRs over time. The acute and well visits of these children were separated by approximately 3 to 4 weeks (detailed information on the timing of the visits is not provided in the report). Among the children reported to be "exposed" to ETS, the mean

CCR was 105 ± 119 ng/ml at the ER visit and 105 ± 85 ng/ml at the follow-up visit, which is consistent with regular ongoing exposures. In addition, this study provides evidence that parents may under-report ETS exposure. Using a urinary CCR of 30 ng/mg as a cut-point for recent ETS exposure, the mean CCR levels in the children reported not to have been exposed at the acute and well visits were 41 ± 30 ng/ml and 83 ± 100, respectively.

There is suggestive recent evidence that ETS exposure may elicit acute symptoms in adults. Ostro *et al.* (1994) investigated the relationships between exposures to indoor combustion products and daily symptoms in a population of adult asthmatics residing in Denver, Colorado. This study included 164 subjects, many of whom had moderate to severe asthma, and some of whom experienced respiratory infections and asthma flares during the period of observation. This investigation also had more than 10,000 observations, which afforded substantial statistical power to detect associations with indoor exposures, including ETS. Both symptom and exposure data were recorded by the study participants in an intake questionnaire and in daily diaries over a three-month period. In multiple logistic regression models corrected for serial correlation and repeated measures, these investigators reported an odds ratios of 1.61 (95% CI = 1.06-2.46) for restricted activity days in relation to ETS exposure. They also reported significantly increased odds ratios for the occurrence of moderate to severe cough and shortness of breath, which were still elevated but no longer significant after correction for autocorrelation. However, having a smoker in the home during the course of the study corresponded to an odds ratio of 2.05 (95% CI = 1.78-2.40) for increased daily moderate to severe shortness of breath, suggesting a relationship of chronic exposure to acute symptoms as well.

The studies reviewed in this section support the previous finding by the U.S. EPA (1992) that there is "sufficient evidence…that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease." There is suggestive evidence that ETS exposure may exacerbate adult asthma. The U.S. EPA (1992) estimated that ETS exposure potentially could exacerbate pre-existing asthma in approximately 20 percent of 2 to 5 million children, *i.e.*, in 0.4 to 1 million children. Assuming that 12 percent of those children reside in California would result in estimates of 48,000 to 120,000 asthmatic children who could experience a worsening of their condition due to exposure to ETS.

6.1.1.2 Evidence from Chamber Studies

Several chamber studies have investigated potential relationships between controlled exposure to ETS and lung function and airway reactivity in asthmatic subjects. The results of these investigations are summarized in Table 6.2. Experimental exposure of human volunteers to various pollutants under controlled laboratory conditions can provide useful pathophysiological information. The principal advantages of this methodology over epidemiological studies is that exposure to the pollutant(s) of interest can, in theory, be precisely measured, and thus exposure-response relationships determined. While exposure conditions can also be controlled in animal experiments, the obvious strength

Table 6.2
Controlled Exposures of Asthmatic Subjects to ETS

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Shephard *et al.* (1979b)	14 mild to moderate asthmatics (aged 19-65; 9M/5F).	2-hr. mechanical smoke generation in a small room. Estimated TSP range = 2-4 mg/m^3; CO average estimated to be 24 ppm.	Sl. ↓ TLC and sl. ↑ FVC for ETS vs. sham exposures. 4 "sensitive" subjects did not differ from others' responses, except for sl. ↑ FEV_1.	Not measured.	3/14 SOB; 5/14 wheeze; 6/14 chest tightness; 5/14 cough. Symptoms reported ranged from trace to moderate severity.	Regular anti-asthma not withheld prior to test (13/14 subjects). One or more subjects may themselves have been smokers. Statistical methodology not described. Exposure concentrations not measured during experiment.
Knight and Breslin (1985)	6 patients with "mild to moderate asthma."	1 hr. Mechanical cigarette smoke generation.	Mean decline from baseline of 11% on ETS exposure vs. an increase of 4% on control day.	↑ with histamine on exposure vs. control days.	3/6- ↑ chest tightness; 2/6-wheeze.	Subjects and methods not well described. Exposure not well characterized. Statistical approach not described.

Table 6.2 (Continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Menon *et al.* (1991)	15 self-reported "smoke-sensitive" asthmatics, including 6 "reactors" and 9 "nonreactors" to prior ETS challenge (aged 25-51, 3M/12F); 15 self-reported "smoke-sensitive" controls with upper respiratory symptoms on exposure to ETS (aged 21-48; 5M/10F). All subjects were atopic.	2- or 6-hr. chamber exposure, with mean TSP = 1145 ±325 µg/m^3, mean nicotine = 205 ±54 µg/m^3. "Reactors" also subject to "sham" exposure in chamber without ETS. "Reactors" subsequently retested after pretreatment with a bronchodilator (albuterol), an anti-inflammatory medication (cromolyn sodium), or both.	5/6 "reactors" showed >20% ↓FEV_1 after 1-2 hr. exposure. None showed ≥20% FEV_1 after sham exposure. The 6th "reactor" showed >20% ↓FEV_1 after 6 hr. exposure. No "nonreactors" or controls experienced significant declines in FEV_1 in either 2-hr. or 6-hr. ETS exposures. Pretreatment with drugs blocked ↓FEV1 (p = 0.06 for single drug; p = 0.03 for combination)	Not tested.	Respiratory symptoms not reported. 2/3 of both asthmatics and nonasthmatics reported severe odor, nasal and eye irritation.	Reproducible reactions of "reactors" and "nonreactors" to ETS challenges separated by 2 yr. suggests existence of susceptible subgroup of asthmatics. All "reactions" required at least 1 hr. of exposure. Negative results of sham exposure of reactors reduces likelihood of "stress" or artifactual explanation of results.
Menon *et al.* (1992)	31 "smoke-sensitive" asthmatics (11M /20F); 39 "smoke-sensitive" controls with upper respiratory symptoms (17M /22F). All subjects aged 12-50; atopic.	4 hr. chamber exposure, with mean TSP = 1266 ±283 µg/m^3, mean nicotine = 226 ±49 µg/m^3.	5/31 asthmatics showed ≥20% ↓FEV_1 vs. 0/39 controls.	↑ with methacholine at 6 hr. (32% vs. 18%) and 24 hr. (29% vs. 10%), for asthmatics vs. controls.	Not reported	Prolonged AHR reported in 13% of asthmatics (2 wk. post-ETS) and in 2 subjects (1 asthmatic and 1 control) for up to 8 wk. post-exposure. Some of these may also have had ETS exposure at home or work.

Table 6.2 (Continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Wiedemann (1986)	9 mild, asymptomatic asthmatics (aged 19-30; 5M/4F). Not selected on basis of smoke sensitivity.	1 hr. chamber exposure, with mean CO = 40-50 ppm. Subjects allowed to wear goggles.	Sl. (2%) ↓FVC (p = 0.01). No change in FEV_1	Sl. ↓ with methacholine immediately post-exposure.	3/9-mild cough; eye and nasopharyngeal irritation.	No test of delayed AHR. Sl. ↓AHR of uncertain clinical significance.
Oldigs *et al.* (1991)	11 mild asthmatic children (aged 8-13, 10M/1F); not selected on basis of smoke sensitivity.	1 hr. chamber exposure, with mean TSP = 2,743 ±348 µg/m^3, mean nicotine = 397 ±78 µg/m^3, mean CO = 20.5 ±0.5ppm. During control exposure, mean TSP = 17 ±57 µg/m^3, mean CO = 0.1 ±0.3 ppm.	No significant difference before and after ETS exposure in FEV_1 or SRaw.	No significant differences with histamine challenge before and after ETS exposure.	Only eye irritation significantly different during ETS vs. control exposure.	No test of delayed AHR. 9/11 were on chronic asthma therapy, which could dampen responses to ETS. Also, 6/11 were chronically exposed to household ETS, which may affect acute response in an experimental setting.
Dahms *et al.* (1981)	10 asthmatics (aged 18-26), 5 of whom were smoke-sensitive, 10 healthy controls (aged 24-53)	1-hour chamber exposure, CO estimated at 15-20 ppm based on ↑ in subjects' carboxyhemoglobin	FVC ↓ 20%, FEV_1 ↓21.4%, FEF_{25-75} ↓19.2% in asthmatics; vs. no change to SC. ↑ in these indices among controls. Progressive linear decrease in asthmatics' PFTs with increasing duration of exposure.	Not tested.	All subjects had similar degrees of eye and nasal irritation.	Smoke exposure concentrations not measured directly. No individual-level data reported

Table 6.2 (Continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Stankus *et al.* (1988a)	21 smoke-sensitive asthmatics (aged 21-50; 5M/16F); 19/21 atopic.	2 hr. "low-level" exposure (mean particle concentration = 852 ±52 µg/m^3, mean CO = 8.7 ±1.7 ppm, mean nicotine = 180 ±44 µg/m^3) for 2 subjects. All others had 2 additional hr. "high-level" ETS exposure (mean particle concentration = 1,421 ±300 µg/m^3, mean CO = 13.3 ±3.2 ppm, mean nicotine = 439 ±121 µg/m^3).	7/21 showed ↓FEV_1 exceeding 20%, maximum decrement ≈50%.	Not tested.	Cough, dyspnea and/or chest tightness in all subjects with ↓FEV_1 > 20%. Eye irritation in all subjects; nasal congestion and headache in several.	"Reactors" and "non-reactors" showed similar responses to subsequent ETS challenge. Response to ETS not related to allergy to tobacco-leaf extract.

Table 6.2 (Continued)

Study	Subjects	Exposure	Lung Function	Airway Responsiveness	Symptoms	Comments
Magnussen *et al.* (1993)	13 atopic children with asthma (aged 8-13, 8M/5F)	1 hr. (54 min. at rest and 6 min. bicycle exercise) mean particle concentration = 3,197±665 µg/m^3, mean CO concentration = 20.2±0.7 ppm). Goggles worn to prevent eye irritation.	Transient FEV_1 ↓ (7.2% ETS vs. 3.2% in ambient air).	ETS exposure did not affect exercise-induced bronchoconstriction.	No significant symptom difference between ETS and clean air exposures.	No test of delayed AHR. 7/13 exposed to ETS at home. Poor reproducibility of symptoms between duplicate exposures.
Danuser *et al.* (1993)	10 healthy and 10 subjects with hyper-reactive airways (aged 24-51; 8M/12F), 5 of latter group had asthma, 3 additional subjects had symptoms suggestive of asthma.	Serially increasing 2-min. exposures to ETS delivered via mouthpiece. CO concentrations = 0,2,4,8,16 and 32 ppm±5%. Subjects wore nose-clips during exposures.	No effect in healthy subjects. 9/10 with AHR had ↓ FEV_1, 5/10 had ↓ FEV_1> 10%. Mean ↓ FEV_1 = -6.5% at 2 ppm CO and -8.7% at 32 ppm CO. ANOVA showed highly significant (p < 0.0001) effect of ETS on FEV_1, FVC and MEF_{50}.	Not tested.	Weak symptomatic responses, though dyspnea, cough and chest tightness increased at higher ETS concentrations.	Small likelihood of "suggestibility" because of mode of ETS delivery. FEV_1 showed decline at 2 ppm CO and a response plateau at higher concentrations. AHR to methacholine and pre-exposure pulmonary function test values did not fully predict response to ETS.

Sl. = slight, TSP = total suspended particulates, CO = carbon monoxide, TLC = total lung capacity, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, SOB = shortness of breath, AHR = airway hyperresponsiveness, SRaw = specific airway resistance, FEF_{25-75} = forced expiratory flow during middle half of expiration, ANOVA = analysis of variance.

of human chamber studies is that no cross-species extrapolation is required. On the other hand, microscopic or biochemical examination of pollutant-induced tissue damage is more limited in humans by both ethical and practical considerations. However, controlled human exposures are also subject to the following structural limitations: (1) only short-term responses to relatively brief exposures (*i.e.*, minutes to hours) can be evaluated; (2) there is often limited statistical power to detect effects, due to the typically small number of subjects; (3) controlling the experimental conditions may result in failure to capture effects found in complex real-world exposures; (4) multiple selection biases in recruiting volunteers reduce the generalizability of such studies (*e.g.,* systematic exclusion of people with a history of recent respiratory infection; relatively few studies of children, adolescents, or other potentially susceptible subgroups). It should be emphasized, however, that these limitations all tend to underestimate pollutant effects. In contrast, the use of ETS concentrations that exceed those likely to occur in most common exposure situations would tend to have the opposite effect (see Table 6-2). Given the potential shortcomings of such investigations, negative findings may in some cases reflect the constraints of study design more than biological reality.

In controlled exposure studies, volunteer subjects are exposed to one or more pollutants through a mouthpiece (oral breathing only) or in a chamber (oronasal breathing). ETS-related studies of asthmatics have mainly been conducted in exposure chambers with resting subjects. Data collected usually have included graded respiratory symptoms and a variety of indices of pulmonary function, such as the amount of air a subject can exhale in one second after a deep inspiration (FEV_1) or the lung's resistance to airflow (airway resistance (R_{aw}) or specific airway resistance (SR_{aw})). Several studies of asthmatics involving ETS exposures have also examined airway responsiveness, also known as bronchial reactivity (described below).

Chronic airway inflammation and episodic, reversible bronchoconstriction are hallmarks of asthma. Inflammation is associated with bronchial hyperreactivity or hyperresponsiveness, which refers to an exaggerated tendency of the airways to constrict when exposed to respiratory irritants or other substances. Airway hyperresponsiveness (AHR) is also observed in many persons with emphysema and bronchitis and in otherwise healthy individuals during and after respiratory tract infections and after exposure to respiratory irritants such as ozone. In general, however, such reactivity is markedly greater in asthmatics compared with nonasthmatics. Airway responsiveness to numerous stimuli can be measured in clinical studies. Methods used to induce and measure nonspecific bronchial reactivity in asthmatics include exercise or hyperventilation with cold or dry air, or inhalation of pharmacological agents (*e.g.,* histamine or methacholine). Although these pharmacological agents also cause bronchoconstriction in healthy individuals, asthmatic airways constrict at much lower exposure concentrations. AHR creates the potential for a flare or exacerbation of asthma, with heightened bronchial responses to other nonspecific airborne irritants.

The series of studies conducted at Tulane University (Stankus *et al.* 1988a; Menon *et al.*, 1991 and 1992) suggests that a substantial fraction of asthmatics with self-reported sensitivity to ETS also appear to demonstrate susceptibility by more objective means of assessment (tests of lung function and airway responsiveness). While such susceptible individuals have increased baseline AHR (as measured by methacholine challenge testing), nonspecific airway reactivity does not fully explain this sensitivity, since other asthmatics with increased AHR do not show marked reactions to ETS inhalation challenge. Although the physiologic basis for susceptibility is not well understood, the effects of exposure on such ETS-reactive and non-reactive individuals appear to be reproducible, suggesting the existence of intrinsic individual characteristics (Stankus *et al.*, 1988a; Menon *et al.,* 1991). Though these acute studies cannot replicate exposure conditions experienced by free-living subjects, the findings of increased AHR support the epidemiological studies described earlier, which indicate that repeated household ETS exposures tend to result in worse control of asthma.

Most of the ETS inhalation chamber studies show slight-to-moderate transient effects on lung function in at least some of the study subjects. In several studies, participants experienced decrements in lung function exceeding 20 percent, which would be considered clinically significant, particularly in conjunction with the occurrence of lower respiratory symptoms such as chest tightness, dyspnea, and cough. To the extent that subjective symptoms of asthma were reported, clinically meaningful respiratory symptoms were identified in some participants in several studies (Knight and Breslin, 1985; Dahms, 1981; Stankus *et al.,* 1988a; Shephard *et al.,* 1979a); however, this was clearly not a universal finding (Magnussen *et al.,* 1993; Oldigs *et al.,* 1991). AHR occurring after ETS exposure was also reported inconsistently in these studies; nevertheless, the only studies that examined delayed AHR at times that would be likely to detect the effects of an inflammatory response did find significant ETS-associated increases (Menon *et al.,* 1991 and 1992).

The controlled exposure studies do not clearly demonstrate a consistent effect of acute ETS exposure on asthmatics as a whole. As noted above, however, general design constraints in such studies militate against finding effects, *e.g.,* small sample size, systematic exclusion of potential participants who have recently been ill or those with brittle asthma, acute exposures only. Each of these studies has one or more weaknesses in design or analysis; thus, neither individually nor collectively can these investigations definitively address the issue of whether acute ETS exposure can precipitate an asthma flare. For instance, in Shephard *et al.* (1979a), anti-asthma medications were not withheld prior to the exposures in 13 of the 14 participants, a fact which may have dampened any potential effects of ETS. Several investigations involved fewer than a dozen subjects (Knight and Breslin, 1985; Wiedemann, 1986; Oldigs *et al.,* 1991); all but two of the remaining studies had fewer than two dozen subjects. In at least two studies (Oldigs *et al.,* 1991; Magnussen *et al.,* 1993), the participants were also regularly exposed to ETS at home, which could affect their responses in an acute experimental setting. Menon *et al.* (1991) indicated that at least 1

hour of exposure was needed to elicit respiratory responses, even among their ETS-sensitive subjects. Several of the chamber studies (including most of the "negative" ones) involved exposure to ETS that was limited to only 1 hour (Knight and Breslin, 1985; Wiedemann, 1986; Oldigs *et al.,* 1991; Dahms, 1981; Magnussen *et al.,* 1993; Danuser *et al.,* 1993). Moreover, there is considerable variability among asthmatics with respect to susceptibility to airborne irritants, including ETS. For instance, adult asthmatics vary at least seven-fold in their susceptibility to the bronchoconstrictive effects of sulfur dioxide, which is probably the most well-studied respiratory irritant in relation to asthma (Horstman *et al.,* 1986). Thus, even apart from differences in study design and experimental conditions, investigations of the effects of acute ETS exposure in asthmatics would be expected to produce variable results.

Finally, one criticism of ETS chamber studies has been that the characteristic odor and mucous membrane irritation make it difficult to blind the participants to the nature of the exposure (ETS versus clean air). This in turn is hypothesized to result in psychological suggestion as a cause of observed symptoms, changes in lung function, and so forth (Witorsch, 1992). Similarly, it has been argued that the physical conditions of participating in an inhalation challenge study create "stress" to which any positive results might be attributed (Witorsch, 1992). As for the latter observation, the use of control exposures, control subjects, or both are intended to provide a basis for "control" for whatever stresses are associated with the experimental procedure. Suggestibility related to the lack of blinding may theoretically augment symptomatic and physiological responses, but experimental evidence suggests that, if present, its influence is weak. In the study by Danuser *et al.* (1993), the subjects wore nose clips and had the ETS administered by mouthpiece, essentially blinding them to the differences in concentration of ETS delivered. Yet most of the symptomatic responses of the subjects with AHR, though not clinically severe, appeared to be dose-related, which would be difficult to attribute to suggestion. Urch *et al.* (1988) investigated the role of suggestibility in 40 nonsmokers, including 16 asthmatic and 24 nonasthmatic adults. Participants were exposed in an exposure chamber on separate occasions for 65 minutes to clean air ("sham"), moderate, or heavy smoke (17 and 31 ppm carbon monoxide, respectively). Though they viewed a bank of burning cigarettes outside the chamber on all occasions, the smoke was diverted during the sham experiment. These investigators reported, among other results, the occurrence of significant dose-related symptoms in asthmatics and nonasthmatics and a dose-response relationship for several measures of lung function. They also administered a battery of psychometric tests to assess the subjects' suggestibility, and found little correlation between physiological changes and indices of suggestibility. Assuming the subjects were unable to distinguish between the moderate and heavy smoke concentrations, Urch *et al.* concluded that the dose-response relationships were more likely of physiological than psychological origin, although the latter may have played a minor role in the observed responses.

In summary, although the design constraints of the chamber studies limit the interpretation of the results, they do suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure. The physiological responses observed in these investigations appear to be reproducible in both "reactors" and "nonreactors." It is unlikely that the physiological and symptomatic responses reported are due exclusively to either stress or suggestion.

6.1.2 Respiratory Infections (children)

Infections of the respiratory tract are the most common acute illness of childhood. Apart from the morbidity (and occasional mortality) attributable to respiratory infections, they also represent risk factors for asthma (both induction and exacerbation of existing disease) and possibly other chronic respiratory effects in later life (Burrows *et al.,* 1977; Gold *et al.,* 1989; Henderson *et al.,* 1992; Schroekenstein and Busse, 1988). The relationship of parental smoking to the risk of respiratory infection has been extensively investigated. It has been clearly established in nearly two dozen reports reviewed by the NRC (1986), the Surgeon General (U.S. DHHS, 1986), and the U.S. EPA (1992) that ETS exposure increases the risk of acute lower respiratory disease in young children by 1.5 to 2-fold.

The estimates of the magnitude of the effect of household ETS exposure on respiratory infections are remarkably consistent among the many studies that have examined this relationship. The effects are most marked in infants and toddlers, and are often not detectable in school children, who may be less exposed than younger children or who may have developed immunity against many respiratory pathogens. Several studies noted the existence of a dose-response relationship, where dose was measured by the number of cigarettes smoked in the household. In studies conducted mainly in Europe and North America, maternal smoking has repeatedly been found to bear a stronger relationship to respiratory illness than paternal smoking. This is likely to be due to the greater amount of time spent by mothers than by fathers with young children, enhancing the frequency and intensity of ETS exposure, strengthening the inference of a causal association. However, the series of reports by Chen (1989) and Chen *et al.* (1986 and 1988), which involved cohorts of infants with nonsmoking mothers, also found dose-response relationships with paternal smoking. The reviews by the U.S. EPA, NRC, and the Surgeon General all noted that most of these studies, while not free of all sources of bias, had adjusted for many identifiable confounding variables and found that the ETS effects were independent of sex, race, maternal age, socioeconomic status (SES), residential crowding, and number of siblings. In some studies, breast-feeding had a protective effect, as did daycare attendance, the latter presumably by decreasing exposure to parental ETS. Low birth weight increased susceptibility to ETS effects (U.S. EPA 1992). As a group, these nearly two dozen investigations are quite consistent and provide convincing evidence of an increased risk of lower respiratory illness in young children.

The discussion of the relationship between ETS exposure and pediatric respiratory illness has been adequately addressed in the reviews by the NRC, the Surgeon General, and the U.S. EPA, and therefore a *de novo* analy-

sis of the primary literature has not been undertaken. More recent published investigations support the conclusions articulated in these reviews. For example, Chen (1994) reported increased risks of hospitalization for respiratory illness during the first 18 months of life in China as follows: ORs = 2.91 (95% CI = 1.41-6.01) and 4.48 (95% CI = 2.07-9.73) among low-birth-weight infants exposed to light and heavy household smoking, respectively, and 1.40 (95% CI = 0.96-2.03) and 1.61 (95% CI = 1.08-2.41) for similar exposures among children of normal birth weight. Similarly, Robertson (1994) found an ETS-associated increased risk of hospitalization (for respiratory and other causes) during the first 6 to 10 months of life in a cohort of 1,877 infants in New Zealand (OR = 1.52, 95% CI = 1.08-2.14). In a prospective study of respiratory illness during the first two years of life in 836 Australian children, Douglas *et al.* (1994) reported that maternal smoking was associated with a significantly increased frequency of respiratory illness in the second, but not the first year of life. While each of these investigations has one or more methodological limitations, they are generally consistent with the reports discussed in the above-noted reviews. These and other recent studies support the conclusions stated in the reports by the NRC, the Surgeon General, and the U.S. EPA., that ETS exposure clearly confers an increased risk of acute lower respiratory disease in young children.

As noted above, ETS exposure in early childhood has been estimated to increase the risk of lower respiratory infection by 1.5 to 2-fold. On a national level, this magnitude of increased risk would correspond to 150,000 to 200,000 ETS-related cases of lower respiratory illness annually in children under 18 months of age (U.S. EPA, 1992). Noting that approximately 5 percent of patients with lower respiratory illness require hospitalization, the U.S. EPA estimated that 7,500 to 15,000 admissions to hospitals are attributable to ETS exposure each year in the U.S. These may be underestimates of effect, since the calculations on which they were based did not account for either exposure to paternal smoking or the likelihood of occurrence of repeated episodes of illness in regularly exposed children. If 12 percent of the population at risk resides in California, these estimates would correspond to 18,000 to 36,000 new cases of lower respiratory illness each year and 900 to 1,800 hospitalizations attributable to ETS exposure.

6.1.3 Otitis Media (children) A number of studies, cited in the preceding subsections, link passive smoking with lower respiratory tract conditions in children. The relationship between ETS exposure and childhood upper respiratory tract conditions, particularly acute and chronic otitis media, constitutes a separate area of concern. This topic has been reviewed extensively by the Surgeon General's Office (U.S. DHHS, 1986), the NRC (1986), and the U.S. EPA (1992). This section briefly summarizes the findings of the above three reports, reviews those studies not included in the reports, and explores related evidence on pathophysiology.

6.1.3.1 Background/Definitions Otitis media is the most commonly diagnosed problem in outpatient pediatrics in the United States today (Etzel *et al.*, 1992). In the context of this discussion, it is useful to consider the anato-

my and physiology of middle ear disease before reviewing the data concerning ETS as a risk factor for otitis media. The middle ear communicates with the nasopharynx via the eustachian tube. The eustachian tube acts as a barrier to microorganisms originating in the pharynx, as a pressure equalization channel, and as a conduit of drainage for secretions originating in the middle ear. Eustachian tube dysfunction of whatever etiology results in a sustained pressure differential between the middle ear and the surrounding atmosphere, with subsequent effusion of serous fluid into the middle ear. Alone, this condition is called "serous otitis media," and produces a sensation of fullness and temporarily decreased hearing. Should the serous fluid become infected (usually with bacteria), "acute otitis media" results, with pain, fever, and the potential for tympanic membrane (TM) perforation. Serious secondary complications (meningitis, mastoiditis) can also occur, as can a self-perpetuating cycle of acute and serous otitis media (Goycoolea, 1991). Chronic serous effusions, with or without intervening infections, may lead to a variety of complications, including mucoid effusion (so-called "glue ear") and stretching of the tympanic membrane ("incompetent TM" or "atelectatic TM"), each resulting in more sustained hearing loss than does simple serous otitis. Tympanic membrane perforation can result, not only in hearing loss, but also in the formation of a "cholesteatoma"—an ingrowth of squamous cells from the exterior of the TM—which, in turn, can expand and destroy the ossicles of the middle ear. Hearing loss, whether from sustained serous otitis media, mucoid effusion, atelectatic TM, TM perforation, or ossicle destruction due to cholesteatoma, can result in communication difficulties and educational impairment in children.

6.1.3.2 Epidemiologic Data The Surgeon General (U.S. DHHS, 1986) and NRC (1986) reviewed five and the U.S. EPA (1992) an additional ten studies on ETS exposure in childhood and upper respiratory tract conditions. Twelve of these 15 studies examined acute or chronic otitis media and/or middle ear effusions. These 12 studies included five case-control, four prospective, and three retrospective or cross-sectional investigations and are summarized in Table 6.3, as well as in the above three reviews. In all but three of these 12 studies, statistically significant relationships between exposure and outcome were apparent.

The reports of both the Surgeon General and the U.S. EPA expressed concern regarding potential misclassification of exposures based solely upon historical measures. Two studies (Strachan *et al.,* 1989; Etzel *et al.*, 1992) used objective measures of ETS exposure (salivary and serum cotinines, respectively), and both found a statistically significant relationship between ETS exposure and outcome. Likewise, two studies (Iverson, 1985; Etzel *et al.*, 1992) employed periodic prospective screening for middle ear disease, thus eliminating differential utilization of medical services by parents as a possible confounder. Again, both of these studies found statistically significant associations between ETS exposure and middle ear disease.

Table 6.4 summarizes an additional ten epidemiologic studies not included in the above summary reports (the Surgeon General's Office, NRC, or U.S. EPA). Several of these additional studies were problematic with

Table 6.3
Studies of Middle Ear Effusion (MEE) and Otitis Media (OM) vs. ETS Exposure Reviewed by the Surgeon General (1986), NRC (1986), or U.S. EPA (1992)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Kraemer *et al.* (1983)	case-control	76 children admitted for ear surgery for persistent MEE compared with nonotologic surgical patients. OR for ear surgery and ≥2 smokers in home = 2.8 (95% CI = 1.1-7.0).
Iverson *et al.* (1985)	prospective	337 children age 0-7 years followed in day care for 3 months with periodic tympanometry. Prevalence rate for MEE significantly associated with parental smoking, as determined by questionnaire (p <0.05).
Black (1985)	case-control	150 children referred for ear surgery for "glue ear" (secretory OM) matched with 2 controls each. Risk ratio for parental smoking = 1.64 (95% CI = 1.03-2.61).
Pukander *et al.* (1985)	case-control	264 cases of acute OM were compared with 207 non-OM outpatients aged 2 to 3 years. Significant trend in proportion of children with historical ETS exposure as a function of increasing number of lifetime OM episodes.
Fleming *et al.* (1987)	retrospective	Phone interview of 449 households. For children under 5 years old, maternal smoking was significant risk factor for upper respiratory tract infection, but not otitis media, within 2 weeks preceding interview (OR = 1.1; p = 0.82 for OM).
Tainio, *et al.* (1988)	prospective	183 infants followed from birth to 2.3 years of age. Parental smoking was significant risk factor for ≥3 OM episodes (RR = 1.7; 95% CI = 1.1-2.7). Also, a significantly higher proportion of parents of children with "recurrent" OM (≥5 episodes) smoked (p < 0.05).

Table 6.3 (Continued)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Reed and Lutz (1988)	cross-sectional	49 children with a prior history of either acute OM (n = 24) or another outpatient diagnosis (n = 25) were examined by tympanometry. OR for MEE and reported parental smoking = 2.31 ($p < 0.05$).
Hinton (1989)	case-control	115 children, age 2-11 years, admitted for ear surgery compared with 26 other ENT clinic patients and 36 children with non-otologic diagnoses. Borderline significant trend in parental smoking comparing surgical to clinic to nonotologic patients (p = 0.06).
Teele *et al.* (1989)	prospective	877 children observed from birth to one year of age, 698 to age 3, and 498 to age 7. Parental smoking was significant risk factor for acute OM in children under age one year only.
Strachan *et al.* (1989)	cross-sectional	Tympanometry and salivary cotinine samples obtained on 872 school children aged 6.5 to 7.5 years. Significant trend in OR for abnormal tympanogram (MEE) as a function of increasing salivary cotinine level.
Takasaka (1990)	case-control	67 children with OM were compared with 134 age- and sex-matched controls. While no association was reported for ETS exposure and OM, numbers were not shown.
Etzel *et al.* (1992)	prospective	132 children followed between age 6 months and 3 years with regular ear checks and semiannual serum samples. Children with serum cotinine concentrations greater than 2.5 ng/mL had a 38 percent excess of new-onset otitis media with effusion compared with unexposed children (incidence density ratio = 1.38; 95% CI = 1.21-1.56). Peak risk occurred before 24 months of age.

Table 6.4
Studies of Middle Ear Effusion (MEE) and Otitis Media (OM) vs. ETS Exposure not Reviewed by the Surgeon General (1986), NRC (1986), or U.S. EPA (1992)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Kallail *et al.* (1987)	case-control	119 school children with hearing loss on audiometry were compared with age- and sex- matched classmates. There was a nonsignificant excess of ETS exposure among the children with hearing problems who were later confirmed by physicians to have "middle ear problems."
Hinton and Buckley (1988)	case-control	70 children aged 1-11 years referred to ENT clinic (n = 26) or optometry clinic (n = 44) were screened; 100% of the former and 41% of the latter had MEE. Comparison of children with and without MEE revealed a nonsignificant excess of cases from smoking homes.
Zielhuis *et al.* (1989)	case-control (nested in prospective)	1,439 preschoolers were followed from age two to four with tympanometry at 3-month intervals. Incident cases of OM with MEE were compared with controls from same cohort. A nonsignificant excess of smoking was apparent among the parents of cases (OR = 1.11; p = 0.643).
Barr and Coatesworth (1991)	case-control	115 children aged 1.5-11.5 years who were referred for ear surgery were compared with surgical patients with nonotologic diagnoses. No difference in self-reported parental smoking habits was observed.
Green and Cooper (1991)	case-control	164 children aged 1.5-8 years who were seen in ENT clinic for ear pain and hearing loss were compared with like number of nonotologic outpatients. OR for ENT clinic attendance and self-reported maternal smoking = 1.92 (95% CI = 1.23-2.99).
Pönka *et al.* (1991)	prospective	2,216 children in daycare centers were followed for average of one year with interview determination of any medical causes of absence, as well as home ETS exposure. "No significant relationship" between historically reported OM episodes and ETS exposure (numbers not given).

Table 6.4 (Continued)

Author/Year	Study Design	Measures of Exposure and Effect/Findings
Ra (1992)	cross-sectional	87 10-month-old infants tested for hearing loss. ETS exposure at home was associated with a 4.9-fold increase in hearing loss (49% prevalence in ETS-exposed children vs. 10% prevalence in nonexposed, $p = 0.001$).
Collet *et al.* (1995)	cohort	918 pre-school children followed from birth to age four. ETS exposure determined prospectively. History of OM determined by parental questionnaire at age four. Maternal smoking of ≥20 cigarettes/day associated with increased risk of recurrent OM (defined as ≥4 occurrences) RR = 1.8 (CI = 1.1-3.0), but not with single episodes RR = 0.9 (CI = 0.6-1.4). Trend of increasing risk of recurrent OM with increasing number of cigarettes smoked. No effect of paternal smoking.
Ey *et al.* (1995)	cohort	1,013 children followed during first year of life. ETS exposure determined by questionnaire at birth and at one year. Episodes of OM determined by review of medical records. Maternal smoking of ≥20 cigarettes/day associated with increased risk of recurrent OM (defined as ≥3 episodes in 6 months or ≥4 episodes in a year): OR = 1.78 (95% CI = 1.01-3.11), but not with single episodes OR = 1.29 (95% CI = 0.74-2.24). Low birth weight (<3.5 kg) and heavy maternal smoking associated with three-fold increased risk of recurrent OM (OR = 3.29, 95% CI = 1.71-6.36). No effect of paternal smoking.
Kitchens (1995)	case-control	History of ETS exposure of 175 children (cases), aged three or younger, with MEE, recurrent OM or adhesive OM requiring tympanostomy tubes compared with 175 age-matched controls. Cases significantly more likely than controls to have household exposure to ETS (OR = 1.66, $p = 0.049$). ORs related to smoking status of primary or secondary caretakers (typically the mother and father, respectively) alone were also elevated, but nonsignificant. Within case group there was no difference in outcome between those exposed and those not exposed to ETS when followed prospectively.

respect to their study designs. For example in the Kallail (1987) study, cases and controls were not subjected to the same screening procedures. In the Pönka (1991) study, parental reporting, rather than medical records or objective surveillance, was the index of disease outcome. Nevertheless, three of the studies reported nonsignificant positive associations between ETS and middle ear disease, five reported a significant relationship, and none reported a protective effect. None of these studies utilized biomarkers of ETS exposure. The one study that used an objective measure applied on a prospective basis (tympanometry) did report a slight, but nonsignificant association (Zielhuis, 1989).

6.1.3.3 Summary of Epidemiologic Data

The Surgeon General's report (U.S. DHHS, 1986) summarized the studies as "show[ing] an excess of chronic middle ear effusions and diseases in children exposed to parental smoke." The U.S. EPA (1992) report concluded that there was "good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS," but only "some evidence [for] acute middle ear infections" (acute otitis media). While the ten studies in Table 6.4 are collectively somewhat less supportive of an association between ETS exposure and middle ear disease than those previously reviewed by the Surgeon General's Office and the U.S. EPA, the study design of some of these studies was problematic.

Ten of the 12 studies reviewed by the Surgeon General's Office or the U.S. EPA reported statistically significant relationships between ETS exposure in the home and middle ear conditions in children. Of the additional ten studies reviewed here, five showed a statistically significant relationship, three showed excesses that did not reach statistical significance, and two showed "no relationship" (in one case without numbers being presented). Overall, no studies show a protective effect (such as would be expected in at least some studies if all findings were a product of random variation). Two of three studies involving objective prospective surveillance (tympanometry or insufflation otoscopy) showed statistically significant associations, and the third a nonsignificant excess of middle ear problems with ETS exposure. Both studies involving biomarkers of ETS exposure showed statistically significant relationships between exposure and outcome. Overall, the epidemiologic data strongly support a relationship between ETS exposure in the home and either acute otitis media with effusion or serous otitis media (middle ear effusion without acute infection), particularly among children under 2 years of age. Limitations of available data on the chronicity of physical findings, as well as the differing patterns of recruitment in the various studies, make it impossible to distinguish separate relationships between ETS exposure and acute serous otitis media, chronic serous otitis media, and acute infectious otitis media.

Several reports on the relationship between ETS exposure and otitis media have been published since the earlier draft release of this chapter (Collet *et al.,* 1995; Ey *et al.,* 1995; Kitchens *et al.,* 1995). The results of these investigations (summarized in Table 6.4) are consistent with the conclusions articulated above.

6.1.3.4 Biological Plausibility Eustachian tube dysfunction (ETD) plays a central role in the pathogenesis of middle ear disease. While the U.S. EPA did not find plausible biological mechanisms for ETS-related acute otitis media, there are at least four mechanisms whereby ETS might produce eustachian tube dysfunction. These include:

1) Decreased mucociliary clearance

At least in active smokers, cigarette smoke is well known to interfere with normal ciliary activity in the tracheobronchial tree (Wanner, 1977). Intact ciliary function is important for the proper barrier function of the eustachian tube against the entrance of microorganisms (Sismanis, 1991). To our knowledge, however, there is no direct experimental evidence regarding the effects of ETS on ciliary function in the eustachian tube at this time.

2) Decreased eustachian tube patency due to adenoidal hyperplasia

Said *et al.* (1978) documented an increased prevalence of ETS exposure among children previously referred for tonsillectomy and/or adenoidectomy, and Corbo *et al.* (1989) found a similar association among children with a history of tonsillectomy and adenoidectomy, rhinitis, or snoring. While many variables may govern whether a given individual has surgery, the common denominator among these conditions is lymphoid hyperplasia and decreased upper airway patency. Adenoidal hyperplasia is a recognized risk factor for the development of otitis media (Sismanis, 1991).

3) Decreased patency due to ETS-induced mucosal swelling

Chronic pathologic changes associated with otitis media with effusion include goblet cell hyperplasia and hypertrophy within the eustachian tube (Sando *et al.*, 1991). While direct evidence of ETS-induced goblet cell pathology in the eustachian tube has not been reported to date in the literature, similar goblet cell hypertrophy has been observed in the lower airways of smokers (Richardson, 1988). Acute upper respiratory tract mucous membrane swelling due to ETS exposure is explored in some detail in Section 6.1.4 (sensory irritation).

4) Decreased patency and impaired mucociliary clearance secondary to increased frequency of viral upper respiratory tract infections (URIs)

An increased frequency of upper respiratory tract infection in ETS-exposed children was demonstrated by Fleming *et al.* (1987), and may accompany some of the lower respiratory tract illnesses documented in Section 6.1.2. Viruses are known to immobilize respiratory tract cilia and to produce vascular, secretory, and interstitial changes that compromise airway patency. URIs frequently precede development of otitis media, and experimental induction of rhinovirus infection (the "common cold") decreases upper airway patency and induces eustachian tube dysfunction (McBride *et al.,* 1989).

6.1.3.5 Dose-response and Attributable Risk Considerations

Etzel *et al.* (1992) estimated that, with the relative risk of otitis media with effusion (OME) as a function of ETS exposure peaking at 1.62 at age 18 months—and with an estimated exposure prevalence of 38 percent (North Carolina)—some 8 percent of otitis media episodes occurring between ages 6 and 24 months are attributable to ETS exposure. Iverson *et al.* (1985) calculated that for Danish children attending daycare (estimated ETS exposure prevalence, 60 percent), 15 percent of middle ear effusions (MEE) may be smoking related, with the ETS-attributable fraction actually greater in the 6-to 7-year-old group than in younger children. Strachan *et al.* (1989) computed the odds ratio for MEE in 6.5 to 7.5-year-old children as a function of a doubling of salivary cotinine as 1.14 (crude) or 1.13 (adjusted for gender and housing type). As median cotinine levels in that study varied by a factor of 25 (or 4.5 doublings) between the unexposed children and those living with at least two smokers, odds ratios as high as 1.69 were observed in the more highly-exposed children.

An estimate of yearly physician office visits for early childhood otitis media episodes attributable to ETS exposure in California can be derived as follows:

1) According to an activity study sponsored by the California Air Resources Board, 38 percent of children under age 12 years, statewide, are exposed to ETS at some time during a typical day, with an average exposure time of 202 minutes (Wiley *et al.*, 1991). Broken down by age and sex, 38 percent of boys and 28 percent of girls under age 3 years are exposed to ETS, yielding a pooled exposure prevalence of 33 percent in this age group.

2) Etzel *et al.* (1992) applied observed incidence densities among ETS- versus non-ETS-exposed children and an estimated exposure prevalence rate of 38 percent to obtain an ETS-attributable fraction of 8.2 percent for OM cases among children between ages 6 months and 2 years in North Carolina. These calculations were repeated using Etzel's data for children ≤3 years, applying California's estimated ETS exposure prevalence (p) of 33 percent for this age group. These figures yielded an ETS-attributable otitis media fraction of 11.2 percent for California children under age 3 years. Using the equation below, a standard approach to calculating attributable risk (Lillienfeld and Lillienfeld, 1980) where R is an estimate of the relative risk, we obtained an ETS-attributable risk fraction (a) of 11.1 percent, with a 95 percent confidence interval of 6.5-15.6 percent.

$$a = p(R - 1) / (p(R - 1) + 1)$$

3) Data from the National Ambulatory Medical Care Survey (NAMCS) indicates that otitis media is the most common outpatient pediatric diagnosis nationwide (accounting for approximately 18 percent of all office visits for children under age 5 years). As of the most recent survey, OM was cited as the principal diagnosis for 102 office visits per 100 children (under 2 years of age) per year in 1990; and for 48 office visits per 100 children aged 2-5 years (Schappert, 1992).

4) In 1990, California had a population of 1,452,250 children under age 3 years (US Department of Commerce, 1992). Of these children, 424,303 were under age 1 year, 524,558 were 1-2 years, and 503,389 were in their third year of life.

5) Assuming that ETS-related otitis media episodes generate the same number of total (initial + follow-up) visits as do non-ETS related episodes, one can combine Etzel's data (pertaining to incident cases of otitis media) and the NAMCS data (pertaining to OM-related office visits—both initial and follow-up). The resulting figure may be an underestimate, since ETS usually constitutes an ongoing insult to normal eustachian tube function, in contrast to such events as viral upper respiratory tract infections.

Combining the above data, one obtains an estimate of almost 135,000 (95 percent confidence limits, 78,615-188,676) office visits per year among California children under age 3 years for ETS-attributable otitis media episodes:

Population Description	Population at Risk	×	Age-specific Otitis Media Visit Rate	=	OM-Related Office Visits	×	ETS Attributable Fraction	=	ETS-Attributable Visits/Year
Age ≤2 yr.	948,861	×	102/100	=	967,838				
Age 2-3 yr.	503,389	×	48/100	=	241,627				
					1,209,465	×	0.111	=	134,251 (95% CI: 78,615-188,676)

At the national level, this would roughly correspond to 700,000 to 1.6 million physician office visits annually, assuming approximately 88 percent of U.S. children under age 3 reside outside California.

6.1.4 Sensory Irritation and Annoyance

A substantial body of literature addresses the acute and reversible irritative effects of ETS on the upper respiratory tract. Symptoms subsumed in this category include eye, throat, and nasal irritation, rhinorrhea, nasal congestion, hoarseness, and odor "annoyance." ETS-related irritant and annoyance effects were reviewed in both the Surgeon General's and NRC reports (U.S. DHHS, 1986; NRC, 1986), and more recently by Samet *et al.* (1991). In the period since these reports were written, additional insight has been gained into the pathophysiology of upper airway irritant responses, and progress has been made in developing objective methods to validate ETS-related symptom complaints. In this section we will first review exposure dynamics and pathophysiology before considering the newer epidemiological and experimental literature. Note, however that whereas ETS is frequently dealt with as a general cofactor in the study of indoor air quality, this literature review has been restricted to studies in which ETS effects are examined directly.

6.1.4.1 Exposure Dynamics As noted in the chapter on *Exposure Measurements and Prevalence*, ETS consists of a complex and dynamic mixture of particulate and vapor-phase constituents. Both odor and irritation associated with ETS appear to derive predominantly from the vapor, rather than particulate phase (Hugod, 1984; Weber, 1984; Samet, 1991). The chemical constituents of ETS thought to be responsible for sensory irritation include organic acids (acetic, proprionic), aldehydes (formaldehyde and acrolein), nicotine, ammonia, pyridine, toluene, sulfur dioxide, and nitrogen oxides, among others (U.S. DHHS, 1986; Ayer and Yeager, 1982; Triebig and Zober, 1984).

The predominant site of deposition of various respiratory tract irritants is thought to be governed by two factors, particle size (for irritants adsorbed to particulates) and water solubility (for gaseous organics and vapor-phase inorganics). In general, the larger the particle or the more water soluble the compound, the higher the proportion of the inhaled dose that is likely to be deposited in the upper respiratory tract, particularly during nasal breathing. Of note, many of the gaseous and vapor phase irritants in ETS have sufficient water solubility to be active on the upper respiratory tract—*i.e.*, nasal cavity, nasopharynx, and hypopharynx (U.S. DHHS, 1986).

Selected investigators have examined the human sensory and reflex respiratory response to specific ETS constituents. Kendal-Reed *et al.* (1996) demonstrated reflex changes in respiration (decreased tidal volume) among human volunteers exposed briefly (15 seconds) to propionic acid vapor at concentrations of 0.12-85 ppm. Walker *et al.* (1996) examined the olfactory and irritant (trigeminal) properties of nicotine in both humans and experimental animals. The investigators pointed out that, on a part-per-million basis, nicotine was more potent than acetic acid, propionic acid, or amyl acetate in eliciting olfactory sensation (in subjects with a normal sense of smell) and subjective nasal irritation (in subjects lacking the sense of smell). The investigators were able to corroborate their estimates of the relative stimulatory potencies of these compounds by obtaining electrophysiologic recordings from the trigeminal nerve in rats, finding a 15 to 60-fold lower response threshold for nicotine versus the other study compounds.

6.1.4.2 Pathophysiology ETS stimulates the sensory apparatus of the upper respiratory tract through four neurological pathways: the olfactory, trigeminal, glossopharyngeal, and vagus nerves (cranial nerves I, V, IX, and X). The olfactory nerve is responsible for the sense of smell and projects to areas of the primitive forebrain responsible for emotional arousal, including the amygdala and portions of the frontal and temporal lobes. The nasal and oral cavities are innervated by the trigeminal nerve, the nasopharynx by the glossopharyngeal nerve, and the oropharynx and hypopharynx by the vagus nerve; these nerves project to various areas of the brainstem. The trigeminal, glossopharyngeal, and vagus nerves are responsible for the perception of touch, temperature, and sensory irritation (or what has been termed the "common chemical sense") in all head and neck mucosae. The two nasal senses—olfaction and irritant chemoreception—as well as the related sense of taste, functionally interact to produce an integrated impres-

sion of one's chemical environment (Cain, 1974; Cain and Murphy, 1980; Frank and Rabin, 1989).

The olfactory epithelium occupies a total area of approximately 5 cm^2 bilaterally in the upper reaches of the nasal cavity. The olfactory apparatus is variably stimulated during normal relaxed nasal breathing; "sniffing," or attentive smelling, creates eddy currents which facilitate the delivery of odorant molecules to the olfactory epithelium. Odorant molecules diffuse through the nasal mucus layer, probably aided by an odorant binding protein, to make contact with receptor sites on olfactory receptor cells (Pevsner *et al.*, 1988). The olfactory receptor cells are the only neurons known to regenerate on a regular basis; this may constitute a functional response to the fact that olfactory receptor cells are directly exposed to a variety of environmental insults (Frank and Rabin, 1989).

In contrast to the limited distribution of olfactory receptor cells, trigeminal nerve endings are located throughout the nasal and oral cavities, as well as the nasopharynx, oropharynx, and hypopharynx—the vagus nerve innervates the lower respiratory tract, including the trachea, and tracheobronchial tree. Trigeminal fibers carry sensory information of a variety of types; of primary interest here is the chemosensory function of irritant perception. The nerve fiber type thought to be responsible for mediating airborne chemical irritation (both in the upper and lower respiratory tract) is the small-diameter, unmyelinated, capsaicin-sensitive C fiber (Lundberg *et al.*, 1988 and 1991; Silver, 1992), although A_2 (delta) fibers have also been implicated in some studies (Hummell *et al.*, 1992).

Important for purposes of understanding the upper airway response to ETS is the fact that trigeminal stimulation can activate both long and short reflex arcs ("neurogenic reflexes"). The long reflex arc involves the trigeminal nerve for the afferent (perceptual) limb and the facial nerve (cranial nerve VII) for the efferent (effector) limb. Exposure to intense irritants anywhere within the nasal or oral cavities produces reflex rhinorrhea and lacrimation via a long reflex arc, autonomic (cholinergic) response. On provocative irritant testing (*e.g.,* after ingestion of horseradish or inhalation of ammonia), subjects typically experience subjective nasal stuffiness and rhinorrhea and have acute increases in nasal airway resistance, dilation of vessels within the nasal mucosa, and increased content of plasma and glandular proteins in nasal secretions (Raphael *et al.*, 1991; McLean *et al.*, 1979). This response is mimicked by local instillation of methacholine (an acetylcholine analog), and is blocked by pretreatment with atropine (an acetylcholine antagonist).

For mild to moderately intense irritant stimuli, local reflexes may predominate over the above-described long-arc autonomic response. The so-called "axon" reflex is a local reaction in which neuropeptides (vasoactive peptides including substance P, neurokinin A, gastrin-releasing peptide, and calcitonin gene-related peptide) are released near the mucosal surface. Interestingly, this reflex involves the sensory limb of the nerve only, and is analogous to the so-called "wheal and flare" reaction observed upon mechanical stimulation of the skin. Depending upon the specific peptides

involved, these mediators produce some combination of engorgement of blood vessels, transudation of fluid and plasma proteins into tissues, stimulation of secretions, and migration of inflammatory cells (Baraniuk and Kaliner, 1990; Lundberg *et al.*, 1991; Silver, 1992; Widdicombe, 1990). Apparent cross-species differences in both the distribution of mediators and their physiological effects have posed a challenge to researchers attempting to understand the axonal response in the human airway (Bascom *et al.*, 1991). Newer studies of airway responses to ETS should be viewed against a background of more traditional methods in irritant toxicology. Animals exposed to highly water soluble upper respiratory tract irritants reveal predictable changes in respiratory pattern, including slowing of respiration, sneezing, coughing, and increased secretions (Alarie, 1973). In humans, the analogous respiratory pattern is an involuntary pause during inspiration or frank breath-holding (Cain *et al.*, 1987a). Exposure levels necessary to produce these responses, however, are generally high, and researchers in the field of indoor air quality and ETS have searched for more sensitive indices of respiratory tract irritation. As noted below, evidence of true allergic (IgE-mediated) upper airway reactions to ETS is quite limited.

6.1.4.3 Specific Health Effects

Definitions

For discussion purposes, "sensory irritation" refers to subjectively reported tingling, stinging, burning, or pain involving the mucous membranes of the upper respiratory tract and/or cornea (in humans), or to (unconditioned) aversive responses to an airborne chemical agent in experimental animals. When associated reflex physiologic alterations are present (*e.g.*, changes in airway caliber, respiratory behavior, or blink rate), they are so indicated. "Pathological irritation" refers to irritant-related changes in tissue structure and/or biochemical function including necrosis, mucosal desquamation, vascular congestion, cellular infiltration, and/or release of inflammatory mediators.

Eye Irritation

In several questionnaire studies, subjective eye irritation was the most commonly reported upper respiratory tract symptom among nonsmokers exposed to ETS (Bascom *et al.*, 1991; Basu *et al.*, 1978; Shephard, 1979b; Speer, 1968; White *et al.*, 1991). The cornea is richly innervated with trigeminal nerve endings that are sensitive to both mechanical and chemical stimuli, and blinking occurs reflexively in response to corneal stimulation. Experimentally, Weber *et al.* (1976, 1984, 1987) and Muramatsu *et al.* (1983) exposed volunteers to progressively increasing concentrations of ETS; as exposure duration and intensity increased, subjects began to report subjective eye irritation, and blink rate also increased. In another human experimental study, researchers measured precorneal (tear) film breakup time, using fluorescein dye both pre- and post-exposure to ETS. A significant decrease in tear-film breakup time occurred after ETS exposure—*i.e.*, the tear film was less stable after ETS exposure (Basu *et al.*, 1978). Both blinking and lacrimation act as protective responses to airborne irritants by restoring the protective tear film and diluting any chemical insult. The literature on ETS-induced eye irritation was reviewed in greater detail in the Surgeon General's report (U.S. DHHS, 1986, pp. 234-238).

Nasal Irritation Bascom *et al.* (1991) and Willes *et al.* (1992) identified a subgroup of research subjects who reported a variety of nasal symptoms (congestion, rhinorrhea, sneezing, and postnasal drip) upon prior exposure to ETS. This group comprised approximately one-third of their study population, and were labeled the "historically ETS-sensitive" subgroup in the authors' subsequent provocative testing protocol. Using a climate-controlled exposure chamber, the investigators conducted sidestream tobacco smoke (STS) challenge testing, examining a variety of endpoints. As a group, historically ETS sensitive, but not ETS non-sensitive, subjects showed significant increases in nasal airway resistance (NAR) by rhinomanometry after 15-minute exposures to STS at levels chosen to simulate a smoking lounge. These changes in objectively measured NAR paralleled the onset of symptoms of nasal stuffiness and rhinorrhea. Although the symptoms described above resemble those of allergic rhinitis, the authors noted that only a small proportion of historically ETS-sensitive subjects have positive skin test reactivity to tobacco-leaf extract (see review of tobacco allergy in Stankus *et al.*, 1988b). To investigate the mechanism(s) underlying the responses they observed, Bascom *et al.* (1991) performed nasal lavage pre- and post-STS exposure. Although allergy-like nasal symptoms were provoked acutely, traditional markers of allergic nasal response (including histamine, various kinins, and albumin) were not found to be increased post-exposure. These findings were taken as evidence that acute nasal responses to STS/ETS may occur via non-allergic, irritative mechanisms (see discussion of neurogenic reflexes, above). Despite a lack of evidence for direct allergic mechanisms, individuals who display both subjective and objective ETS sensitivity are more likely than non-responders to have documented non-tobacco allergies, implying a modulatory effect of allergy upon the irritant chemoreceptive system (Bascom, 1991 and 1992; Cummings *et al.*, 1991).

Alteration of Sensory Thresholds Cigarette smoking has the ability to change apparent chemosensory sensitivity to airborne odorants and irritants; in at least one case, these observations extend to passive smokers. Ahlstrom *et al.* (1987) tested smokers, nonsmokers, and passive smokers for odor acuity to n-butanol and pyridine (the latter being a constituent of tobacco smoke). Both active and passive smokers reported lower perceived odor intensities (*i.e.*, were less sensitive) than nonsmokers. Cometto-Muñiz *et al.* (1982) and Dunn *et al.* (1982) examined the endpoint of altered respiration (reflex transitory inspiratory pause) as a measure of nasal irritant sensitivity. Both studies reported higher irritation thresholds (*i.e.*, lower sensitivity) among smokers versus nonsmokers exposed to a non-odorant stimulus (high-level carbon dioxide). This finding was recently replicated using a CO_2-detection threshold as the endpoint of interest (Shusterman and Balmes, 1997). On the other hand, Kjaergaard *et al.* (1990 and 1992) exposed smokers and nonsmokers to carbon dioxide by mask to determine eye irritation thresholds, and found no appreciable difference in sensitivity between the two groups. No published studies were identified which examined trigeminal irritant thresholds among passive smokers.

A number of mechanisms could explain observed sensory shifts in active and passive smokers. Decreased odor acuity among smoke-exposed

individuals could result from increased nasal secretions, which in turn would pose an increased diffusion barrier to odorant molecules. Alternatively, habituation (in effect, ignoring the stimulus) may explain the odor perception findings; Ahlstrom *et al.* (1987) emphasized the latter possibility because passive smokers did not differ from nonsmokers in the number of "zero intensity" responses given. Shifts in irritant thresholds could result from depletion of neuropeptides in trigeminal sensory fibers; this phenomenon has been documented after high-level treatment with capsaicin, the irritant constituent in hot peppers (Lundberg and Saria, 1983). As noted above, however, irritant thresholds have not been studied among passive smokers to date.

Odor "Annoyance" "Annoyance" is a subjective state of displeasure resulting from a defined environmental stimulus. In the context of ambient (outdoor) air pollution, citizen reactions to unpleasant odors are responsible for the majority of publicly initiated complaints to air quality management districts in California, and provide the rationale for a significant fraction of so-called "nuisance" abatement actions. ETS contains a number of odorant compounds (*e.g.,* pyridine) which are typically described as unpleasant. It is not surprising, then, that even in the absence of eye, nose or throat irritation, nonsmoking citizens often complain of annoyance from the odor of ETS in indoor settings. This endpoint has been discussed extensively in the National Research Council report (NRC, 1986, pp. 166-181) and by Samet *et al.* (1991, pp. 152-160). In addition to annoyance, indoor air quality researchers have shown that unpleasant odors detract from the sense of well-being of building occupants and, at times, interfere with concentration and productivity (Rotton, 1983; Knasko, 1992)).

Cain *et al.* (1983) demonstrated that nonsmokers, on the average, are more likely than smokers to complain of an offensive odor when exposed to a given dilution of smoke-contaminated indoor air. They also showed that when smokers and nonsmokers occupy the same air space, air dilution rates required to render odorant levels acceptable to nonsmokers may be unrealistically high from an engineering standpoint. The practical implication of these findings is that apparently a strict no-smoking policy or segregation of smokers into areas with separate, nonrecirculating air supplies may be necessary in order to protect nonsmoking building occupants from annoyance and associated effects.

6.1.4.4. Dose-Response Considerations Cain *et al.* (1987b), using a climate-controlled exposure chamber, found that 10 percent of nonsmoking subjects complained of unacceptable air quality (either due to eye irritation or odor annoyance) when ETS raised carbon monoxide (CO) levels by 2 ppm over background, and over 20 percent expressed dissatisfaction at 5 ppm over background. Muramatsu *et al.* (1983) reported that nearly 30 percent of experimental subjects had complaints of moderate-to-severe eye irritation with ETS-derived CO levels 2.5 ppm over background. By comparison, CO levels can reach up to 10 ppm over background in smoking-permitted offices (average, 2.5-2.8 ppm), and as high as 29 ppm (average, 4.8-17 ppm) in taverns (Triebig and Zober, 1984). Although most experimental work on

sensory annoyance has been performed using CO as an index of ETS exposure, some investigators believe that CO is an insensitive and unreliable surrogate measure for irritant and odorant exposure (Chapelle and Parker, 1977).

6.1.4.5. Summary ETS exposure produces a variety of irritative symptoms involving the upper respiratory tract; increasingly, these endpoints are able to be objectively documented and quantified. In addition to irritation, odor annoyance may detract significantly from subjective well-being and productivity among building occupants. Experimental studies conducted by investigators familiar with building ventilation practice suggest that, short of prohibiting indoor smoking, protection of nonsmokers against both sensory irritation and odor annoyance can only be achieved through relatively extreme engineering measures.

6.2 CHRONIC HEALTH EFFECTS

6.2.1 Asthma (induction)

There is considerable evidence that continuing exposure to cigarette smoke results in the induction of asthma in children. Two large cross-sectional studies involving a total of about 8,000 children and adolescents resulted in odds ratios of approximately two for the presence of asthma with parental smoking (Burchfiel *et al.,* 1986) or maternal smoking of greater than 10 cigarettes a day (Weitzman *et al.,* 1990). In a longitudinal investigation of asthma incidence among 774 children up to 5 years of age at entry, Martinez *et al.* (1992) reported a relative risk of 2.5 (95% CI = 1.4-4.6) when maternal smoking exceeded 10 cigarettes/day and the mother had at most a high-school education. Another prospective study of 770 school children, however, found no effect of maternal smoking on asthma prevalence at the inception of the study or on incidence during 11 years of follow-up (RR = 1.1, 95% CI = 0.7-1.7; Sherman *et al.,* 1990). The U.S. EPA (1992, pp. 7-51) reviewed these and other studies and stated that, "The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association but is not conclusive."

To investigate the relationship between ETS exposure and childhood asthma more thoroughly, a meta-analysis of studies purporting to examine this issue was undertaken. A MEDLINE search was conducted to identify all epidemiologic studies published between 1975 and 1995 examining ETS exposure as a risk factor for the induction of childhood asthma. Sixty-eight studies were identified as potentially relevant. Studies were selected for inclusion if they met the following four criteria. First, the endpoint studied must represent the development of asthma in persons ≤18 years of age. Because of difficulties related to the diagnosis of asthma, particularly in young children, studies that examined outcomes of "wheezy bronchitis" or "constant wheeze/whistling in chest" were also included and analyzed both separately and jointly with those studies which examined only physician-diagnosed asthma. Second, the exposure studied must represent postnatal household sources of ETS. While studies were not excluded for failure to evaluate separately the effects of post- and prenatal exposures, they were excluded if they only examined *in utero* exposures to ETS. Third, odds

ratios or relative risks must be reported or sufficient data must be presented to allow for calculation of risk ratios and estimates of their standard errors. Lastly, studies must be independent. If more than one study reported on the same cohort of children, then the study that best met the previous three criteria was selected for inclusion.

Thirty-one studies were excluded for failure to meet one or more of the inclusion criteria (see Table 6.5). Risk ratios and standard errors were extracted from each of the remaining 37 studies or were calculated using formulae given by Greenland (1987).

The random-effects model proposed by DerSimonian and Laird (1986) was used for this analysis. Under the DerSimonian and Laird model, a pooled risk ratio (pooled RR) is calculated as a weighted average of the risk sizes reported by each study. Each study is weighted by a factor equal to the inverse of the variance of the true underlying effect size (estimated by the among-study variance (t^2) added to its own within-study variance (s^2)). Because significant among-study variance was detected, potential sources of heterogeneity by subset analysis and linear meta-regressions were evaluated. Indicator variables were created *a priori* to characterize study design (case-control, cohort, or cross-sectional), exposure metric (level and method of measurement), outcome metric (wheeze or asthma), method for identifying cases (parental reporting or medical record extraction), year of publication, age of study participants (preschool, school-age, or all ages), location (North America, Europe, or elsewhere), and covariates controlled for in the analysis (age, sex, socioeconomic status, family history of atopy/asthma, reporting of parental respiratory symptoms, early childhood respiratory illness, history of breast-feeding, and in studies involving children older than 10 years of age, the children's own smoking habits). These indicator variables were then used in the subset and meta-regression analyses to explore sources of heterogeneity.

Of the 37 studies included in this analysis, all but three reported a risk ratio (RR) greater than 1.0, albeit many were not statistically significant at $\alpha = 0.05$. The pooled RR for those studies with clinically diagnosed asthma as the outcome was 1.44 (95% CI = 1.27-1.64) and did not significantly differ from that of studies examining "wheezy bronchitis" or "chronic wheeze/whistling in chest" (pooled RR = 1.47, 95% CI = 1.34-1.61; See Figures 6.1 and 6.2). Subset analyses revealed several potentially important sources of heterogeneity. Significantly higher pooled estimates of risk were derived from the subset of case-control studies that used population-based controls (pooled RR = 2.43, 95% CI = 1.67-3.53) and the subset of studies of preschool children in North America or Europe (pooled RR = 2.00, 95% CI = 1.58-2.54). There was little evidence of heterogeneity in either of these groups. Both subsets, however, consisted of relatively few studies. Stratifying the data on other study characteristics yielded pooled RRs ranging from 1.14 to 1.86. The subset analyses substantially reduced the inter-study heterogeneity, but did not eliminate it.

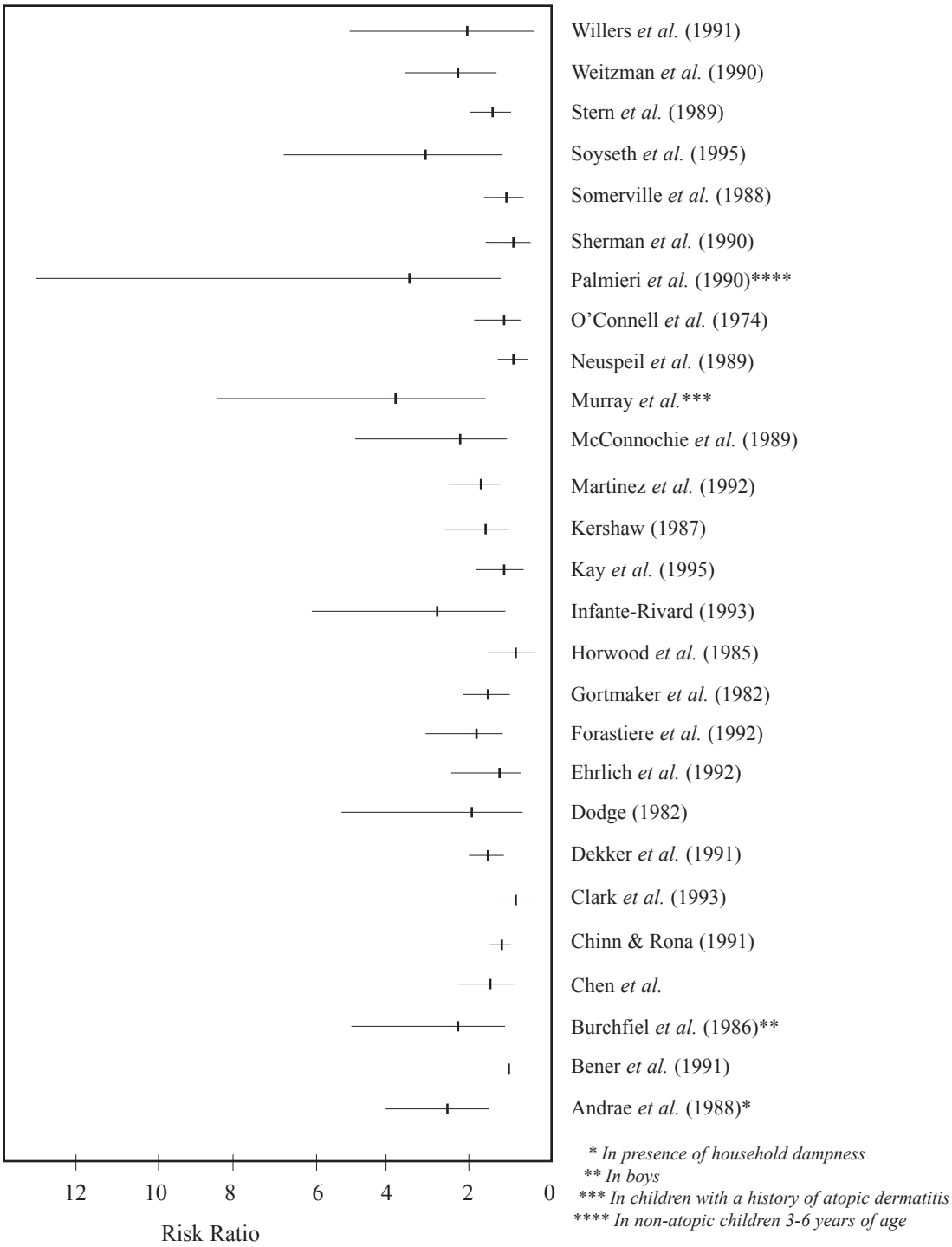
Because substantial heterogeneity persisted even after the subset analyses, linear meta-regressions were fit to evaluate the influence of the

Table 6.5
Studies Excluded from Meta-Analysis of ETS and Childhood Asthma Induction

Study Author (year)	Reason for Exclusion of Study
Chen *et al.* (1986) Chen (1989) Leibowitz & Burrow (1976) Pedreira *et al.* (1985) Kerribijn *et al.* (1977) Wittig *et al.* (1978)	Did not specifically analyze asthma or wheezing as outcome; lumped asthma/wheeze together with other respiratory illnesses of childhood
Chilmoncyk *et al.* (1993) Evans *et al.* (1987) Murray & Morrison (1993) Ogborn *et al.* (1994)	Examined exacerbations of symptoms in asthmatic children (rather than prevalence or incidence)
Frischer *et al.* (1992) Cunningham *et al.* (1994) Rona & Chinn (1993) Tager *et al.* (1993) Young *et al.* (1991)	Used lung function as the outcome measure
Anderson *et al.*(1987) Holberg *et al.* (1993) Leeder *et al.* (1976) Peat *et al.* (1980) Stanhope *et al.* (1979) Wilkie *et al.* (1995) Lebowitz *et al.* (1990)	Did not specifically address household sources of postnatal ETS exposure
Shilling *et al.* (1977) Jin & MacKay (1993) Schenker *et al.* (1983) Tominaga & Itoh (1985) Tsimoyianis *et al.* (1987) Toyoshima *et al.* (1987)	Insufficient presentation of data (*i.e.*, odds ratios, relative risks or sufficient data to allow for calculation of risk ratios and estimates of their standard errors were not included)
Lewis *et al.* (1985) Fergusson *et al.* (1985) McConnochie & Roghmann (1989)	Redundancy with other studies

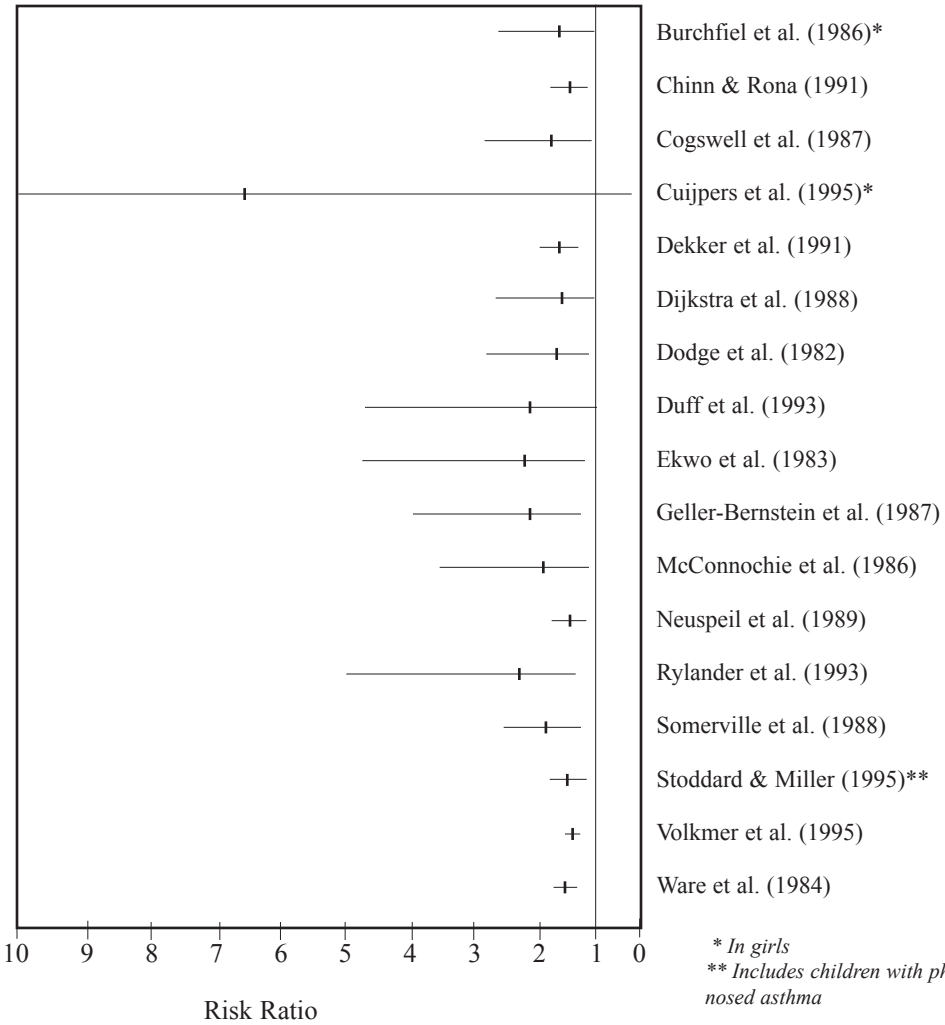
study characteristics simultaneously. This multivariate approach identified several additional sources of heterogeneity. Studies of preschool children yielded approximately 50 percent higher risk ratios than those that included older children. Studies that adjusted for gender also tended to yield significantly higher risk estimates than those that did not. Furthermore, while studies controlling for a family history of atopy did not yield significantly different estimates of risk than those studies that did not, limiting the study population to atopic children or to children with a family history of atopy

Figure 6.1
Reported Risk Ratios and 95% Confidence Intervals for Studies that Used Clinically Recognized Asthma as an Outcome



* *In presence of household dampness*
** *In boys*
*** *In children with a history of atopic dermatitis*
**** *In non-atopic children 3-6 years of age*

Figure 6.2
Reported Risk Ratios and 95% Confidence Intervals for Studies that Used "Wheezing Bronchitis" or "Chronic Wheezing/Whistling in the Chest" as an Outcome



** In girls*
*** Includes children with physician-diagnosed asthma*

yielded approximately 60 percent higher estimates of risk. The overall fit of the model was reasonably good (p = 0.40), indicating little evidence of unmodeled heterogeneity.

Though the meta-analysis was not restricted to studies examining only maternal exposure, OEHHA compared the pooled estimates for asthma RRs for studies in which there were separate estimates for maternal smoking versus those for general household smoking. When exposure was related to maternal smoking the pooled RR was 1.60 (95% CI = 1.29-1.99), while that for household smoking generally was 1.34 (95% CI = 1.11-1.61).

The smoking status of the children being studied was a commonly omitted and potentially important confounder in the studies included in this analysis. To evaluate the influence of this factor on the pooled RRs, the analysis was repeated excluding studies involving children who were 10 years of age or older that did not control for the children's own smoking. This did not change the results, although the confidence intervals became slightly wider (pooled RR = 1.48, 95% CI = 1.28-1.71).

OEHHA staff also undertook an influence analysis, in which one study at a time was dropped, and the pooled RRs were re-estimated. No single study had a significant effect on the pooled estimates.

Most studies relied on crude measures of ETS exposure, *i.e.,* parental reporting of the presence of household smokers or the estimated number of cigarettes smoked in the home. Four studies, however, reported risk ratios in relation to exposures assessed by measurement of salivary or urinary concentrations of cotinine as well as by parental reporting (Clark *et al.*, 1993; Duff *et al.*, 1993; Ehrlich *et al.*, 1992; Willers *et al.*, 1991). In all four, the estimated risk ratios associated with exposure to ETS were higher when exposure classification was based on cotinine levels rather than on parental reporting and produced a pooled RR of 2.52 (95% CI = 1.61-3.95). Because this estimate was based on only four studies, it combined the outcome categories of wheeze and clinical asthma.

The results of this meta-analysis indicate a strong and consistent association between exposure to ETS and development of childhood asthma. This relationship persisted throughout various influence and sensitivity analyses. As anticipated, there was significant heterogeneity of results across studies. The subset and meta-regression analyses revealed several important sources of heterogeneity related to elements of study design, particularly with respect to exposure assessment.

The studies reviewed by U.S. EPA (1992) and those published subsequently indicate that ETS is clearly a risk factor for induction of asthma, particularly in young children. To discriminate between causal and non-causal associations, Hill (1965) listed the following considerations: strength of the association, consistency in results among different studies, the existence of a biological gradient or dose-response, an appropriate temporal sequence between the effect and its putative cause, "coherence" with existing knowledge of the natural history of the disease, and biological plausibility (which is often closely related to, if not indistinguishable from, "coherence"). Other criteria for causal inference listed by Hill (1965) are either obsolete ("specificity") or superfluous in this instance ("analogy" and "experimental evidence"). As can be seen in Figures 6.1 and 6.2, most of the estimates of relative risk extracted from the investigations were statistically significant. Of the 37 studies included in the meta-analysis, 14 had point estimates greater than 2.0, suggesting a strong association between ETS exposure and the occurrence of childhood asthma ("strength of association"). The effect estimates tend to be higher in those studies involving pre-school-aged children and in those that used more precise measures of exposure. Recognizing the heterogeneity indicated during the process of

creating pooled estimates in the meta-analysis, almost all studies had point estimates of relative risk significantly greater than one, and most were statistically significant, whether the outcome was clinically diagnosed asthma or wheezy bronchitis. If there were no relationship between ETS and childhood asthma, one would expect a random distribution of point estimates above and below the null value. This consistency is apparent despite the diversity of study designs and populations ("consistency").

There appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the mother smoked 10 or more cigarettes per day (*e.g.,* Martinez *et al.* 1992). This finding suggests that a threshold of ETS exposure intensity is required in order to evoke this response. The temporal relation between childhood asthma and parental smoking is not at issue here, since asthma in children is unlikely to precede active smoking by their parents. However, it might be argued that, since the association seems to be strongest between maternal smoking and asthma prevalence in pre-school children, the key exposures may have taken place *in utero*. Several recent studies suggest that prenatal exposures may cause persistent decrements in lung growth and development (Cunningham *et al.* 1994 and 1995; Hanrahan *et al.* 1992). It is possible that prenatal effects may play a role as well in the etiology of childhood asthma. However, the studies by Chen (1986, 1988, 1989), showing effects of paternal smoking alone, as well as studies of ETS exposure linked to increased risks of asthma in non-smoking adults (Leuenberger *et al.,* 1994), indicate that postnatal exposures can be sufficient to elicit this outcome. Development of asthma as a result of ETS exposure is "coherent" with other investigations demonstrating that both active and passive exposure to cigarette smoke are associated with increases in airway responsiveness, which (as noted above) is a characteristic feature of asthma. The biological plausibility of this relationship is strong: 1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; 2) ETS causes airway hyperresponsiveness; 3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; and 4) cigarette smoke causes airway inflammation in active smokers (Niewohner, 1974) and may have similar (but lower-level) effects in people exposed to side-stream smoke. Taken as a whole, the epidemiologic evidence of causation is compelling.

Though not typically considered part of the Bradford Hill criteria, the potential role of confounding should also be considered in causal inference. In epidemiological studies, a confounder is a factor or variable that is associated with both the disease outcome and with the exposure of interest, and can produce a distortion of the relationship (or lack thereof) between the exposure and the disease outcome. The effect of a potential confounding variable can be addressed in the design phase of a study, or if data on the putative confounder are collected during the study, then the potentially distorting effects of the confounder can be controlled for, statistically, during the analysis. In any given study, there are likely to be few potentially

confounding exposures sufficiently important to control for. For studies examining the relationship between childhood asthma and ETS exposure, probably the most important variables to be evaluated as potential confounders, given the current state of knowledge, include the child's age, history of atopy or allergy, parental history of asthma, allergy, or other respiratory symptoms, and an indicator of family socioeconomic status. Other variables that ideally should be examined and adjusted for, if necessary, would include the child's gender, whether the child was breast-fed in infancy, type of fuel used for heating and cooking, the presence of allergens recognized to be risk factors for induction of asthma (*e.g.*, from household pets or dust mites), home dampness and/or mold, serious lower respiratory infection in early childhood, number of siblings, and maternal smoking during pregnancy (to the extent that it can be segregated from postnatal exposure). Approximately two-thirds of the studies included in the meta-analysis controlled for three or more potential confounders and effect modifiers, and these studies tended to have greater estimates of relative risk of asthma than those studies that adjusted for fewer than three covariates. The association of ETS exposure with asthma was usually found to be independent of these various risk factors. Several studies examined or adjusted for ten or more potential confounders, and some adjusted for many more; for example, Infante-Rivarde (1993) apparently adjusted for nearly two dozen variables, reporting an odds ratio of 2.77 (95% CI = 1.35-5.66) for maternal smoking of at least one pack of cigarettes/day. Nevertheless, routine adjustment for a long list of putative confounders is methodologically undesirable, as it may affect the precision and therefore the significance of the estimate of the relationship between ETS exposure and disease.

The U.S. EPA derived a quantitative estimate of risk of asthma induction associated with maternal ETS exposure (U.S. EPA, 1992, pp. 8-10 to 8-13). Using a threshold model and assuming relative risks ranging from 1.75 to 2.25 for children of mothers smoking more than ten cigarettes/day, U.S. EPA estimated that 7 to 9 percent of "all cases of asthma" (presumably pediatric cases only) could be attributable to maternal ETS exposure. This translated to an annual incidence of 8,000 to 26,000 cases attributable to ETS. U.S. EPA also calculated an annual incidence range of 13,000 to 60,000 using a nonthreshold model, noting, however, that a threshold model is more consistent with current epidemiologic data.

There are no California-specific data on asthma prevalence or incidence. Thus, an admittedly simplistic approach to estimating the attributable risk of ETS-induced pediatric asthma in California would be to multiply U.S. EPA's estimates by the percentage of the U.S. population living in this state, *i.e.*, about 12 percent. This would lead to estimates of 960 to 3,120 new cases of childhood asthma each year using U.S. EPA's threshold model or 1,560 to 7,200 cases using the nonthreshold model.

6.2.2 Chronic Respiratory Symptoms (Children)

Dozens of epidemiologic studies have linked chronic domestic ETS exposure with recurrent symptoms of cough, wheeze, and excess phlegm production in children. The NRC report (1986) concluded, based on a review of nine such studies involving approximately 25,000 subjects:

> "Children of parents who smoke compared with the children of parents who do not smoke show increased prevalences of respiratory symptoms, usually cough, sputum, and wheezing. The odds ratios from the larger studies, adjusted for the presence of parental symptoms, were 1.2 to 1.8, depending on the symptoms."

This range may underestimate the effects of ETS, since adjustment for parental symptoms, which is intended to address possible biased parental reporting of symptoms because of greater somatic awareness, may actually overcorrect for children's symptoms in that it also corrects for parental smoking (Ferris *et al.,* 1985). The Surgeon General's report (1986), reviewing ten large epidemiologic studies that examined chronic symptoms in approximately 31,500 children, came to a similar conclusion:

> "[C]hildren whose parents smoke had a 30 to 80 percent excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over six-fold among the studies reviewed. Many studies showed an exposure-related increase in the percentage of children with reported chronic symptoms as the number of parental smokers in the home increased" (p. 48).

The U.S. EPA report (1992) reviewed an additional 14 studies published since 1986, which basically confirmed the findings of the previous major reviews. The U.S. EPA concluded:

> "There is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children. The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS…and respiratory symptoms in the children, with odds ratios generally ranging between 1.2 and 2.4. …The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0 …[T]here are significant differences in susceptibility to ETS between individuals. [S]everal factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illnesses in early childhood, and being exposed to other environmental pollutants."

The reports by the Surgeon General (U.S. DHHS, 1986), the National Research Council (1986), and the U.S. EPA (1992) concluded that a causal relationship is the most likely explanation of the consistently observed associations between ETS exposure and respiratory symptoms in children. Because this issue has been adequately addressed in these reports, a *de novo* analysis of the primary literature has not been undertaken. More recent published investigations tend to support the conclusions articulated in these reviews. In a study of 343 children, aged 7-12, Henderson *et al.* (1995) found odds ratios of 2.9 (95% C.I = 1.2-7.0) for ETS exposure in rela-

tion to risk of wheeze in nonallergic children and 4.4 (95% C.I = 1.2-16.1) in allergic girls but not allergic boys. Goren *et al.* (1995) found significantly increased prevalences of a variety of respiratory symptoms and conditions (cough and sputum, wheeze with and without respiratory infection, bronchitis, and others) associated with maternal or paternal smoking among 8,259 elementary school children in Israel.

Bråbäck *et al.* (1995) undertook a cross-sectional study of 2,594 children, aged 10-12, in cities in Sweden, Poland, and Estonia, examining a variety of risk factors for respiratory symptoms and for atopic sensitization. The relevant odds ratios, derived from multiple logistic regression analysis, for "coughing attacks" (defined as either nocturnal cough lasting at least 4 weeks or exercise-induced cough) are presented in the following summary:

Maternal smoking	**All**	**Sweden**	**Poland**	**Estonia**
1-9 cigarettes/day	1.55 (1.07-2.24)*	0.67 (0.25-1.78)	1.38 (0.52-3.70)	1.80 (1.15-2.80)**
>9 cigarettes/day	2.60 (1.69-4.01)***	1.40 (0.70-2.80)	2.88 (1.23-6.74)**	4.27 (2.04-8.91)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

There were findings of other significant associations between maternal smoking and respiratory symptom indices in Poland and Estonia, but not in Sweden. The difference in results between Sweden and the other two countries may be related to the intensity of smoke exposure related to dwelling size and crowding, since most families in Poland and Estonia lived in apartments, while only about one-third of Swedish families did, and the average number of persons per room was 0.9 in Sweden, 1.7 in Poland, and 1.5 in Estonia. In addition, the authors noted that in Sweden there is widespread public awareness of health hazards associated with ETS exposure, leading many parents to smoke outdoors.

Cuijpers *et al.* (1995) undertook a cross-sectional examination of a variety of potential indoor environmental influences on respiratory symptoms and lung function in 535 Dutch children, aged 6-12. This study reported significant associations between ETS exposure and cough for 11-20 cigarettes per day in boys, but not for <11 or >20 cigarettes per day, and it found no significant associations for girls. However, the numbers of symptomatic boys and girls were small (*e.g.*, 33 and 26, respectively). The "significant" result for 11-20 cigarettes per day was based on a significance level of 0.10 rather than the more conventional level of 0.05. Examining the symptom of shortness of breath, Cuijpers *et al.* reported an exposure-response relationship for boys: the odds ratios for <11, 11-20, and >20 cigarettes per day for maternal smoking were 1.61 (0.58-4.50), 2.80 (1.13-6.95), and 4.58 (1.19-17.65) (again with the significance level set at 0.10, so these represent 90 percent confidence intervals, which would be even wider had the investigators set $\alpha = 0.05$). While there was no relationship between

paternal smoking and boys' symptoms, the odds ratio for <11 cigarettes per day for girls was elevated (2.85) and significant at $\alpha = 0.10$. In this study, it appears that boys might be more susceptible to ETS-related effects; however, because the numbers of children affected were so small, the confidence intervals are quite wide.

Moyes *et al.* (1995) conducted a cross-sectional investigation of asthma and allergy in 2,614 primary school and 2,752 secondary school children in six districts bordering the Bay of Plenty in New Zealand. They reported that parental ETS exposure was related to nocturnal cough, nasal symptoms, and wheeze in the older (ages 13-14) but not the younger (ages 6-7) children. The odds ratios for nocturnal cough and wheeze were highly significant ($p < 0.01$). While this study does not have the same statistical power issues as that reported by Cuijpers *et al.* (1995), the analysis of passive smoking was crude (*i.e.*, "Parental smoking"- yes/no, without stratification by maternal versus paternal smoking or quantification of numbers of cigarettes smoked/day) and the only other variable adjusted for was ethnicity (European versus Maori).

Forastiere *et al.* (1992) examined the relationships between a variety of predictors and respiratory illness in 2,929 Italian children, aged 7-11 years old, in a cross-sectional study in 1987, and found significantly elevated odds ratios in relation to the children's exposure to passive smoking. For example, the odds ratios (and 95 percent confidence intervals) for any smoker in the house were 1.3 (95% CI = 1.03-1.6) for early respiratory infection and 1.8 (95% CI = 1.2-2.7) for night cough. Though the odds ratios were elevated for either maternal or paternal smoking alone, they were not statistically significant, probably because of reduced power that accompanied dividing the responses by gender.

Wolf-Ostermann *et al.* (1995) undertook a prospective cohort investigation of respiratory illness in 8,514 German children, with data collection in 1977, 1979, and 1985. They also found a variety of significantly increased odds ratios for several adverse respiratory outcomes—*e.g.*, 1.26 (1.07-1.49) for bronchitis, and 1.55 (1.30-1.85) for fall and winter cough.

Mannino *et al.* (1996) analyzed data from the 1991 National Health Interview survey to estimate the relationships between parental smoking and the occurrence of respiratory illness in children aged 1-10 in the 2 weeks preceding the interview. They found that ETS-exposed children had 21 percent more restricted activity days, 31 percent more days of bed confinement, and 39 percent more days of school absence than those not exposed (all relationships were highly significant $p < 0.01$). Adjusting for age, sex, family size, socioeconomic status, season, and region, Mannino *et al.* found a higher incidence of acute respiratory illness (RR = 1.10, 95% CI = 0.95-1.26) and a higher prevalence of chronic respiratory illness (OR = 1.28, 95% CI = 0.99-1.67). Though these latter estimates were not statistically significant, Mannino *et al.* indicated that, because of the nature of the survey, the study had a power of 0.30 to detect a 10 percent increase in the two-week incidence of acute illness and 0.60 to detect a 25 percent increase in the prevalence of chronic disease. The investigators also pointed out a

variety of other considerations that would bias their results towards the null hypothesis, such as the dichotomous exposure classification (exposed versus not exposed).

These and other studies support the conclusion, also stated in the reports by the NRC, the Surgeon General, and the U.S. EPA, that there is sufficient evidence that ETS exposure at home is causally associated with chronic respiratory symptoms (cough, phlegm, or wheezing) in children, particularly infants and young children.

6.2.3 Decreased Lung Development (Children) Numerous cross-sectional and cohort studies have been published since the late 1970s examining the relationship of ETS exposure to various indices of lung function in children. A total of 29 studies, involving lung function measurements on approximately 77,000 subjects, were reviewed by the Surgeon General (U.S. DHHS, 1986), the National Research Council (1986), and the U.S. EPA (1992). While the results from all the studies reviewed were not wholly consistent, there was sufficient evidence for these three reviews to reach the conclusion that childhood exposure to ETS affects lung growth and development as measured by pulmonary function tests (PFTs). Conclusions reported in these reviews are listed below, followed by a description of clinical implications of these findings, plus brief summaries of several more recent studies.

The three major ETS reviews found that:

1) Some longitudinal (or cohort) studies report a small, but statistically significant, decrease in the rate of lung growth in children (as measured by multiple indices of lung function) exposed to ETS compared with nonexposed children. The magnitude of this decrement in naturally occurring growth, if projected through adolescence, appeared to be 3 to 5 percent or less (Surgeon General, NRC, U.S. EPA).

2) In a majority of cross-sectional studies, ETS-exposed children had modestly lower PFT values, on average, than nonexposed children. These effects were greater in at least some susceptible subgroups (*e.g.,* low birth weight, younger children) or in low SES families (*e.g.,* in which the mothers had less than 12 years of education; U.S. EPA).

3) Maternal smoking had a more marked impact on children's PFTs than paternal smoking, though in a data set from China in which all the mothers were nonsmokers, there was an effect of paternal smoking, as well (Chen *et al.,* 1986, Surgeon General, NRC).

4) In several studies, lower PFT values tended to be found with an increasing number of smokers in the child's household. In other words, in these investigations there appeared to be an exposure-response relationship (Surgeon General, NRC).

How ETS causes lung function decrements in otherwise healthy children is not known, but the observed effects may be related (at least in young children) to increased susceptibility to respiratory infection or to

delayed developmental effects attributable to *in utero* exposure to maternal smoking. Several recent papers suggest that *in utero* or early childhood exposures to ETS may result in changes in lung development that may persist through childhood and adolescence (Cunningham *et al.*, 1994 and 1995; Hanrahan, 1992; Brown, 1995). The short-term clinical consequences of these apparent reductions in children's PFTs are likely to be of less importance, however, than their potential long-term implications. As was observed in the Surgeon General's report (U.S. DHHS, 1986), "The absolute magnitude of the difference in lung function is small on average. A small reduction of function, on the order of 1 to 5 percent of predicted value, would not be expected to have functional consequences." Nonetheless, reductions of lung function in childhood may persist into adulthood and increase the risk of developing chronic obstructive pulmonary disease (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992).The likelihood of such potential long-term consequences, however, has not yet been fully evaluated.

Several investigations of the relationship between childhood ETS exposure and lung function have been published since the U.S. EPA reviewed the data on this topic. As with previous studies, the evidence from these investigations is somewhat heterogeneous. The results from several large cross-sectional studies, in particular, tend to support the existence of a relationship between household ETS exposure and decreased lung function. Lebowitz *et al.* (1992) reported an analysis of ETS exposure on PFTs measured at least three times over a 13-year period in 138 Caucasian children (67 boys and 71 girls), aged 5 through 15 upon entrance into the study. ETS exposure was assessed by parental survey: there was no distinction made between light and heavy smoking. The analysis was stratified by gender and by level of lung function (normal or low) at the initiation of the study. This group of investigators had previously reported that, in comparison with children with normal lung function, children with lower initial PFTs experienced their peak lung growth at an earlier age and at a lower absolute value. In this report, there was no ETS effect detected in females who started with either normal or low lung function. Similarly, no effect was detected in males starting with normal lung function. In contrast, boys starting with low lung function who were ETS-exposed had a decreased FEV_1 (forced expiratory volume in one second) between ages 13 and 16, relative to unexposed boys with low initial lung function. Interestingly, growth of the forced vital capacity (FVC, which is a rough indicator of lung volume), in the ETS-exposed boys exceeded that in the nonexposed group between the ages of 17.5 and 23.5. Within this age interval, the ratio of FEV_1/FVC (and another similar index of airway obstruction) decreased significantly in the exposed versus the unexposed low-function subjects (and versus the subjects with normal initial lung function). The clinical implications of these findings are unclear, since the apparent accelerated decline in the lung function ratios is at least partly attributable to the increase in the denominator (FVC). Furthermore, though there were a total of 142 lung function measurements made over the course of this study in the low-function males, there were only 28 in this group, including both smokers and nonsmokers. Thus, though it appears that the low-function ETS-exposed

males began adult life with an accelerated decline from a lower-than-normal baseline, no definite conclusions can be made until this type of analysis is replicated with a larger sample size.

Sherrill *et al.* (1992) recently reported results from a longitudinal study of lung function in a cohort of 634 children (327 males, 307 females) in New Zealand. The children were part of a larger birth cohort whose health status was assessed by questionnaire every 2 years from 3 to 15 years of age. Questions regarding parental smoking were asked only at ages 7, 9, and 11. Spirometric measurements were performed at ages 9, 11, 13, and 15. There were no statistically significant ETS-related effects on FEV_1 or FVC in males, though females whose parents both smoked tended to have a slower rate of growth in FEV_1 and those exposed to maternal smoking tended to have a lower FVC than the nonexposed ($p < 0.1$ for both findings). The investigators indicated that because of a potential disjunction between somatic growth and lung-function growth in adolescence, the ratio of FEV_1 to FVC might be a more accurate measure of lung-function growth than either index alone. Using the FEV_1/FVC ratio, detrimental effects of ETS were identified; males, but not females, showed a nonprogressive decrease related to parental smoking. Moreover, in children with asthma or a history of wheezing, progressive decrements in FEV_1/FVC were observed in children of both sexes, compared with an increase in this ratio observed in nonexposed children with wheeze. The average reduction in FEV_1/FVC by age 15 was 3.9 percent in ETS-exposed boys with wheeze and 2.3 percent in girls. As noted by the authors of this report, there does appear to be an ETS-related effect on the subgroup of children with a history of wheezing, but the lack of an obvious separate effect on FEV_1 or FVC weakens this conclusion somewhat.

Wang *et al.* (1994) investigated the relationship between several measures of childhood ETS exposure and annual lung function measurements made in 8,706 nonsmoking white children between the ages of 6 and 18 who were participants in the Harvard Six Cities Study. ETS exposure metrics included: pre-school exposures (during the first 5 years of life), cumulative exposure from age 6 to the year before each annual examination, and current maternal and paternal smoking as reported each year. In this report, the investigators used regression splines to model pulmonary function growth as a function of ETS exposure, adjusting for age, height, city of residence, and parental education (a surrogate for socioeconomic status). Both current maternal smoking and pre-school exposure to maternal smoking were significant predictors of the children's pulmonary function: there were no significant differences of effect observed in boys versus girls. Both of these measures were associated with small, but statistically significant reductions in FEV_1/FVC and FEF_{25-75} (an indicator of flow rates in the smaller airways) through adolescence. Interestingly, early maternal smoking was also associated with a small increase in FVC, which was statistically significant only in children aged 11 to 18. In children aged 6 to 10, current maternal smoking was related to slower growth rates of both FVC and FEV_1, and in older children, with a reduction in the growth rate of FEF_{25-75}. The findings of an increased FVC and reduced FEV_1 and FEF_{25-75} are similar to

those of Lebowitz *et al.* (1992), and suggest that early childhood ETS exposure may induce an exaggerated disjunction in growth rates for airways (as measured by FEV_1 and FEF_{25-75}) and lung parenchyma (lung volume as indicated by FVC), a process referred to as "dysanapsis." Moreover, after controlling statistically for current ETS exposure, this report suggests that early childhood exposures appear to exert long-lasting effects on lung maturation as measured by pulmonary function tests.

Rona and Chinn (1993) studied lung function in relation to reported home ETS exposure in 2,756 children, aged 6½ to 12, who took part in a cross-sectional national health survey in 1987 and 1988 in Great Britain. ETS exposure was assessed by parental questionnaire. A large number of potentially confounding variables were controlled for in the analysis, including age, height, ethnic group, weight, birth weight, percentage body fat (as measured by triceps skinfold thickness), reported parental heights, mother's age at child's birth, family size, father's social class, "overcrowding," whether the child resided with one or both parents, mother's educational level, father's employment status, type of cooking fuel, study area, type of school meals, and a variety of the child's respiratory symptoms. The investigators found significant associations of maternal smoking with reduced FEF_{25-75} and FEF_{75-85} in boys, but not girls. They also found similar gender-associated reductions of FEV_1 with maternal ETS exposure and of FEF_{25-75} with total parental smoking, which were of borderline statistical significance. The results of this study are consistent with numerous others in showing an association between reduced childhood lung function and maternal but not paternal smoking. However, the differential effects on boys versus girls remains unexplained and, as the investigators noted, "illustrate the difficulties in making generalizations about the association between lung function and passive smoking in childhood."

Haby and colleagues (1994) assessed the relationship of several variables to spirometric indices (FVC, FEV_1, PEFR, and FEF_{25-75}) in a cross-sectional study of Australian children in grades three to five (ages 7-12). ETS exposure was assessed by parental questionnaire and was included as a continuous variable in stepwise multiple regression analyses of predictors of lung function in a group of 2,765 children. Other variables entered in the final models included height, weight, age, gender, current and past asthma, and the presence of a respiratory infection. The investigators reported a linear, dose-related reduction in FEV_1, PEFR, FEF_{25-75}, but not in FVC, where dose referred to the number of cigarettes smoked daily in the home. The magnitude of the reduction was small: a 10-year-old child would be expected to have a 2.4 percent reduction of FEF_{25-75} if more than one pack of cigarettes were smoked in the home every day. The investigators did not report effects of prenatal or early childhood exposure to ETS, whether there were gender differences in the relationship of ETS exposure to spirometry, or the effects of maternal versus paternal smoking. As in several studies described above, Haby *et al.* speculated that the differential effects of ETS on FVC versus the flow-related measures of lung function may be due to dysanaptic growth of the lung.

Cook *et al.* (1993) examined the relationships between several lung-function measures and ETS exposure in a population-based sample of 5.0- to 7.9-year-old children randomly selected from elementary schools in 10 towns in England and Wales. ETS assessment was conducted by both parental questionnaire and by measurement of salivary cotinine obtained from the participants. Multiple regression models relating the spirometric indices to salivary cotinine were based on data from 2,511 children who had provided complete, acceptable data. The analysis relating lung function to questionnaire-based ETS assessment contained data from 2,500 children. In analyses adjusted for age, gender, height, body mass index, lung function technician, and town of residence, several indices of lung function (FVC, FEV_1, FEF_{25}, FEF_{50}, FEF_{75}) were negatively associated with salivary cotinine; all were highly significant statistically. Only the ratio FEV_1/FVC was not correlated with salivary cotinine. Additional adjustment for birth weight, presence or absence of a gas-burning stove, and the head of household's social class (an indicator of SES) did not materially change the estimates. FEV_1 declined linearly with increasing salivary cotinine. The results from the questionnaire-based ETS exposure assessment were more ambiguous, reflecting the increased uncertainty and measurement error associated with such data. Though there was no clear exposure-response relationship between FEV_1 and the numbers of cigarettes reportedly smoked by the mother or the father, when ETS exposure was categorized by the number of smokers to which the child was exposed on a regular basis, all of the above indices except FVC declined with increasing numbers of smokers, though this negative association was significant only for FEF_{25}, FEF_{50}, FEF_{75}, and FEV_1/FVC. As was true of the cotinine analysis, the strongest association was with FEF_{50}. For a small subset of the children (n = 111), salivary cotinine was sampled twice (6 months apart), and though the mean levels were slightly different (1.59 versus 1.37 ng/ml), the difference was not significant, indicating the stability of ongoing exposure patterns. The cotinine-based analysis supports the existence of an exposure-response relationship between ETS and childhood lung function; however, these investigators could not distinguish between the effects of current versus early childhood exposures.

Two recent reports by Cunningham *et al.* (1994 and 1995) suggest that prenatal or very early postnatal exposures to tobacco smoke components may affect lung development, inducing persistent effects that may be detected throughout childhood. As part of the Harvard 24-Cities Study, Cunningham *et al.* presented results of an analysis of 8,863 nonsmoking white children, aged 8-12, in which they examined the relationships of a variety of lung-function measures to maternal smoking during pregnancy as well as to current maternal smoking. In regression models adjusted for sex, height, weight, age, parental education, city of residence, and interaction between sex and height, the investigators found decrements in $FEV_{0.75}$, FEV_1, FEV_1/FVC, PEFR, $FEF_{25\text{-}75}$, and $FEF_{65\text{-}75}$ that were highly significantly related to both maternal smoking during pregnancy and to maternal ETS exposure in the year preceding the examination. However, when adjusted for current maternal smoking, the associations of these measures with

maternal smoking during pregnancy were slightly reduced, but remained highly significant statistically. In contrast, when adjusted for maternal smoking during pregnancy, the effects of current smoking on the children's lung function were markedly decreased and were no longer significant. Boys showed greater ETS-related deficits than girls in all the above measures of lung function, but this was due to the greater effects in boys with a history of allergy, asthma, parental asthma, or severe respiratory illness. Among boys and girls with none of these risk factors for decreased lung function, the estimates of ETS-related effects were of similar magnitude. In general, mothers who smoked during pregnancy are likely to continue to smoke afterwards, so these two measures of ETS tend to be highly correlated. However, because of the large size of this study, the investigators were able to undertake a variety of subgroup analyses that highlighted the importance of *in utero* and possibly very early childhood exposure to maternal ETS. Paternal smoking was not a significant predictor of the participants' lung function.

Cunningham *et al.* (1995) undertook a similar analysis with a sample of 493 white and 383 black children, aged 9-11, in Philadelphia. ETS exposure history was obtained through the children's mothers' answers to questionnaires. In the statistical analysis, exposures were modeled as dichotomous variables for maternal smoking and for current smoking, and as a continuous variable for the number of cigarettes smoked per day. Pulmonary function testing was conducted at school. Multiple regression techniques were employed to model several lung function measurements as a function of ETS exposure, adjusting for height, weight, age, area of residence, parental education, mother's primary language, and single-parent family status. Models that included boys and girls or members of both races required additional adjustments for gender, race, interaction of gender and height, race and gender, race and height, race and weight, and race and age. In regression models for the whole study population, maternal smoking during pregnancy was associated with statistically significant decrements of -8.1 percent FEF_{25-75} (95% CI = -12.9 to -3.1 percent) and -2.0 percent in FEV_1/FVC (95% CI = -3.0 to - 0.9 percent), while a decrease in FEV_1 was not significant. No decrease in FVC was observed. Larger deficits were observed in black than in white children, with the greatest decreases detected in African-American boys (-19.6 percent FEF_{25-75} (95% CI = -31.1 to -6.1 percent), -5.9 percent in FEV_1/FVC (95% CI = -8.7 to -2.9 percent); FEV_1 = -6.0; (95% CI = -10.4 to -1.4 percent)). These differences could not be explained by potential confounding by SES, prior respiratory illness, or housing characteristics. Current ETS exposure was not associated with lung function deficits after adjustment for maternal smoking during pregnancy.

Casale *et al.* (1991), in a study of 143 Italian children aged 6-11, found dose-dependent relationships between several measures of lung function (particularly those related to airflow at low lung volumes) and ETS exposure. In this study, ETS exposure was measured by both urinary cotinine and parental questionnaire. Goren and Hellman (1995), in a cross-sectional study of 8,259 Israeli second- and fifth-graders, found no relationship of parental smoking with measures of lung volume and central or large air-

way caliber (FVC, FEV_1, PEF, and FEV_1/FVC). Guneser *et al.* (1994), in a study of 617 Turkish school children (287 boys and 330 girls), aged 9-12, found that all measures of lung function were lower in boys exposed to ETS compared with those who were not (with the exception of FEV_1 in 12-year olds), but that these differences were significant only for FVC in 9-year-olds, FEV_1 in 9- and 10-year-olds, peak flow in 10-year-olds, FEF_{25} in 10-year-olds, and FEF_{25-75} in 9-year-olds. No data were presented for girls. Soyseth *et al.* (1995), in a study of parental smoking and asthma, bronchial hyperresponsiveness, and atopy in 620 Norwegian children aged 7-13, reported that, of the 573 children performing spirometry, there was a slight, but not statistically significant decrease in the FEV_1/FVC ratio (one measure of airway obstruction) in relation to maternal smoking (-0.7 percent), that was even less for paternal smoking (-0.2 percent). This was the only spirometry result reported in this paper. Cuijpers *et al.* (1995), in a study of 535 Dutch children aged 6-12, found significant decreases in several indices of lung function (FVC, FEV_1, PEF and FEF_{25-75}) in boys related to cumulative lifetime exposure to ETS, with larger decrements related to exposure during their entire lives versus part of their lives. As with respiratory symptoms, a lesser effect was seen in girls, with only one index (FEF_{25-75}) showing a similar trend that was significant. Finally, Richards *et al.* (1996), in a cross-sectional study of 395 South African adolescents aged 14-18, found no significant differences in FEV_1 and FEF_{25-75} between exposed and non-exposed children.

In their ensemble, these studies, especially the cross-sectional investigations, tend to support the conclusions reached in the earlier reviews by the NRC, the Surgeon General, and the U.S. EPA regarding the relationships between ETS exposure and lung function in children. However, as noted above, the data are not entirely consistent. Some of the differences may be explicable by the crudeness of questionnaire-based exposure assessment, which is likely to result in nondifferential misclassification of exposure and a consequent bias towards the null hypothesis of no relationship. In this regard, the study by Cook *et al.* (1993) is instructive. In this investigation of 2,500 English and Welsh school children, aged 5-7, there were significant, consistent relationships between ETS exposure as measured by salivary cotinine and several indices of lung function. These associations were weaker and insignificant when based on questionnaire score, suggesting that this more commonly used method of exposure assessment may well result in a bias towards the null hypothesis. Some inter-study discrepancies may also be attributable to the different age ranges of the study populations, especially since early childhood or *in utero* exposures appear to exert long-lasting effects, which may diminish over time. Finally, although the mean changes observed have generally been of small magnitude and uncertain clinical significance, the potential long-term implications of these lung function decrements warrant additional investigation.

6.2.4 Chronic Pulmonary Disease and Respiratory Symptoms (Adults)

Several investigators have examined the question of chronic chest symptoms and/or pulmonary function changes in adults exposed to ETS. It is well established that active smoking leads to increased age-related decrements in pulmonary function. For example, in a large multi-center longitudinal study,

the yearly decline in FEV_1 was 30-40 percent greater in smokers than in nonsmokers (Xu *et al.*, 1992). Smoking also can lead to chronic obstructive pulmonary disease (COPD). COPD is characterized by mucus hypersecretion/infection (chronic bronchitis) and loss of elastic recoil and alveolar integrity (emphysema), resulting in varying degrees of airway obstruction (particularly during expiration) and sputum production. Mechanisms underlying these changes include cigarette smoke-induced bronchopulmonary inflammation, induction of airway hyperresponsiveness, inhibition of mucociliary clearance (and other antimicrobial defenses), goblet cell hyperplasia, release of proteolytic enzymes from inflammatory cells, and possibly inhibition of antiproteases (Snider, 1989 and 1991; Wagner, 1992). This section reviews the epidemiologic evidence bearing on the question of chronic exposure to ETS, lung function, and chronic respiratory symptoms in adults.

The Surgeon General's Office (U.S. DHHS, 1986) and NRC (1986) reviewed five, and the U.S. EPA (1992) an additional six, studies of chronic respiratory symptoms and/or pulmonary function among adults exposed to environmental tobacco smoke in the home or workplace; these are summarized below. Several additional studies were found which were not summarized in any of the above reviews.

White and Froeb (1980) surveyed 2,100 middle-aged subjects who enrolled in a physical fitness course sponsored by the University of California, San Diego over a 10-year period. Roughly 87 percent of the registrants were white collar workers. For both sexes, nonsmokers who reported chronic workplace exposure to ETS had, as a group, significantly lower FEF_{25-75} (forced expiratory flow during the middle half of the forced vital capacity maneuver) and FEF_{75-85} values than did non-ETS exposed nonsmokers; comparable decrements were found in the above parameters among light smokers and smokers who did not inhale. By comparison, persons actively smoking at least one pack-per-day for 20 years or more had decrements in the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC), which were not seen in passive smokers or light smokers.

Comstock (1981) analyzed cross-sectional data on 1,724 adult participants in two different studies of respiratory symptoms. Non-significant excesses of subjects with an FEV_1 <80 percent of predicted or an FEV_1/FVC of <70 percent were observed among males exposed to ETS; no such excesses were seen among women. Most respiratory tract symptoms were equally prevalent among those exposed and not exposed.

Kauffman *et al.* (1983 and 1989) analyzed questionnaire and pulmonary function data in two cross-sectional studies that included 3,855 French women (aged 25 to 59 years) and 2,220 American women (aged 25 to 74). For most lower respiratory symptoms, odds ratios comparing passive smokers with nonsmokers were elevated, but not to a statistically significant degree. Among French women over age 40, both FEV_1 and FVC were significantly lower among the passive smokers. In the U.S. sample, there was a significantly elevated rate of self-reported wheezing among passive smokers compared to the unexposed group.

Kentner *et al.* (1984) conducted a cross-sectional study of 1,351 office workers, including both a questionnaire and pulmonary function testing. Smokers, ex-smokers, and passive smokers were compared to lifetime nonsmokers. Whereas active and prior smokers had significantly lower age- and sex-standardized ventilatory parameters, no such changes were evident among persons whose sole lifetime exposure was passive smoking.

Brunekreef *et al.* (1985) followed 97 nonsmoking rural Dutch females for approximately 15 years with serial measures of pulmonary function. Analyzed cross-sectionally, those women 40 to 60 years of age at the time of the latest measurement who were passively exposed to cigarette smoke in the home had significantly lower peak expiratory flow (PEF) than did the unexposed group. Among those with passive smoke exposure throughout the period of the study, forced expiratory flow at 75 percent of total lung volume (FEF_{75}) was also significantly lower. Other lung function parameters, while generally lower among passive smokers, were not significantly so. Analyzed longitudinally, however, there was no significant difference in yearly age-related pulmonary function loss between the two groups.

Svendsen *et al.* (1987) analyzed data from the Multiple Risk Factor Intervention Trial on 1,245 married men aged 35-57 years who had never smoked, roughly a quarter of whom had wives who smoked. Upon entry into the study, the latter had FEV_1 values, on average, 99 ml (2.8 percent) lower than those with nonsmoking wives (95% CI = 5-192 ml lower). However, separating subjects whose wives smoked less than one pack per day versus greater than one pack per day did not provide evidence of a dose-response relationship. Passive smoking histories were validated with serum thiocyanate levels (no difference observed by spousal smoking) and expired air carbon monoxide (significant trend with increasing spousal smoking).

Kalandidi *et al.* (1987 and 1990) conducted a case-control study, comparing 103 nonsmoking Greek women aged 40-79 who were admitted to the hospital for an initial diagnosis of COPD with 179 similarly aged nonsmoking visitors (*i.e.*, friends and family of patients). A significant trend was observed in the odds ratio for COPD and spousal smoking as the husband's estimated (during-marriage) total cigarette consumption increased, with the OR equaling 1.3 for fewer than $3x10^5$ cigarettes and 1.8 for greater than $3x10^5$—*i.e.*, greater than approximately 40 pack-years of spousal cigarette smoking ($p = 0.01$ crude, $p = 0.03$ adjusted). Factors adjusted for in the analysis included age, education, rural versus urban residence, and employment status.

Euler *et al.* (1988) performed a multivariate logistic regression analysis of questionnaire data from 7,445 nonsmoking Seventh Day Adventists in California. The study, which focused mainly on the effects of air pollution, looked at passive smoking as a covariate. Among other variables, self-reported ETS exposure, both in the workplace and in the home, was significantly related to self-reported symptoms of COPD (breathlessness, sputum production, and wheezing).

Masi *et al.* (1988) did a cross-sectional analysis of 293 nonsmoking men and women, 15-35 years of age, who had previously been recruited for a study of lung function in adolescence and young adulthood. There was a significant decrement in FEF_{25-75}, FEF_{50}, and residual volume as a function of cumulative lifetime exposure to ETS at home (but not at work) among males only. Females showed a significant trend toward lower carbon monoxide diffusion capacity (D_LCO) with increasing cumulative ETS exposure at work (but not at home). The analysis involved a total of 40 test statistics. Of note, the observation of a significantly lower residual volume (RV) in males exposed to ETS at home runs counter to the hypothesis that ETS exposure produces clinically significant COPD, since an elevated RV is normally observed in COPD.

Hole *et al.* (1989) interviewed and examined 671 lifetime nonsmoking Scottish men and women, 243 of whom lived with one or more smokers. Age-, height-, and sex-adjusted FEV_1 values were significantly lower among those exposed to ETS compared to those not exposed (difference = 3.5 percent). A variety of respiratory symptoms (*e.g.,* shortness of breath, sputum production) were elevated to a nonsignificant degree among the ETS-exposed group.

Schwartz and Zeger (1990) re-analyzed data from a diary study of acute respiratory symptoms among 100 student nurses. Subjects completed daily entries for as long as 3 years. Variables used in the analysis included smoking and ETS exposure history, allergy status, and various measures of outdoor air quality. Controlling for personal smoking, self-reported phlegm production was significantly more common among students with smoking, as opposed to nonsmoking, roommates (OR = 1.41; $p < 0.001$).

The studies described below were not included in the Surgeon General's (U.S. DHHS), NRC, or U.S. EPA reports.

Schilling *et al.* (1977) conducted a cross-sectional analysis of questionnaire and pulmonary function data from 376 families in Connecticut and South Carolina. They found no significant differences in adult symptom reporting rates or, controlling for prior smoking history, in pulmonary function measures as a function of spousal smoking habit.

Masjedi *et al.* (1990) administered a questionnaire to (and performed pulmonary function tests on) 275 lifetime nonsmoking hospital employees and physicians. Among male subjects (n = 167), significantly lower spirometric values (FEV_1, FVC, and FEF_{25-75}) were observed for those who reported ETS exposure at work (not home) versus those who did not. Among females, no systematic differences were found with ETS exposure at either work or home. A potential confounder in the study was the high level of ambient air pollution in the area surrounding the recruiting hospital (Teheran, Iran).

More recently, Jaakkola *et al.* (1995) reported the results of a longitudinal study of lung function in 117 nonsmoking young adults (aged 15 to 35) in Montreal, Canada who were tested in 1981-1983 and again in 1988-

1989. ETS exposures at home and at work during and prior to the study were assessed by questionnaire. In multiple linear regression analyses controlling for age, gender, height, Quetelet index (wt/ht^2), baseline FEV_1, baseline FEF_{25-75}, atopic status, and the presence of wheeze at baseline, these investigators did not find a significant relationship between either current or past home or work exposure to ETS and the change in FEV_1 or in FEF_{25-75} during the study period. In a subanalysis of the subjects who were 25 years of age or younger at baseline (n = 62), Jaakkola and colleagues found that work-related ETS exposure during the study period was associated with a slight, but significant increase in the rate of decline of FEV_1. They also calculated 95 percent confidence intervals on their estimates, indicating that, given the exposure conditions and baseline health of their study population, the changes in lung function during young adulthood potentially attributable to ETS would be approximately (1.0 ml/yr per pack-year, which would be of little clinical importance. It should be noted, however, that 80 percent of the men (total n = 60) in this study had no ETS exposure at home during the study period, while another 8 percent were exposed to fewer than 10 cigarettes/day; only one man was exposed to a pack or more on a daily basis. For women (n = 57), the corresponding numbers were 45 percent with no ETS exposure at home, 33 percent with exposure to less than half a pack, and six who were exposed to a pack or more. The frequencies of work-related exposures were greater, but still reflected light to moderate exposure at most. Thus, as the investigators acknowledged, their findings would not necessarily be representative of what might occur with more frequent exposure in smaller indoor spaces with poorer ventilation. Also, the authors of this small study focused only on changes during the study period and did not report whether baseline lung function was related to prior ETS exposure.

Dayal *et al.* (1994) undertook a case-control study of the relationship between self-reported, previously diagnosed obstructive lung disease (including asthma, chronic bronchitis, and emphysema), where cases and controls were selected from a probability sample of 4,200 individuals residing in nine Philadelphia neighborhoods in 1985-1986. In an analysis restricted to never-smokers, the cases (n = 219) were matched on age, gender, and neighborhood with three randomly selected controls. The matching on neighborhood was intended to control both for SES and local environmental conditions, such as air pollution. In conditional logistic regression analysis that also controlled for type of heating and whether a gas stove was present (and possibly other variables), Dayal *et al.* found a significant relationship between reported obstructive lung disease and household ETS exposure involving one or more packs a day, corresponding to an odds ratio of 1.86 (95% CI = 1.21-2.86). While this result suggests that household ETS exposure increases the risk of obstructive lung disease, the interpretation of this study is limited by a lack of information about the study populations (*e.g.*, basic demographics) and about the temporal character of the disease outcomes in relation to the study date—in other words, whether the disease(s) reported by the participants were "ever-diagnosed" or still present (*i.e.*, asthma and chronic bronchitis).

Xu and Li (1995) analyzed relationships of household and occupational ETS exposure on pulmonary function in 1,033 adults (including 502 never-smokers), aged 40 to 69, in a residential area of Beijing. Current ETS exposure was assessed by questionnaire. In stratified multiple regression analyses controlling for age, income, educational level, personal smoking status, indoor use of coal stoves for heating or cooking, and occupational exposures to dusts, gases, or fumes, Xu and Li reported reduced levels of FEV_1 and FVC associated with ETS exposure, which were statistically significant in never-smoking men, but not women. While almost all of the estimates of effect of ETS exposure on lung function in ever-smokers were also negative, these were significant only for the pooled group (men and women) exposed both at home and at work. Also, when the exposures were categorized as low (1-5 cigarettes/day) versus high (>6/day), Xu and Li found evidence of linear exposure-response relationships, which were statistically significant for FEV_1 and FVC in never-smoking men and for ever-smoking women. In this study, the magnitudes of the lung function decrements reported to be associated with ETS exposure were substantial (4.2 ± 1.8 ml/cigarette smoked in the household for FEV_1 and 5.2 ± 1.9 ml/cigarette for FVC). However, the exposure conditions in Beijing are clearly different from those in California or the U.S., potentially limiting the generalizability of these findings.

Robbins *et al.* (1993) reported that several measures of childhood and adult ETS exposure were associated with onset of airway obstructive disease (AOD, comprised of asthma, chronic bronchitis, and emphysema) in 3,914 nonsmoking Seventh Day Adventist adults in a prospective investigation. Questionnaires about both symptoms and historical ETS exposure were administered to study participants in California in 1977 and again in 1987. Though all three disease entities constituting AOD were self-reported, the questions about both asthma and emphysema were structured to require a physician's diagnosis. Statistical analysis relied on multiple logistic regression modeling of AOD onset over the 10-year period, controlling for age, education level (an indicator of SES), gender, years of past smoking (15 percent of the study population), and an indicator of chronic exposure to particulate air pollution. Robbins *et al.* reported that several, but not all, qualitative measures of ETS exposure were associated with an increased relative risk of developing AOD during this interval, including adult plus childhood exposure (RR = 1.72, 95% CI = 1.31-2.23), but not childhood or adult exposure alone (RR = 1.09, 95% CI = 0.69-1.79 and RR = 1.28, 95% CI = 0.90-1.79, respectively). Similarly, examining the outcomes of chronic bronchitis and asthma separately, they reported increased RRs for both outcomes in relation to combined adult and childhood ETS exposures: RR = 1.71 (95% CI = 1.27-2.27) for chronic bronchitis and RR = 1.89 (95% CI = 1.13-3.15) for asthma. Several sensitivity analyses indicated that these findings were robust: specifically, the ETS risk estimates changed little when the analysis was restricted to never-smokers, and when terms were included in these regressions for childhood respiratory illness and frequency of childhood colds. One unexpected finding in this report, however, was that the RR for AOD corresponding to having actively smoked for 10 years was

lower (RR = 1.27, 95% CI = 1.10-1.47) than those estimated for the combined adult and childhood ETS exposures. The authors explained this unusual result as a combination of factors: the low prevalence of ever-smoking adults in the study population (15 percent), the long time that had elapsed since the active smokers had quit (mean = 21.4 years), and the "short" period of time during which active smoking had taken place (mean = 14.8 years).

In a separate analysis of virtually the same data set, Greer *et al.* (1993) examined the incidence of new cases of asthma as a function of adult ETS exposure ("years lived with a smoker" and "years worked with a smoker"), controlling for years of active smoking, ozone and particulate air pollution, occupational dust and vapor exposures, childhood history of AOD, age, gender, and education. In the final models that Greer *et al.* reported, the incidence of "definite asthma" by reported symptoms or reported physician diagnosis during the 10-year interval was significantly related to occupational ETS exposure, with a relative risk of 1.45 (95% CI = 1.21-1.80). Separate subanalyses for men and women produced similar results. Greer *et al.* (1993) also obtained medical records for 49 of the self-reported cases of asthma and validated the diagnosis in 30 (61 percent), suggesting a reason for caution in interpreting the results of these investigations. Although these investigators indicated that the relative risks for occupational ETS exposure remained significant when only the validated asthma cases were used in the regression models, the magnitudes of the risks were not specified. Based on the results of these two studies, it seems likely that ETS exposure is significantly related to self-reported symptoms of AOD, but the extent to which this relationship holds true for each of the subsets of AOD (*i.e.*, asthma and chronic bronchitis) would require additional research.

In a cross-sectional study of nonsmoking women in Singapore, Ng *et al.* (1993) reported increased risks of chronic respiratory symptoms and reduced FEV_1 associated with household ETS exposure. Symptom and ETS exposure data were collected from 1,438 women, 1,282 of whom were lifelong nonsmokers. Of the latter, 1,008 provided acceptable FEV_1 tracings for analysis. In multiple logistic regressions that adjusted for age, race, employment status, and area and size of residence (indicators of SES)—adjustments were also made for chronic rhinitis and eczema when examining odds ratios for wheeze and physician-diagnosed asthma—Ng *et al.* found elevated odds ratios for all respiratory symptoms where the women were exposed to one or more heavy smokers (defined as those who smoked ≥ 20 cigarettes/day). ORs were significantly elevated for chronic or usual cough (OR = 3.79, 95% CI = 1.76-8.14), cough at least 3 months out of the year (OR = 3.01, 95% CI = 1.13-8.03), breathlessness on exertion (OR = 1.83, 95% CI = 1.30-2.58), and wheeze (OR = 2.69, 95% CI = 1.23-5.88). For women exposed to one or more light smokers (*i.e.*, those consuming < 20 cigarettes/day), the only significantly increased OR was for usual or chronic cough (OR = 2.84, 95% CI = 1.29-6.24). Restricting the analysis to housewives (n = 548), who would be expected to be exposed to ETS only at home, resulted in elevated ORs for all symptoms examined except for physician-

diagnosed asthma, though these increases were statistically significant only for chronic cough and breathlessness on exertion. Analysis of FEV_1 in relation to ETS, controlling for the same potentially confounding factors and effect modifiers (with the addition of the variable height), indicated that small, but statistically significant reductions in lung function were associated with the presence of one or more light or heavy smokers in the home, whether the analysis included all women or only housewives. In this study population, frequency of gas cooking was not associated with increased risks of respiratory symptoms (except breathlessness on exertion), but was associated with small reductions in lung function. The investigators' conclusions would have been strengthened had they also controlled for this potential confounder in the ETS analyses.

In a cross-sectional study of 4,197 never-smoking adults, aged 18 to 60, Leuenberger *et al.* (1994) examined the relationships between ETS exposure and a variety of symptoms. Information on both exposure and symptoms were obtained through structured interviews. Analysis involved multiple logistic regression that controlled for age, gender, body mass index (weight/height^2), area of residence, parental and sibling history of asthma, and atopy (determined by a serum immunofluorescence assay for specific IgE against common inhalant allergens). Leuenberger *et al.* found elevated odds ratios for all respiratory symptoms examined except allergic rhinitis; specific ratios were elevated as follows: wheezing apart from colds (OR = 1.94, 95% CI = 1.39-2.70), physician diagnosed asthma (OR = 1.39, 95% CI = 1.04-1.86), dyspnea on exertion (OR = 1.45, 95% CI = 1.20-1.76), symptoms of bronchitis (OR = 1.59, 95% CI = 1.17-2.15), and symptoms of chronic bronchitis (OR = 1.65, 95% CI = 1.28-2.16). These estimates of elevated risk did not change significantly when a variety of sensitivity analyses were undertaken, such as excluding subjects whose mothers had ever smoked, excluding subjects who were likely to have been active smokers (determined by measuring the concentration of exhaled carbon monoxide in their breath) and controlling statistically for low educational level (an indicator of SES), and for occupational exposures. Moreover, these investigators found evidence of a dose-related increase in risk for all these symptoms where dose was represented as either reported hours per day or years of passive smoke exposure. This study addressed most concerns usually raised about potential confounders in epidemiological studies of ETS-related health effects, notably differential symptom reporting by those whose mothers smoked during pregnancy or during the subjects' early childhood, by active smokers claiming to be nonsmokers, by factors related to SES, and by occupational exposures. On the basis of the studies reviewed prior to 1987, the Surgeon General's Office (U.S. DHHS, 1986) concluded, "The small magnitude of effect implies that a previously healthy individual would not develop chronic lung disease solely on the basis of involuntary tobacco smoke exposure in adult life." On the basis of more recent studies (particularly Hole *et al.*, 1989 and Svendsen *et al.*, 1987) the U.S. EPA (1992) estimated a 2.5 percent lower FEV_1 and a 30-60 percent increase in respiratory symptoms among passive smokers as compared to unexposed individuals. U.S. EPA further concluded that the "...effects of passive smoking on

lung function are approximately comparable to those reported for light (<10 cigarettes/day), male active smokers." The report did point out that several of the studies reviewed were problematic with respect to control for potential confounding variables.

Prior to the publication of relevant recent studies, it appeared that the effect of chronic ETS exposure on pulmonary function in otherwise healthy adults was likely to be small in comparison with active smoking, and was unlikely, by itself, to result in clinically significant chronic disease, as concluded by the Surgeon General's Office and the U.S. EPA. The results of Leuenberger *et al.* (1994), Robbins *et al.* (1993) and other recent papers, however, suggest that ETS exposure may make a significant contribution to chronic respiratory symptoms in adults. In conjunction with reports of acute lower respiratory tract symptoms among individuals with pre-existing asthma (see Section 6.1.1), the small differences in lung function found in epidemiological studies are a basis for concern and further study.

6.2.5 Studies on Lung Development in Animals

Evidence for effects of mainstream smoke (MS) exposure of pregnant rodents on fetal lung development has been provided over the past 10 years. More recently, effects of sidestream smoke (SS) on both prenatal and postnatal lung development, function and airway reactivity have been studied in rats. In animal studies, MS and SS are distinguished by the mode of generating the smoke, but all exposures have been passive or environmental (*i.e.*, smoke has been inhaled from ambient air). SS differs from ETS in that it does not contain exhaled mainstream components.

Studies of lung development were undertaken after data indicated a proportionally greater growth retardation in fetal lung than in other organs as a result of MS exposure of pregnant rats (Bassi *et al.*, 1984). Histopathology and morphometry studies of the growth-retarded lungs demonstrated increased sizes and reduced numbers of primitive alveoli (saccules) leading to a reduced surface area available for gas exchange in the term fetus (Collins *et al.*, 1985). When 15-day-old rats were examined after *in utero* smoke exposure, gas diffusion capacity of the lung as determined from histomorphometry was similar to that of controls (Lichtenbeld and Vidic, 1989). Nonetheless, biochemical measures suggested delayed septal growth and development of lung interstitial cells (Vidic *et al.*, 1989). Since septa subdivide existing alveoli to produce new alveoli, these findings are consistent with the lower number of alveoli seen in fetuses at term (Collins *et al.*, 1985). However, functional lung parameters (respiratory capacity, reactivity, immune defense) were not evaluated in these studies.

Developmental studies of lung function and reactivity have recently been undertaken in rats using methodologies specifically designed for producing SS exposure (Teague *et al.*, 1994).

Joad *et al.* (1993 and 1995b) studied functional lung parameters (compliance, resistance, reactivity) in adult rats exposed to SS prenatally and/or postnatally. The rats were 7-10 weeks of age (sexual maturation in

rats occurs at 5-6 weeks of age) at the time of the lung function tests. As measured in isolated perfused lungs, compliance was decreased 24 percent, and reactivity (to methacholine challenge) was 200 percent greater in rats exposed to SS both prenatally and postnatally. Furthermore, the number of neuroendocrine cells, an immature cell type in the lung, was 22-fold greater after the combined gestation/lactation exposure. Hyperplasia and persistence of neuroendocrine cells, which contain mediators of bronchoconstriction, were considered the basis for reduced compliance and increased reactivity. The SS air concentration in this study was 1 mg/m^3, which is at the top of the range of ETS exposures recorded in any environment (U.S. EPA, 1993).

These effects were not seen when exposures occurred only prenatally or only postnatally (Joad *et al.*, 1993). The postnatal exposures were given from day 2 through 7-15 weeks of age, or only at 15 weeks of age, and thus covered the entire period of postnatal lung development. The lack of effect emphasizes the importance of exposure during fetal as well as postnatal stages of lung development. In rats exposed only postnatally to SS, cell division in epithelial cells of terminal but not proximal bronchi was lower than in controls at 7 and 14 days of age. Since cell division is an immature property of the bronchiolar epithelium, this indicated stimulation of lung maturation, as also suggested by studies of enzyme induction.

Induction of metabolic enzymes by SS in the immature lung has been studied in the postnatal period. The establishment of metabolic competence of the lung is delayed well into the postnatal period in laboratory animals as well as in humans. Aryl-hydrocarbon hydroxylase (AHH), also known as cytochrome P450 1A1, was induced in lungs of rat offspring who were exposed to MS constituents *in utero*, by nursing, or directly through inhalation after birth (Bilimoria and Ecobichon, 1989). This enzyme is known to be induced by polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke (Bilimoria and Ecobichon, 1980). Little or no induction was seen in hamster or guinea pig offspring. The results seen in rats demonstrate that tobacco smoke components can reach the fetal lung of rats and produce a biochemical response. Other studies demonstrated that SS exposure can alter the ontogenetic time course of appearance of lung enzymes (Ji *et al.*, 1994). In rat pups exposed to SS from birth at a concentration of 1 mg/m^3, cytochrome P450 1A1 was seen earlier, and persisted at high levels longer after the normal developmental peak. Clara cells, an epithelial cell type that contains P450, also demonstrated reduced cell proliferation in late maturing areas and increased NADPH reductase expression, two indicators of early maturation. Two other Clara cell enzymes, cytochrome P450 2B and Clara cell secretory protein, were not affected. Premature induction of metabolic pathways could be seen to serve a protective function in the immature lung; however, production of reactive intermediates that induce oxidative damage and genotoxicity is also possible.

Postnatal SS exposure has also been studied in connection with lung responsiveness associated with the C-fiber system. C-fibers in the lung mediate an airway defense response which includes mucus secretion, bron-

choconstriction, and coughing in response to irritants. Compliance, resistance, and lung morphology were measured in the isolated, perfused lungs of 43-day-old guinea pigs that had been exposed to SS at a concentration of one mg/m^3 from 8 days of age (Joad *et al.*, 1995a). Baseline compliance was increased modestly (17 percent) by SS exposure, but lung morphology and baseline resistance were not altered. The response of the lung to capsaicin, a specific C-fiber agonist, was reduced by SS exposure, but the response to substance P, which is released by the C-fiber, was not affected; this suggests a down-regulation of C-fiber responsiveness (*i.e.*, the lung is still able to respond directly to substance P, but doesn't respond to capsaicin, indicating that decreased responsiveness to capsaicin involves the C-fibers). Reduced C-fiber responsiveness indicates a depressed defense response that could result in greater penetration of toxicants and infectious agents into the lung and be responsible for higher incidence of respiratory problems.

6.3 SUSCEPTIBLE POPULATIONS

6.3.1 Atopy/Atopic Dermatitis

Atopy refers to an inherited predisposition to develop IgE antibodies against common environmental and dietary allergens. This predisposition is manifested in several chronic conditions: allergic asthma, atopic dermatitis, allergic rhinitis, and allergic gastroenteropathy. Allergy (atopy with or without high serum levels of IgE) can be documented in most cases of asthma (Burrows *et al.*, 1989, as cited in U.S. EPA, 1992), although exercise-induced bronchospasm, reactive airways dysfunction syndrome, and many types of occupational asthma can occur in nonatopic individuals.

The evidence relating ETS exposure to the development of atopy is mixed. Several studies have shown that exposure to passive smoke is significantly associated with total serum IgE concentration and may therefore affect the development of allergic disease. Studies that showed a relationship between active smoking and IgE levels, such as those reviewed in U.S. EPA (1992) (Gerrard *et al.*, 1980; Burrows *et al.,* 1981; Zetterstrom *et al.,* 1981; Taylor *et al.,* 1985), prompted researchers to investigate the relationship of passive smoke exposure and allergic sensitization in children. Several studies have shown up to a 2.2-fold increased risk of atopy in children of smoking mothers (Weiss *et al.*, 1985; Martinez *et al.*, 1988). Ronchetti *et al.* (1990) analyzed the same population used by Martinez *et al.* (1988) and found that total serum IgE levels and eosinophil counts were significantly greater in children of smoking parents.

In contrast, two studies of maternal active and passive smoking during pregnancy showed no association of *in utero* ETS exposure and umbilical cord blood IgE (Oryszczyn *et al.*, 1991; Ownby *et al.,* 1991). High levels of cord blood IgE are predictive of the development of childhood allergy. A group of 99 singleton births in a hospital in Paris, France, were used to validate use of cord blood cotinine and maternal urinary cotinine concentrations in a study of *in utero* exposure to parental smoking (Oryszczyn *et al.*, 1991). Twenty percent of the mothers smoked at least one cigarette per day during one of three trimesters. Infants whose mothers smoked or had been passively exposed to ETS had significantly higher cord blood cotinine levels

than infants whose mothers neither smoked nor been exposed to ETS. However, no association was observed between cord blood IgE and maternal smoking as assessed by either questionnaire or cord blood cotinine. This study did not examine postnatal ETS exposure.

Ownby *et al.* (1991) followed 114 infants born to subscribers of a health maintenance organization in Michigan. The infants were selected from a stratified sample chosen to assure nearly equal proportions of infants from nonsmoking, light, and heavy smoking households, although the definitions for each category are not stated in the report. As in the previous study, cord cotinine concentrations were measured to assess the validity of self-reported maternal smoking. Neither univariate analyses nor analyses that adjusted for the children's gender, birth weight, birth length, paternal history of allergies, maternal history of allergies or asthma, maternal visit to an allergist, history of skin testing, or immunotherapy were significantly related to cord blood IgE. The authors speculated that if passive smoking induces atopy only in those with a familial tendency, such a study design might mask an association if atopics are less likely to smoke. Therefore, regression models were run both with and without adjustment for parental history of allergic disease. The association was also nonsignificant for a subgroup of infants whose parents were not atopic. When multiple regression models were used, the authors detected an association of immunoglobulin D (IgD) and paternal, but not maternal, smoking. However, the function of IgD and its relationship, if any, to the development of atopy and allergy, have not yet been elucidated.

Recently, Soyseth *et al.* (1995) investigated the relationship of prenatal and postnatal household smoking to the prevalence of atopy, defined as at least one positive skin prick test, in a cross-sectional study of 556 Norwegian school children, aged 7 to 13 years. Questionnaire assessment of ETS exposure addressed smoking by either parent during the mother's pregnancy, as well as several indices of parental postnatal smoking. In multivariate analyses that initially included age, gender, reported bronchitis before 2 years of age, and parental history of asthma or hay fever, Soyseth *et al.* reported that prenatal maternal smoking was negatively associated with atopy (OR = 0.6, 95% CI = 0.4-0.9), while postnatal ETS exposure was not associated with this condition (OR = 1.2, 95% CI = 0.7-2.1). No index of paternal smoking was associated with atopy. The authors did not believe that this negative association of prenatal smoking with atopy was causal, but hypothesized rather that it may have been due to selective avoidance of smoking during pregnancy by women whose offspring might have been at higher risk of developing atopy (*e.g.,* because of a family history of allergy). Regardless of the validity of this hypothesis, these results do not indicate an increased risk of allergic sensitization due to parental smoking, either prenatally or postnatally.

Investigators have also examined both the interactive effect of passive smoke exposure in children with atopic dermatitis (AD) and subsequent development of asthma. AD is characterized by a chronic or relapsing pruritic (itchy) rash. Murray and Morrison (1990) studied 240 asthmat-

ic children aged 6 to 17 years. They found a relationship between AD and subsequent development of asthma in children with mothers who smoked. In a reanalysis of the data (Murray and Morrison, 1992), asthmatic children with smoking mothers were found to have significantly greater asthma severity than those with nonsmoking mothers. The authors concluded that passive smoking may cause asthma only in children who have a history of atopic dermatitis, while exacerbating severity in those who are already symptomatic.

In summary, whether there is a relationship between the development of atopy and prenatal or postnatal exposure to ETS has not been as thoroughly researched as have other outcomes discussed in this report. Published investigations of this issue have produced mixed results.

6.3.2. Cystic Fibrosis Cystic fibrosis (CF) is an autosomal recessive disease characterized by thickened mucus, a nonfunctional mucociliary clearance pathway, and recurrent and chronic pulmonary infections. Among whites in the United States, it is the most common life-threatening genetic disease, occurring in one in 2,500 live births. Incidence of CF is much lower in U.S. black populations, affecting only 1 in 17,000 live births. Certain patients with CF have severe pancreatic insufficiency with intestinal malabsorption and growth retardation. Life expectancy for patients with CF has improved dramatically over the past 2 decades. In 1978, only 18 percent of CF patients were aged 18 and older. By 1991, this had risen to 33 percent. Patients with CF are now living into the sixth and seventh decades of life (Boat and Boucher, 1994). Only a few studies have examined potential effects of ETS on patients with CF: these are summarized in Table 6.6

In a cross-sectional study, Gilljam *et al.* (1990) studied 32 Swedish children with CF, aged 1 to 20 years, 22 of whom had at least one parent who smoked one or more cigarettes per day in the home. A clinical index was computed for each child using the Shwachman score (the lower the score, the more severe the disease). The number of severe respiratory infections was assessed by the number of days of antibiotic treatment in a hospital during a 1-year interval. Pulmonary function tests were administered, and the number of weekly scheduled physical activities per week was counted. Gilljam *et al.* found that there was no significant association between passive smoking and clinical score; however, six of seven children with low scores came from smoking families. There was a significant difference between days of antibiotic treatment in a hospital if the mother was a smoker compared to if only the father smoked ($p < 0.05$). High physical activity level appeared to dampen the negative effects of ETS. Lung function was not associated with passive smoking.

In another cross-sectional study, Rubin (1990) studied 43 Canadian children (18 girls and 25 boys) aged 6 to 11 years at a CF summer camp to assess the relationship of passive smoke exposure to growth, nutritional status, lung function, clinical condition, and number of hospital admissions. More than half (24) of the children came from homes with smokers—nearly 40 percent from families in which the mother smoked. None of the children smoked. Although statistical analyses were normalized for age, no further adjustments were made.

Hospital admission rates (defined as the total number of admissions adjusted for the child's age) were strongly correlated with number of cigarettes smoked in the home ($r = 0.58$, $p < 0.0001$) for the group as a whole and for the subset of children with smoke exposure in the home. When analyses were stratified by gender, this relationship was apparent for female subjects only. A significant correlation of ETS exposure and clinical score was apparently confounded by nutritional status, attributed largely to the strong correlation between nutritional subscore and ETS exposure. In addition, those children assessed as having poor nutritional status who were exposed to passive smoke had higher admission rates than those with poor nutrition from nonsmoking homes ($p = 0.10$).

Rubin also found a significant interaction between lung function and ETS in relation to hospital admission rates ($p = 0.05$); among children with lower lung function, smoking in the home was associated with significantly more hospitalizations. There was also a significant association between percentage of predicted peak expiratory flow rate (PEFR) and smoke exposure, but no significant associations were found for other pulmonary function measures. For girls, there was a significant inverse correlation between number of cigarettes smoked per day in the home and height and weight ($p < 0.05$); for boys, there was a near-significant correlation with height ($p = 0.067$). There was no association of coughing, sputum production, or nasal polyps with passive smoke exposure.

This study did not adjust for socioeconomic status (SES). However, changes in clinical status that could be related to economic barriers to health access are unlikely to have affected the results because Canada has national health insurance. Moreover, this CF population was in fairly good health, with participants scoring an average of 22 points on the 25-point Shwachman score. Although the camp population might not be representative of all children with CF, the camp was free and open to anyone with the disease. On the other hand, in epidemiological studies of ETS, SES may be a confounder, not only because people in lower SES brackets tend to have a greater prevalence of smoking, but also because their residences tend to be smaller, increasing the probability of exposure to more concentrated ETS and other household respiratory irritants that could exacerbate CF.

Campbell *et al.* (1992) studied 44 CF patients aged 1 to 22 years, who were homozygous for the F508 deletion (the most prevalent CF mutation) to examine the effect of ETS exposure on clinical status after controlling for age and SES. All patients had pancreatic insufficiency, a condition associated with more severe disease. Of the 44 patients, 22 lived in homes with light smoke exposure (1-2 packs per day) and six lived in homes with heavy exposure (3-4 packs per day). The data were analyzed using a generalized linear model. There were no significant differences between the light-exposure and no-exposure groups, so these two groups were combined in later analyses and compared to the heavy smoking group. Heavy exposure was significantly associated with disease severity as measured by the Shwachman score, FEV_1 ($p = 0.007$), forced vital capacity ($p < 0.0001$) and a five-fold increase in the number of pulmonary related hospital admissions

($p < 10^{-6}$). Models were adjusted for age and SES. Since the heavy-exposure group contained only six people, other investigators have cautioned that the results of this study may have been due to a chance clustering of high ETS exposure and poor nutritional status. The authors did conduct a "sensitivity analysis" in which two of six people were given normal pulmonary function levels and severity scores; however this did not reduce the results to nonsignificance.

More recently, Smyth *et al.* (1994) assessed the relationship of ETS exposure as measured by questionnaire and urinary cotinine in 57 children with CF and 51 controls. The age range of both groups was 5 to 16 years. The investigators examined the relationship of ETS to pulmonary function (FEV_1 and FVC) in the CF patients. Urinary cotinine levels and ETS exposure assessed by questionnaire ("smoking index") were both significantly greater in the homes of control children. FEV_1 and FVC (both expressed as a percentage of predicted for height) were regressed on cotinine concentration, smoking index, parental occupations, and patient's age and sex. Smoking index was a significant predictor of decreased FEV_1 ($p = 0.022$) and FVC ($p = 0.047$)—for each ten-cigarette increment in the smoking index, the investigators predicted a 4 percent decrement in FEV_1 and a 3 percent decline in FVC. However, urinary cotinine was not predictive of either measure of lung function, which Smyth *et al.* speculated might have been due to the flatness of the cotinine versus lung-function curve in the lowest three-fifths of the cotinine distribution. The geometric mean urinary cotinine concentration was 5.12 ng/ml, which lends credibility to the investigators' hypothesis; however, not enough detail is provided in this brief report to evaluate adequately the discrepancy between the results of the smoking index and cotinine analyses. Smyth *et al.* did not examine the relationship of ETS to either disease severity or hospitalizations in these CF patients.

Kovesi *et al.* (1993) examined relationships between household ETS exposure and several clinical parameters in 325 patients attending the Cystic Fibrosis Clinic at the Hospital for Sick Children in Toronto in 1990 to 1991. Data on household smoking were routinely obtained by clinic nurses on standardized forms, and included whether anyone in the household (including the patient) smoked cigarettes and, if so, the total number of cigarettes consumed in the home by all smokers. The age range of 1 to 42 years was considerably larger than in any of the other studies (Kovesi, personal communication), but separate analyses were done on children aged 6 to 11 for comparison to the study by Rubin (1990). The percentage of participants exposed only to maternal smoking was not identified. Given the reported mean age in both exposed and nonexposed groups, some of these patients were probably not living with their parents, which might distinguish this study population from the others described above. Comparing patients from smoking versus nonsmoking households, there were no significant differences in Shwachman scores, spirometry (FVC, FEV_1, FEF_{25-75}), height and weight percentiles, colonization by *Pseudomonas* species, or other variables. However, patients with ETS exposure were younger, with a mean age of 14.4 years versus 17.0 years for the unexposed. Linear regression analysis showed no relationship between the number of

cigarettes smoked in the household and the children's weight or weight percentiles, weight for height, Shwachman or Brasfield scores (different measures of clinical status), spirometric indices, number of hospital admissions, or number of days spent in the hospital. When households with smokers (n = 97) were analyzed separately, similar results were obtained. When the subset of children aged 6 to 11 were analyzed, the results were similar to those obtained for the entire study population, except that there was a significant inverse correlation between the number of cigarettes smoked in the household and the patients' height percentile (r = -0.27, p = 0.04).

The authors also conducted separate longitudinal analyses of spirometry, weight and height percentiles for 182 patients who had had smoking and spirometric data collected between 1977 and 1985. ANOVA was used to compare various clinical parameters among three groups: those who reported no smoke exposure in either data collection period ("NEVER"), those reporting ETS exposure both times ("ALWAYS"), and those reporting such exposure between 1977 and 1985, but not in 1990 or 1991 ("QUIT"). A fourth "STARTED" group was too small and heterogeneous to be used in analysis. The height percentile increased for the NEVER group, while the index decreased for the ALWAYS group and decreased even more for the QUIT group. This same relative order was observed for changes in weight percentile and weight for height percentile. Though all groups experienced a decline in their percent predicted spirometric indices (FVC, FEV_1, FEF_{25-75}), the decrease was greatest in the QUIT group and least in the NEVER group. When the analysis was restricted to the subgroup of CF patients homozygous for the ΔF_{508} mutation, similar results were found, after an "outlying" patient with "extremely heavy smoking exposure" was excluded from the analysis.

In this large study, Kovesi *et al.* confirmed the existence of a negative dose-response relationship between household ETS exposure and linear growth in children with CF aged 6 to 11, reported previously by Rubin (1990). In the longitudinal component of the investigation, they found that exposure to household ETS was associated with growth suppression. In contrast to the findings of Campbell *et al.* (1992) and Smyth *et al.* (1994), but similar to Rubin (1990), those investigators did not find a relation between ETS exposure and lung function. In the Campbell study, which examined patients homozygous for the ΔF_{508} deletion, effects were found only in six patients with relatively high reported ETS exposure. Moreover, the distribution of reported smoking levels in the investigation by Kovesi *et al.* was such that all patients would have been classified in the "light-exposure" group in the Campbell study, thus the results of these two reports are not inconsistent.

In the Kovesi study population, there was considerable inter-child variability in spirometry, which is characteristic of CF patients, making small mean lung function differences difficult to detect. Kovesi *et al.* also could not confirm the relationship between ETS and hospital admissions reported by both Rubin and Campbell *et al.* However, whereas Rubin examined age-adjusted hospitalizations over the children's lifetimes, Kovesi *et al.* appear to have examined only hospitalizations (and days in hospital) over

the year preceding the children's clinic visit. Furthermore, although the initial analysis comprised a much larger study population than previous studies, the subsample of children aged 6 to 11 was not much larger than that of Rubin. In addition, the study by Kovesi *et al.* included older patients than the other five studies, although the investigators were not able to detect an interaction of age and smoking exposure on any of the outcomes. As noted above, the reported exposure distribution of ETS-exposed children in the Kovesi study was comparable to Campbell *et al.*'s "light-exposure" group, for which the latter investigators found no effect of ETS exposure on hospitalizations. Thus, the results of the Kovesi study with respect to hospital admissions are not necessarily inconsistent with those reported by others. In addition, the identities of household smokers (other than the few actively smoking study participants) were not obtained. In other settings (*e.g.,* induction of childhood asthma), maternal smoking appears to be more strongly related to young children's actual ETS exposure than paternal smoking. Thus, here, as elsewhere, misclassification of exposure may have produced a bias towards the null hypothesis of no effect. Finally, in the regression analysis conducted by Kovesi *et al.*, it appears that they did not adjust for SES, which could also have confounded the results (see above).

In part because CF is such an uncommon disease, four of these five studies have small sample sizes and low statistical power. Given this limitation, the finding that ETS is associated with hospitalizations for respiratory infection in three of four studies is striking. This relationship was observed in Rubin's (1990) study, which included relatively healthy children, and Campbell's study in which the children presumably had more severe disease. Rubin (1990) also detected interactions of ETS with the number of hospitalizations in those with lower pulmonary function and poor nutrition. While Gilljam *et al.* (1989) did not observe a direct effect of ETS on hospitalizations, they did find effects in those exposed to maternal smoking. In contrast, Kovesi *et al.* (1993) did not find any relationship between ETS exposure and hospitalizations.

The relationship between ETS exposure and pulmonary function in CF patients is less clear. Campbell *et al.* (1992) observed an association between ETS exposure and pulmonary function, whereas Gilljam *et al.* (1990), and Kovesi *et al.* (1993) in a much larger study, did not. Smyth *et al.* (1994) observed a relationship between ETS and lung function, as measured by FEV_1 and FVC, when questionnaire data were used but not when ETS was assessed using salivary cotinine levels. Rubin (1990) found an association with PEFR but not with other spirometric measures. People with CF demonstrate greater variability on pulmonary function tests than healthy subjects. This variability combined with the rarity of the disease make it difficult to demonstrate effects on pulmonary function.

Disease severity was investigated in four of the five studies. Only one study, that of Campbell *et al.* (1992) found a relationship with ETS exposure. Gilljam *et al.* (1989) found a positive but nonsignificant relationship with disease severity, Rubin's analysis was confounded by nutritional status, and Kovesi *et al.* found no effect of ETS on disease severity in their

large study population. Finally, in the two studies that looked at effects on growth, both found effects in the 6- to 11-year-old age group. Rubin observed age-adjusted relationships with height and weight in girls and with height in boys. Kovesi *et al.* also found a significant relationship with height by household smoking group in their longitudinal analysis.

In reviewing these five studies, it is important to note that the age ranges of the study populations were different. Two studies included children only (Smyth *et al.*, 1994; Rubin, 1990), two study populations were comprised of infants, children and young adults (Campbell, 1992; Gilljam *et al.*, 1989) and one included infants, children, and young and older adults (Kovesi *et al.*, 1993). Some of the differences in study findings are potentially attributable to this variation in composition. In particular, if young children with CF are most sensitive to ETS or are likely to experience the greatest intensity of exposure, the study population of Kovesi *et al.* would have had any ETS-related effects diluted by the inclusion of relatively older participants.

In summary, although several reports suggest that passive smoke exposure can affect patients with CF, the extent and magnitude of such effects are still uncertain. The evidence for an effect on hospitalizations is compelling, while the studies are less conclusive in showing an effect on pulmonary function or disease severity. The two studies that have looked at growth have both found an inverse relationship between ETS exposure and linear growth. Because of the rarity of CF, relatively few children with CF in California are likely to be affected by ETS exposure. In all five studies, however, the proportion of CF patients with ETS exposure was quite high, ranging from 42 percent in the study by Kovesi *et al.* (1993) to 69 percent in the study by Gilljam *et al.* (1989).

6.4 CHAPTER SUMMARY AND CONCLUSIONS

ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. ETS exposure can exacerbate asthma in children, perhaps affecting 48,000 to 120,000 children annually in California; adults may also be affected. Parental smoking is associated with an increased risk of acute lower respiratory tract illnesses in children, as well as acute and chronic otitis media with middle ear effusions. In California, ETS-related otitis media cases may result in an estimated 78,000 to 188,000 office visits per year among children under three years of age. From 18,000 to 36,000 cases of ETS-related bronchitis or pneumonia can be predicted to occur in children 18 months of age and under, based on national statistics. Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS; in addition, odor annoyance from indoor exposure to ETS has been shown in several studies. Experimental studies conducted by investigators familiar with building ventilation practice suggest that, short of prohibiting indoor smoking, protection of nonsmokers against both sensory irritation and odor annoyance can only be achieved through extensive engineering measures.

Table 6.6
ETS Exposure Relationship with Pulmonary Function, Hospitalizations, and Disease Severity in Children with Cystic Fibrosis

Study	Age of Subjects (N)	ETS Exposure Prevalence	Pulmonary Function	Hospitalizations for Cystic Fibrosis	Cystic Fibrosis Severity	Growth
Gilljam *et al.* (1989)	1-20 (32)	22/32 (69%)	NS	In those exposed to maternal smoking, an effect of ETS on number of days of antibiotic treatment in hospital	Positive but not significant	Not examined
Rubin (1990)	6-11 (43)	24/53 (56%)	Significant only for PEFR, not for FEV_1 or FVC	Significant, overall and in ETS group, but only for girl-ETS. Interaction with both poor nutrition and low pulmonary function	Yes, but confounded by nutrition (Unadjusted)	In girls, relationship of ETS to height and weight. In boys, only height
Campbell *et al.* (1992)	1-22 (44)	28/44 (64%)	Significant for both FEV_1 and FVC	Significant, RR = 4.7 (95% CI = 1.8-7.6)	Significant	Not examined
Smyth *et al.* (1994)	5-16 (57)	33/57 (58%)	Assessment of ETS exposure by questionnaire but not cotinine related to both FEV_1 and FVC	Not examined	Not examined	Not examined
Kovesi *et al.* (1993)	1-42 (325)	97/228 (43%)	NS in cross-sectional study; in longitudinal study, QUIT group was significantly worse than NEVER group	ns	ns	In 6-11 yr. group, a relationship with height percentile. Relationship with height by household smoking group in longitudinal analysis

Abbreviations: N = study size; PEFR = peak expiratory flow rate; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RR = relative risk; ns = nonsignificant

There is consistent and compelling evidence that ETS is a risk factor for induction of new cases of asthma; in California, between 960 and 3,120 new cases per year may be ETS-related. In addition, chronic respiratory symptoms in children, such as cough, phlegm, or wheezing, are associated with parental smoking. While the results from all studies are not wholly consistent, there is substantial evidence that childhood exposure to ETS affects lung growth and development, as measured by small, but statistically significant decrements in pulmonary function tests; associated reductions of lung function may persist into adulthood. The effect of chronic ETS exposure upon pulmonary function in otherwise healthy adults is likely to be small, and is unlikely by itself to result in clinically significant chronic disease. However, in combination with other insults (*e.g.,* prior smoking history, exposure to occupational irritants, or ambient air pollutants), ETS exposure could contribute to chronic respiratory impairment in adults. In addition, regular ETS exposure in adults has been reported to increase the risk of occurrence of a variety of lower respiratory symptoms.

Children are especially sensitive to the respiratory effects of ETS exposure. Children with cystic fibrosis are likely to be more sensitive than healthy individuals. Several studies of patients with cystic fibrosis, a disease characterized by recurrent and chronic pulmonary infections, suggest that ETS can exacerbate the condition. Several studies have shown an increased risk of atopy (a predisposition to develop IgE antibodies against common allergens, which can then be manifested as a variety of allergic conditions) in children of smoking mothers, though the evidence regarding this issue is mixed.

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Carcinogenic Effects

7.0 INTRODUCTION It has been estimated that 22 percent of all cancer deaths in women and 45 percent of all cancer deaths in men can be attributed to personal smoking habits (Shopland *et al.*, 1991). Smoking is an established cause of cancers of the lung, larynx, oral cavity (including pharynx), esophagus, and bladder. It is a probable cause of cancers of the kidney, pancreas, and stomach in men and women, and of cervical cancer in women (IARC, 1986; U.S. DHHS, 1989). Environmental tobacco smoke (ETS) has been established as a cause of lung cancer in nonsmokers (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992). This document explores the role of ETS in the etiology of cancers, including lung cancer and cancers other than lung, in nonsmokers.

In the first part of this review, available data is presented on the relationship between ETS and all cancers combined, in adults (Section 7.1.1), and in children (Section 7.1.2). Second, evidence is discussed regarding the role of ETS in the etiology of specific cancer sites. Section 7.2 presents the data on ETS and lung cancer. In Section 7.3, the evidence is discussed on ETS exposure and cancer sites other than lung which are causally linked to active smoking. The evidence on ETS and cancer sites where the role of active smoking is equivocal (*e.g.*, cancers of the breast, stomach, brain, and hematopoietic system) is discussed in Section 7.4. That section also includes the evidence on ETS exposure and risk of childhood cancers (specific sites). Individual studies are described briefly, and the results, including the point estimates of relative risks and corresponding 95 percent confidence intervals, are presented. Findings from the studies are evaluated, taking into account the quality of the studies with respect to their study design, sample size, assessment of exposure, adjustment for potential confounders, and consideration of sources of biases. For cancers that are causally associated with active smoking, we also compare the magnitude of the risk associated with ETS exposure versus that of active smoking.

7.0.1 Misclassification of Smoking Status The 1986 National Research Council report (NRC, 1986) and a subsequent paper, Wald *et al.* (1986) pointed out that because smokers tend to marry smokers, if a study contains smokers who are misclassified as nonsmokers, they are more likely to be classified as exposed to ETS. Therefore, the estimate of relative risk to ETS exposure will be exaggerated due to the association of lung cancer with active smoking for this group of misclassified subjects. Wald *et al.* (1986) estimated the proportion of ever-smokers who are misclassified as lifelong nonsmokers to be about 7 percent. This estimate was based on the percentage of self-

reported nonsmokers (2.1 percent) who have levels of nicotine and cotinine in the range of those of smokers and the percentage of smokers who, on subsequent re-interview, claimed to have never smoked (4.9 percent). Lee (1986, 1989, 1992) has argued that the extent of this misclassification bias is higher—about 12 percent. As discussed in detail below, two recent studies (Riboli *et al.*, 1995; Nyberg *et al.*, 1997) using different methodologies conclude that, while there is some misclassification of smokers as nonsmokers, the misclassification rate is low and is unlikely to explain the observed lung cancer risk from ETS exposure.

Riboli *et al.* (1995) reported the results of a multicenter (13 centers) international (10 countries) study organized by the International Agency for Research on Cancer (IARC) to validate self-reported exposure to ETS from different sources by analysis of urinary cotinine levels. Questionnaire data and urine samples were collected from 1,369 nonsmoking women who had not used any tobacco products for at least 2 years. Forty-seven women had urine cotinine levels above 50 ng/mg creatinine, a level used to discriminate smokers from nonsmokers in some previous studies. Further investigation of these 47 women showed that 27 had levels between 50-150 ng/mg while 20 had levels exceeding 150 ng/mg. In fact, the majority of women (16 of 27) with levels between 50-150 ng/mg had reported long daily exposure to ETS (>5 hours per day) 4 to 8 days prior to sample collection and were exposed to at least eight cigarettes per day. On the other hand, a significantly lower percentage of women with cotinine levels exceeding 150 ng/mg had long daily exposure to ETS or were exposed to at least eight cigarettes per day. These investigators concluded that most of the women with levels between 50 to 150 ng/mg were truly heavily exposed to ETS, while those with levels above 150 ng/mg were more likely to be deceivers and may have smoked. Thus the percentage of deceivers (1.5 percent, 20 of 1,369) in this cross-sectional study is quite comparable to that reported by Fontham *et al.* (1994) in which 0.6 percent of lung cancer cases (2 of 356) (prescreened for smoking status on the basis of medical history and other factors) and 2.3 percent of population controls (25 of 1,064) showed cotinine/creatinine concentrations of 100 ng/mg or higher. Results from this study also illustrate that cotinine levels of 50-150 ng/mg are quite plausible when nonsmokers are very heavily exposed to ETS.

Nyberg *et al.* (1997) investigated misclassification rates in two large Swedish cohorts in which smoking habits were assessed on two separate occasions some 6 to 10 years apart. Two types of misclassification rates were presented. The first misclassification rate was calculated based on the number of ever-smokers misclassified as never-smokers divided by the total population of ever-smokers. The second misclassification rate was calculated based on the number of reported never-smokers who really were smokers divided by the total population of never-smokers. In this study, the proportion of ever-smokers misclassified as never-smokers was 4.9 percent among men and 4.5 percent among women in the first cohort studies; the corresponding figures in the second cohort were 5.0 percent and 7.3 percent. The misclassification rate expressed as the proportion of never-smokers who really were smokers was 11.1 percent in men and 1.3 percent in women in

the first cohort study and 11.5 percent and 2.2 percent, respectively, in the second cohort study. Nyberg *et al.* (1997) noted that there is good agreement in most studies in terms of the first misclassification rate irrespective of geographic area or gender of subjects. On the other hand, the second misclassification rate is much more variable from study to study, and that rate can be misleading because it is dependent on the number of nonsmokers in a particular study. Aside from the rate of misclassification, these investigators also showed that in this, as in other study populations, most of the ever-smokers who were misclassified as nonsmokers had quit smoking some time earlier and smoked less than the average smokers. Thus, this study also suggested that there is limited smoker misclassification and that misclassification bias does not explain the observed lung cancer risk associated with ETS exposure.

Both of these studies suggest that to a large extent, misclassification of smokers as nonsmokers can be minimized if adequate screening questions are used to ensure that former smokers are identified and are excluded from studies of lifetime nonsmokers. Although cotinine is only a marker of recent tobacco exposure, it is still useful to be able to exclude current smokers from a study. In fact, multiple sources of information and questions designed to screen out current or former smokers were used in many of the newer studies of ETS and lung cancer (such as Fontham *et al.*, 1994) so that this source of misclassification bias has been minimized. Thus, the collective evidence from the newer studies (Riboli *et al.*, 1995; Nyberg *et al.*, 1997), as well as the studies reviewed by the U.S. EPA (1992), indicates that misclassification bias does not explain the observed lung cancer risk associated with ETS exposure.

7.1 ALL CANCERS (COMBINED)

Overall cancer related death rates for smokers are about two times higher than for nonsmokers (U.S. DHEW, 1979). Those nonsmokers who are exposed to tobacco smoke are exposed to the same toxic constituents of tobacco smoke as smokers (U.S. DHHS, 1986), although active smokers and those exposed to ETS may differ in the relative amounts of carcinogens to which they are exposed. Furthermore, the phase distributions of compounds differ between mainstream smoke and ETS. More of the constituents appear in the vapor phase (versus the particulate phases) in ETS compared to mainstream smoke, and particle sizes are smaller in ETS. Components also enter the vapor phase from the particulate phase as ETS ages. Therefore, the relative uptake and deposition of these components potentially differ between active and passive smokers (Guerin *et al.*, 1992). Because of these differences, it is not apparent which cancer sites may be most affected by ETS exposure. This section describes studies addressing the overall risk of cancer (all sites combined) from ETS exposure, in adults and in children.

7.1.1 All Cancers In Adults

Cancer risk in adult life may be due to an accumulation of exposures incurred transplacentally, during childhood, and during adult life. To study the potential role of ETS exposure in the etiology of various cancers in adults, most of the studies have focused on the association between adult exposure to ETS and subsequent risk (Hirayama,

1984; Sandler *et al.*, 1989; Reynolds *et al.*, 1987; Sandler *et al.*, 1985a), although the role of ETS exposure during childhood as a risk factor for adult cancers has also been investigated (Sandler *et al.*, 1985b).

7.1.1.1 Cohort Studies Risk of all cancers in nonsmokers exposed to ETS (based on spousal smoking) was evaluated in three cohort studies.

Hirayama (1984) In the first cohort study, the mortality of 91,540 nonsmoking wives in relation to the smoking habits of their husbands was investigated in Japan (Hirayama, 1984). Mortality of the cohort was monitored by review of death certificates and the annual census of residents. After 16 years of follow-up, there were a total of 2,705 cancer deaths (all sites) among the nonsmoking women. The relative risks (RRs) were 1.00, 1.12 (95% CI = 1.03-1.21), and 1.23 (95% CI = 1.12-1.35) for women whose husbands were nonsmokers, ex-smokers or smokers of 1-19 cigarettes per day, and smokers of 20 or more cigarettes per day, respectively, when adjustment was made for husband's age and occupation. In this population, the increased risk for all cancers combined was due mainly to the increased risk observed for cancers of the lung, nasal sinus, and brain. These respectively accounted for 7 percent, 1 percent, and 1 percent of the tumors in this population. Stomach cancer, representing 31 percent of the cancers in this population, was not associated with passive smoking (Hirayama, 1984). There was a small increased risk of cervical cancer in passive smokers (see Section 7.2.2) (Table 7.1).

Sandler et al. (1989) Using a cohort surveyed in 1963 in Western Maryland, Sandler *et al.* (1989) evaluated the all-cancer mortality in nonsmokers who lived with smokers. A total of 22,973 Caucasian men and 25,369 Caucasian women were enrolled; 4,162 men and 14,873 women were lifetime nonsmokers. In 1975, death records were reviewed to evaluate the risk of mortality, and specific causes of mortality, in passive smokers compared to nonsmokers not exposed to ETS. In brief, a score ranging from 0-12 was assigned to each adult in the household based on his/her smoking history. A total household smoking score was then calculated by summing the smoking contribution scores of all persons living in that household. Each individual's household ETS exposure was calculated by subtracting his or her own contribution from the total household score. Among nonsmokers, 1,248 men (30.0 percent) and 9,551 women (64.2 percent) were exposed to household tobacco smoke and were considered to be passive smokers. Exposure to ETS did not increase the risk for all cancers combined in nonsmoking men (RR = 1.01, 95% CI = 0.66-1.53) and nonsmoking women (RR = 1.00, 95% CI = 0.82-1.21) after adjusting for age, marital status, education, and housing quality. When the analysis was conducted separately for tumors related to smoking and tumors not related to smoking, exposure to ETS was associated with a small increased risk for smoking-related tumors in women (RR = 1.45, 95% CI = 0.88-2.40), but not in men (RR = 0.96, 95% CI = 0.66-1.53). In men and women, there was no association between ETS exposure and risk of non-smoking-related tumors (Table 7.1).

Table 7.1
Exposure to Spouse's Smoking and Relative Risk (RR) of all Cancers in Adults

Cohort Studies	# Cases	Exposure to Passive Smoking	RR (95% CI) for Spouse's Smoking
Hirayama, 1984		Husband's smoking	
All cancers[a]	634	Nonsmoking	1.00
	1,341	Ex-/1-19/day	1.12 (1.03-1.21)[b]
	730	20+/day	1.23 (1.12-1.35)
Sandler *et al.*, 1989	Males	Household smoking	
All cancers[a]	84	No	1.0
	31	Yes	1.01 (0.66-1.53)
	Females		
	211	No	1.00
	290	Yes	1.00 (0.82-1.21)
All cancers classified as:			
Smoking-related cancers	Males		
	24	No	1.0
	8	Yes	0.96 (0.43-2.62)
	Females		
	27	No	1.0
	49	Yes	1.45 (0.88-2.40)
Other cancers	Males		
	60	No	1.0
	23	Yes	1.03 (0.40-2.62)
	Females		
	184	No	1.0
	241	Yes	0.93 (0.76-1.54)
Reynold *et al.*, 1987		Husband's smoking	
All cancers[a]	71[c]	No	1.00
		Yes	1.68 (1.12-1.5)[b]
Smoking-related cancers	4[c]	No	1.00
		Yes	7.01 (1.05-47.0)

[a] *There were 200 lung cancers in Hirayama (1984); 2 lung cancers in Sandler et al., 1989; and an unspecified number in Reynold et al., 1987.*
[b] *90% CI confidence intervals.*
[c] *The distribution of the 71 cancers by husband's smoking was not presented; the specific cancer sites were not presented.*

Reynolds et al. (1987) Reynolds *et al.* (1987) reported results from a small cohort of 2,413 married women (46 percent had never smoked) who participated in a population-based survey in Alameda County, California in 1965. Smoking history was independently ascertained for each spouse. Based on 71 cancers diagnosed among the 1,111 nonsmoking women during the 17 years of follow-up, nonsmoking women whose husbands smoked showed a RR of 1.68 (90% CI = 1.1-2.5) for all cancers combined compared to women whose husbands did not smoke. The authors also reported a 7-fold increased risk (90% CI = 1.1-47.0) of smoking-related cancers in relation to husband's smoking (Table 7.1), but this was based on four cases only (smoking-related cancers included cancers of the lung, mouth, esophagus, bladder, pancreas, liver, kidney, and uterine cervix); the specific sites of the four cases were not presented.

7.1.1.2 Case-Control Studies Overall cancer risk in relation to ETS exposure from spouses and parents was evaluated in a case-control study conducted by Sandler *et al.* (1985a). This study included all cancers (excluding skin cancers) diagnosed between ages 15 and 59, during July 1979 through March 1981, from the hospital-based tumor registry affiliated with the University of North Carolina. Of the 740 eligible cancer cases, 518 completed a mailed questionnaire which included information on ETS exposure during childhood and adult life. For 360 of the 518 cases, a friend/acquaintance of the same race, gender, and within 5 years of age of the case served as a control in the study. The remaining controls were identified by systematic telephone sampling using the telephone numbers of the cases as a starting point. Passive smoke exposure during childhood was based on whether their natural parents ever smoked, smoked before the subject's birth, smoked in the house for most of the years before the subject was 10 years old, and whether mothers smoked while pregnant with the index subject. Passive smoke exposure during adult life was based on the number of years of marriage during which a spouse smoked at least one cigarette per day for as long as 6 months. The average number of cigarettes smoked by spouses was also obtained. Among the 518 cases and controls, 231 cases and 235 controls were lifetime nonsmokers.

Sandler et al. (1985a and b)

Among lifetime nonsmokers, there was a significant 2-fold increased risk (95% CI = 1.4-3.0) associated with spouses' smoking after adjustment for gender, race, and age. When the effect of ETS exposure was examined by age group, gender, and race, the effect was more apparent for subjects aged 40-49 (adjusted RR = 2.0, 95% CI = 1.4-2.9), females (adjusted RR = 2.0, 95% CI = 1.3-2.9), and non-whites (adjusted RR = 2.0, 95% CI = 1.4-3.0). However, no dose-response relationship was observed between risk and either the number of years married to a smoker or number of cigarettes husbands smoked per day (data not presented). The role of ETS exposure was also investigated by site of tumor. The increased risk was not limited to lung cancer and other smoking-related tumors, such as cervical cancer. Increased risks were also observed for breast and endocrine gland cancers—tumors not causally associated with active smoking.

In a second report of the same adult study population, Sandler *et al.*, (1985b) evaluated the association between ETS exposure from parents and risk of all cancers. Mothers and father's smoking habits were available on 438 cases and 470 controls; 197 cases and 223 controls were lifetime nonsmokers. Maternal and paternal smoking were each associated with a nonsignificant 20 percent increased risk for all cancers among nonsmokers. The effect of maternal and paternal smoking was evaluated for 'smoking-related' and 'non-smoking related' cancers. 'Smoking-related' cancers included tumors of the oral cavity and pharynx, esophagus, pancreas, respiratory and intrathoracic organs, urinary tract and cervix, and accounted for some 25 percent of tumors in nonsmokers. For 'smoking-related' tumors, the RR was 0.76 (95% CI = 0.25-2.30) for maternal smoking and 1.68 (95% CI = 0.86-3.29) for paternal smoking. For cancers not related to smoking, the RR was 1.24 (95% CI = 0.65-2.36) for maternal smoking and 1.13 (95% CI = 0.73-1.75) for paternal smoking.

7.1.1.3 Summary In summary, there is limited evidence from two cohort studies (Hirayama, 1984; Reynolds *et al.*, 1987) and one case-control study (Sandler *et al.*, 1985a) that exposure to spouses' smoking may increase overall risk of cancer in nonsmoking women. In one study, the increase is explained primarily by an elevated risk observed for lung cancer (Hirayama, 1984). However, in two studies, elevated risks were observed for sites not typically related to active smoking, as well as sites related to smoking (Reynolds *et al.*, 1987; Sandler *et al.*, 1985a). In the study by Reynolds *et al.* (1987), the strong association between husbands' smoking and smoking-related tumors was based on very few cases, accounting for only 6 percent of all cancers. In the study by Sandler *et al.* (1985a), increased risks were observed for both smoking-related (lung, cervix), and nonsmoking-related sites (breast and endocrine gland) after adjustment for age and education. Although the results on nonsmoking-related cancers are intriguing, they are difficult to interpret given that known risk factors for the specific cancers under study were not adjusted for (Sandler *et al.*, 1985a). Possible effects of potential confounders are a concern and should be more carefully researched in further studies. For example, sexual activity is a risk factor for cervical cancer and exposure to ETS may be associated with sexual activity. Alcohol intake is a risk factor for breast cancer and exposure to ETS may be positively associated with alcohol use.

7.1.2 All Cancers In Children Exposure to ETS has been investigated as a risk factor for all childhood cancers combined and for specific childhood tumors (see Sections 7.3.3 to 7.3.6). Exposure to ETS may occur during the prenatal or postnatal period. Prenatally, the fetus may be exposed to tobacco smoke constituents when the mother smokes during pregnancy (*i.e.*, transplacental effects) or if the mother is exposed to someone else's smoking, most likely the father's smoking. Postnatally, the child may be exposed to ETS directly by inhalation. The main sources of postnatal ETS exposure for a child whose parents both smoke are likely to be from the mother, and to a lesser extent the father.

In this chapter, mothers' smoking during pregnancy is considered to be a surrogate measure of mothers' smoking postnatally (see below). However, since studies on childhood cancers included subjects who were diagnosed with cancer up to age 24, it is reasonable that tobacco smoke exposure both *in utero* and postnatally would be important. Thus, study findings require cautious interpretation.

The extent of information on passive smoke exposure varied in the different studies. Two case-control studies conducted in the 1950's asked about mothers' or fathers' smoking habits at the time of interview or study enrollment. In one study, this pertained to smoking habits of parents at the time of interview which was after the death of the subject under study (Stewart *et al.*, 1958). The other study focused on the mothers' smoking habits when study subjects were enrolled (Manning and Carroll, 1957). In more recent studies, mothers' smoking habits during pregnancy were available (Neutel and Buck, 1971; Stjernfeldt *et al.*, 1986a & b; Pershagen *et al.*, 1992; Severson *et al.*, 1993). Several studies offered more detailed information by including mothers' smoking habits 1-2 years before and during the pregnancy (Gold *et al.*, 1979; Van Steensel-Moll *et al.*, 1985; John *et al.*, 1991; Gold *et al.*, 1993). Mothers' smoking during pregnancy represents transplacental exposure to tobacco smoke constituents and may also be used as a proxy variable of postnatal ETS exposure of the child. There are data to support the assumption that mothers' smoking habits during pregnancy represent an unbiased estimate of their smoking habits after pregnancy. In a study of childhood cancers and maternal smoking (Stjernfeldt *et al.*, 1986a & b), comparison of mothers' smoking habits 5 years before, during, and after pregnancy showed that a similar percentage (8 percent) of cases' and controls' mothers reported they smoked after pregnancy when they had not smoked during pregnancy. In a study of childhood brain tumors (Gold *et al.*, 1993), comparable percentages of mothers of cases (72 percent) and of population controls (73 percent) who had ever smoked reported they were smoking during the birth year of the child. However, some women may quit during pregnancy and resume afterwards so there is potential misclassification when smoking status is based only on smoking habits during pregnancy.

Other studies on childhood cancers obtained information on both mothers' and fathers' smoking habits during the index pregnancy (Preston-Martin *et al.*, 1982; McKinney and Stiller, 1986; Buckley *et al.*, 1986; Howe *et al.*, 1989; John *et al.*, 1991; Gold *et al.*, 1993; Kuijten *et al.*, 1990; McCredie *et al.*, 1994). Children whose nonsmoking mothers were exposed to spouses' smoking were thus considered exposed to ETS prenatally. In some studies, the effect of fathers' smoking was evaluated among children of nonsmoking mothers (John *et al.*, 1991; McCredie *et al.*, 1994; Gold *et al.*, 1993). None of the studies collected information on fathers' smoking postnatally. However, on the basis of the above-mentioned data that showed mother's smoking during pregnancy to be an unbiased estimate of her smoking postnatally (Stjernfeldt *et al.*, 1986a & b) or ever smoking (Gold *et al.*, 1993), it is assumed that father's smoking during pregnancy is also an unbiased proxy for father's smoking postnatally.

7.1.2.1 Biomarkers Studies of Exposure to Tobacco Smoke Constituents *In Utero* and Postnatally

The effects of transplacental exposure to tobacco smoke constituents due to maternal active smoking during pregnancy are difficult to distinguish from those of postnatal ETS exposure. Recent studies investigating the levels of three different biomarkers of tobacco-smoke exposure in the offspring of mothers who smoke have demonstrated that the fetus (Coghlin *et al.*, 1991; Hammond *et al.*, 1993), the newborn (Eliopoulos *et al.*, 1994), and the young child (Crawford *et al.*, 1994) are all exposed to considerable amounts of tobacco products.

Eliopoulos et al. (1994)

In one of the studies (Eliopoulos *et al.*, 1994), mothers were identified 1 to 3 days after delivery and five to seven hair shafts were obtained near the skull from both the mothers and their newborns for determination of nicotine and cotinine levels (Table 7.2a). Although previous studies typically measured cotinine and nicotine levels in saliva, serum, or urine, levels measured in hair samples provide more long-term assessment of ETS exposure. Nicotine and cotinine levels were highest in mothers who were active smokers, intermediate in nonsmokers who were passive smokers, and lowest in nonsmokers not exposed to ETS. The respective mean levels were 19.2, 3.2, and 1.2 for nicotine (ng/mg) and 6.3, 0.9, and 0.3. for cotinine (ng/mg). Newborns of smokers showed significantly higher mean levels of nicotine (2.4 ng/mg) than newborns of passive smokers (0.28 ng/mg) or nonsmokers (0.4 ng/mg). Nicotine levels in newborns of passive smokers were not higher than those of nonsmokers but the difference in levels was not statistically significant. On the other hand, mean levels of cotinine were highest in newborns of smokers (2.8 ng/mg), intermediate in passive smokers (0.6 ng/mg), and lowest in nonsmokers (0.26 ng/mg). The cotinine levels in newborns of passive smokers were significantly higher than levels in newborns of nonsmokers, and were significantly lower than levels in newborns of smokers. The authors explained that nicotine may be a less sensitive marker than cotinine because of its shorter half-life (1-3 hours for nicotine compared to 10-14 hours for cotinine).

Coghlin et al. (1991)
Hammond et al. (1993)

In a study conducted by Coghlin *et al.* (1991), maternal-fetal exchange of a potent tobacco-related human carcinogen, 4-aminobiphenyl (4-ABP), was studied in smoking (n = 14) and nonsmoking (n = 38) pregnant women. N-hydroxy-4-ABP, the active metabolite of 4-ABP, forms chemical adducts with hemoglobin. Levels of 4-ABP hemoglobin adducts were detected in all maternal-fetal paired blood samples. The mean levels of such adducts were 183 (pg/g of hemoglobin) in smoking women, 92 in fetal blood samples from smokers, 22 in nonsmoking women, and 17 in fetal blood samples from nonsmokers. In a related study conducted by the same investigators (Hammond *et al.*, 1993), the relationship between levels of 4-ABP-hemoglobin adducts and exposure to ETS in nonsmoking women (based on nicotine levels measured by passive monitors) was investigated. The median level of 4-ABP adduct was 26 pg/g among nonsmoking women in the highest ETS exposure category (±2 $\mu g/m^3$ weekly average nicotine) compared to median levels of 15 pg/g among those with the lowest ETS exposure (<0.5 $\mu g/m^3$ weekly average nicotine). The levels of 4-ABP hemoglobin adducts in nonsmoking women

Table 7.2a
Hair Concentrations of Nicotine and Cotinine in Women and their Newborn Infants

	Mean (SEM)* Concentration of Nicotine (ng/ml)	Mean (SEM) Concentration of Cotinine (ng/ml)
Active smoking women (*n* = 36)	19.2 (4.9)	6.3 (4.0)
Newborn of active smoking women	2.4 (0.9)	2.8 (0.8)
Passive smoking women[a] (*n* = 23)	3.2 (0.8)	0.9 (0.3)
Newborn of passive smoking women	0.28 (0.05)	0.6 (0.15)[b]
Nonsmoking women (*n* = 35)	1.2 (0.4)	0.3 (0.06)
Newborn of nonsmoking women	0.4 (0.09)	0.26 (0.04)

Reference: Eliopoulos et al. (1994)
** (SEM) = Standard error of the mean.*
[a] *Defined as regular and steady gestational exposure to other person's cigarette smoke, either at home or in the workplace.*
[b] *$p < 0.01$ when compared to newborns of active smoking women and newborns of nonsmokers.*

Table 7.2b
4-Aminobiphenyl Hemoglobin Adduct Concentrations in Pregnant Women and Fetuses by Exposure to Tobacco Smoke

		Mean Concentration (pg/g of hemoglobin)	Standard Deviation
Nonsmoking pregnant women[a] (*n* = 40)		22	8
Smoking pregnant women (*n* = 15)		183	108
Nonsmoking women by levels of exposure to passive smoking based on nicotine concentrations[b,c]			
µg/m³			
<0.5	(*n* = 7)	17.6	2.4
0.5-1.9	(*n* = 20)	20.8	2.0
≥2.0	(*n* = 9)	27.8	1.4
Fetuses of nonsmoking mothers[b] (*n* = 40)		17	13
Fetuses of smoking mothers (*n* = 16)		92	54

[a] *Reference: Coghlin et al. (1991)*
[b] *Reference: Hammond et al. (1993)*
[c] *This represented weekly average nicotine concentrations measured during the third trimester when each subject wore a lightweight monitor. Nonsmoking women in this study were the same nonsmoking pregnant women reported in Coghlin et al. 1991.*

Table 7.2c
Cotinine and PAH-Albumin Levels in Mothers and their Preshool Children

	Mean (SE) Cotinine Level (ng/ml)	Mean (SE) PAH-albumin Level (fmol/µg)
Active smoking women (*n* = 31)	170 (21.2)	0.80 (0.15)
Preschool children of active smoking women	4.14 (0.54)	0.35 (0.07)
Passive smoking women[a] (*n* = 32)	1.64 (0.97)	0.49 (0.08)
Preschool children of passive smoking women	0.87 (0.20)[b]	0.18 (0.04)[c]
Nonsmoking women (*n* = 24)	0.96 (0.79)	0.31 (0.08)
Preschool children of nonsmoking women	0.25 (0.12)	0.15 (0.02)

Reference: Crawford et al. (1994)
Abbreviations: PAH = polyaromatic hydrocarbon; SE = standard error
[a] *Exposure to ETS at home from other household members and visitors.*
[b] *Levels in preschool children in households with ETS exposure were significantly higher (p <0.01) than those in children in nonsmoking households.*
[c] *Levels in preschool children in households with ETS exposure were not significantly higher than those in children in nonsmoking households.*

were 12 percent of those in smokers whereas levels in fetuses of nonsmoking women were about 9 percent of those of smoking women. These two studies provided evidence that 4-ABP crosses the human placenta and binds to fetal hemoglobin in both nonsmoking and smoking mothers and that among nonsmoking women, the levels of 4-ABP adducts increased significantly with increasing levels of ETS exposure (Hammond *et al.*, 1993).

Crawford et al. (1994) In the third study, Crawford *et al.* (1994) evaluated levels of serum cotinine and polycyclic aromatic hydrocarbon (PAH)-albumin adducts in Hispanic and African-American preschool children and their mothers. In this study, mean serum cotinine levels were highest in mothers who smoked (170 ng/ml), intermediate in nonsmoking mothers exposed to passive smokers in the household (1.64 ng/ml), and lowest in nonsmoking mothers not exposed to ETS in the household (0.96 ng/ml). A similar gradient in serum cotinine was observed in preschool children whose mothers were smokers (4.14 ng/ml), passive smokers (0.87 ng/ml), and nonsmokers not exposed to household ETS (0.25 ng/ml). Levels of PAH-albumin adducts (fmol/µg) followed the same pattern in mothers who were smokers, passive smokers, and nonsmokers; the respective levels were 0.80, 0.49, and 0.31. In preschool children of smokers, passive smokers, and nonsmokers

not exposed to ETS, the corresponding levels of PAH-albumin adducts were 0.35, 0.18, and 0.15. Comparisons between the three groups of mothers and between the three groups of preschool children show that there were statistically significant differences in levels of cotinine and PAH-albumin adducts, with those in smokers (and their children) higher than those in passive smokers and nonsmokers not exposed to ETS (and their children). Although levels in passive smokers (and their children) were also higher than those in nonsmokers not exposed to ETS (and their children), the differences were not statistically significant. Levels of cotinine and PAH-adducts in children whose mothers were passive smokers (*i.e.*, exposed to household ETS) were lower than those of their mothers who were living in the same ETS-exposed households (levels were about one-third to one-half), presumably because mothers had more opportunities to be exposed to ETS outside the home than did their preschool children.

In this study, young children exposed to ETS via their mothers' smoking showed increases in cotinine and PAH-albumin adducts. These results suggest that exposed children can take up and metabolically activate respiratory carcinogens. Children with nonsmoking mothers who were exposed to ETS from other household members also showed increases in levels of cotinine and PAH-albumin adducts, although the increases were smaller.

7.1.2.2 Cohort Studies Two prospective studies and a case-cohort study investigated the effect of maternal smoking during pregnancy and risk of cancer in children (Table 7.3).

Neutel and Buck (1971) A study by Neutel and Buck (1971) was based on 89,302 births registered in Canada and the United Kingdom. The cohort included all births registered in ten Canadian hospitals between 1958 and 1961, as well as those registered in all hospitals in England and Wales during a one-week period. Smoking habits of mothers during pregnancy were recorded before or just after the birth of the child. For 74 percent of the cohort (n = 66,456), mothers were classified as nonsmokers, smokers of less than one pack per day, or smokers of one or more packs per day. In the remainder of the cohort, nonsmoking mothers and those smoking less than one pack per day could not be distinguished and thus are excluded from this discussion. A total of 65 cancer deaths (22 leukemias, 20 nervous system tumors, and 23 other sites) occurred before age 10 among the 66,456 births. There was a small increased risk for all cancers combined (RR = 1.31, 95% CI = 0.8, 2.2) among children whose mothers smoked compared to children whose mothers did not smoke. There were few cases in the heavy smoking category, and no consistent dose trend of increasing risk with increasing amounts smoked by mothers during pregnancy was observed.

Pershagen et al. (1992) A second cohort study was conducted by Pershagen *et al.* (1992) who utilized data from the Swedish Medical Birth Registry and the Swedish Cancer Registry. Cancer incidence in a cohort of 497,051 children born between 1982-1987 was determined and compared by maternal smoking at 2-3 months of pregnancy (none, <10 cigarettes/day, or >10 cigarettes/day). Relative risks were adjusted for potential confounders which included maternal age, birth order, year and county of birth of index sub-

Table 7.3
Maternal Smoking During Index Pregnancy and Risk of all Childhood Cancers Combined

Cohort Studies (Age of Subjects)	**# Cases**	**Smoking Habits (cig/day)**	**Odds Ratio (95% CI) for Maternal Smoking**
Neutel and Buck, 1970	34	No	1.0
(Age ≤ 10)	30	Yes	1.3 (0.8-2.2)
Pershagen *et al.*, 1992	230	No	1.0
(Age ≤ 5)	61	<10	1.04 (0.8-1.4)
	36	≥10	0.92 (0.6-1.3)
Case-Control Studies (Age of Subjects)	**# Cases/ # Controls**	**Smoking Habits (cig/day)**	**Odds Ratio (95% CI) for Maternal Smoking**
Stjernfeldt *et al.*, 1986a	177/220	0	1.0
(Age ≤ 16)	30/35	1-9	1.07 (0.6-1.8)
	73/58	10+	1.56 (1.1-2.3)
McKinney *et al.*, 1986	555/1,100[a]	0	1.0
(Age ≤ 15)		1-10	1.12 (0.9-1.5)
		11+	0.84 (0.7-1.1)
Buckley *et al.*, 1986	1,814/720[a]	0	1.0
(Age ≤ 15)		1-9	1.31 (0.9-1.9)
		10+	0.97 (0.8-1.2)
Golding *et al.*, 1990[b]	13/61	<5	1.0
(Age ≤ 10)	20/38	≥5	2.47 (1.2-5.1)
John *et al.*, 1991	223/196[a]	0	1.0
(Age ≤ 14)		1-10	1.4 (0.7-2.7)
		11+	1.5 (0.8-2.7)

[a] *Numbers represent total cases/controls. Case/control distribution of maternal smoking by case/control status was not presented.*
[b] *Case-cohort study.*

ject. There were a total of 327 cancers for which maternal smoking habits were known—198 solid tumors and 129 tumors of the lymphatic and hematopoietic system. There was no association between maternal smoking and risk of all cancers combined (adjusted RR = 0.99, 95% CI = 0.78-1.27). The lack of an association persisted when the analysis was conducted separately for solid tumors combined (adjusted RR = 0.96, 95% CI = 0.70-1.32), and for lymphatic and hematopoietic tumors combined (adjusted RR = 1.04, 95% CI = 0.71-1.52).

The study by Pershagen *et al.*, (1992) has several strengths, but also a major limitation. The compilation of the cohort of births was nearly complete (99 percent). Of the 422 childhood cancer cases identified in the Swedish Cancer Registry during this time period, 408 could be linked to a subject in the birth cohort (we assumed that 81 of 408 cases were excluded from the analysis because data on maternal smoking habits were missing). Data on mothers' smoking habits at 2-3 months of pregnancy were available on over 90 percent of children born between 1983 to 1987 and for about 50 percent of children born in 1982. The lower figure in 1982 was due mainly to logistical problems during this first year when the birth registry started to collect information on smoking. Results remained unchanged when births in 1982 were excluded from the analysis. The percentage of mothers who smoked in this study was also similar to that reported in other Swedish studies, so that underreporting of smoking during pregnancy cannot explain the lack of an association. The main limitation of this study is that the maximum follow-up was to 5 years of age, and thus an effect of maternal smoking on cancers occurring at older ages was not assessed; there were small numbers of cancers diagnosed among the 4-5 year olds.

Golding et al. (1990) A case-cohort study was conducted by Golding *et al.* (1990), who collected information prospectively on 16,193 infants delivered over a one-week period in 1970 in the United Kingdom. These children were followed up at ages 5 and 10; 80 percent and 94 percent respectively were successfully contacted. By 1980, 33 children had developed cancer (9 leukemia, 5 lymphoma, 8 brain, 5 Wilm's tumor, 6 other). For each cancer case, three controls were selected and matched to cases on factors including maternal age at birth of index subject, parity, and social class. Significantly more mothers of cases had smoked five cigarettes or more per day throughout pregnancy compared to the controls (RR = 2.47, 95% CI = 1.2-5.1). Maternal smoking remained statistically significant in logistic regression analysis when other risk factors were controlled for (*e.g.*, social class, X-ray in pregnancies, use of various medications).

7.1.2.3 Case-control Studies One of the first case-control studies to examine the role of parental smoking and risk of childhood cancers was a hospital-based study conducted in the U.S. (Manning and Carroll, 1957). Smoking habits of mothers (at time of study enrollment) of children with cancers (188 leukemias, 42 lymphomas, and 93 other cancers) were compared to mothers of children with orthopedic diseases (n = 50). There was no difference in the percentage of mothers of children with cancer who smoked ten or more cigarettes per day (37.4 percent) compared to mothers of controls (38.0 percent). A second study was conducted by Stewart *et al.* (1958) who included as cases all children in England and Wales who had died of leukemia or other cancers before their tenth birthday between 1953 and 1955. Controls were individually matched to cases on gender, age (plus or minus 6 months of the birth date of the cases), and locality of residence. A total of 1,416 case/control pairs were available for analysis. Fathers and mothers of the index subjects were classified as heavy, moderate, light, or nonsmokers. The smoking habits of fathers of children with cancer (82.9 percent smoked at least one cigarette or pipe per day) were similar to those

of fathers of control children (80.9 percent smoked). There was a small excess of mothers of cases who smoked (47.8 percent) compared to mothers of controls (43.8 percent) (OR = 1.09, $p = 0.04$), but this was not adjusted for potential confounding factors. The authors cautioned that since parents were interviewed after the death of the index patients, their smoking habits may be affected by bereavement.

Results from five case-control studies conducted since the 1980's offer better information on smoking habits of parents during pregnancy (Table 7.3).

Stjernfeldt et al. (1986a, 1986b, 1992) Stjernfeldt *et al.* (1986a, 1986b, 1992) conducted a population-based, nationwide case-control study of childhood cancer in Sweden. A total of 305 children, aged 16 or younger, diagnosed with cancer during 1978 and 1981 were identified by the Swedish Child Leukemia Group. Cases were compared to 340 control children with insulin-dependent diabetes mellitus. Families of cases and controls completed a self-administered questionnaire with an overall participation rate of about 95 percent in both groups. Controls were not individually- or frequency-matched to cases on age or gender, but these variables were controlled for in the analysis. Information on smoking habits of mothers was obtained on 92 percent of cases and controls for the 5-year period before pregnancy, during pregnancy, and postnatally to onset of disease in the index subject.

There was some suggestion of an increased risk for all cancers combined in relation to mother's smoking during pregnancy. Compared to children whose mothers were nonsmokers, children whose mothers smoked 1-9, and 10+ cigarettes per day showed RRs of 1.07 (95% CI = 0.63-1.80) and 1.56 (95% CI = 1.05-2.33) respectively. The increase in risk was not observed for solid tumors but was restricted to tumors of the reticuloendothelial system, primarily acute lymphoblastic leukemias. The authors did not present results separately for mother's smoking after birth of the index subject, but suggested that since mothers who smoked during pregnancy generally smoked after the child was born, it would be difficult to separate the effect of *in utero* exposure to tobacco smoke constituents versus postnatal ETS exposure.

Despite concerns raised regarding the choice of controls and possible selective recall bias among cases (McKinney and Stiller, 1986; Buckley *et al.*, 1986; Dahlquist and Wall, 1986; Li, 1986; Cunningham, 1986), none of these biases appear to explain the study's findings. It can be argued that mothers of diabetic children would recall more similarly to mothers of children with cancer if there is any recall bias associated with having a disease. Smoking habits of mothers of diabetic children were representative of the general population since their smoking prevalences were comparable to those of Swedish women surveyed in studies conducted during the same time period. Moreover, differences between cases and controls in ages at diagnosis, geographic location, and socioeconomic status could not explain the apparent findings (Stjernfeldt *et al.*, 1986b). The increased risk associated with maternal smoking was observed after adjustment for factors including maternal age, birth order of index subject, and parental occupation.

McKinney and Stiller (1986) In response to the findings of Stjernfeldt *et al.* (1986a & b), McKinney and Stiller (1986) published a letter to the editor and a more detailed paper (McKinney *et al.*, 1987) presenting data collected for the Inter-Regional Epidemiology Study of Childhood Cancer (IRESCC), a collaborative study conducted in three health regions in the United Kingdom (Yorkshire, West Midlands, and North West) between 1980 and 1983. Study subjects included 555 children (under age 15) diagnosed with childhood cancer. Two healthy, age- and sex-matched control children were identified for each case using the general practitioner lists and admissions to hospital for minor conditions. Parents of cases and controls were asked identical questions regarding the antenatal period of the index subject—*e.g.*, illness, use of medications, complications, smoking and drinking habits (McKinney *et al.*, 1987). Maternal smoking habits during pregnancy were not associated with risk for all cancers combined; the RRs were 1.0, 1.12 (95% CI = 0.85-1.47) and 0.84 (95% CI = 0.65-1.09), respectively for mothers smoking 0, 1-10, and 11+ cigarettes/day. Leukemias and lymphomas, which accounted for 44 percent of the childhood cancers in this population, were not associated with maternal smoking. However, maternal smoking was associated with nonsignificant increased risks for soft-tissue sarcomas and bone tumors (see Section 7.4.6.4: Bone and Soft-Tissue Sarcomas).

Buckley et al. (1986) Also in response to Stjernfeldt's findings, Buckley *et al.* (1986) investigated the role of maternal smoking during pregnancy and the risk of childhood cancer using data gathered by the US Children's Cancer Study Group. Since 1983, the parents of 1,814 children have completed a questionnaire which included smoking histories of the mother and father before and during the pregnancy of the index subject. Controls were drawn at random from approximately the same geographic regions as cases in the US and Canada. There was no association between maternal smoking during pregnancy and risk of all cancers combined; the RRs were 1.31, and 0.97 respectively, for mothers smoking 1-9, and 10+ cigarettes/day during pregnancy compared to nonsmokers. Acute lymphoblastic leukemia, representing 41 percent of cancers in this study, was not related to mother's smoking. Paternal smoking during the index pregnancy was also not associated with all childhood cancers combined (data were not presented). Adjustment for potential confounders (*e.g.*, birth year of the child, maternal age, illnesses during the pregnancy, and socioeconomic factors) did not alter the results.

John et al. (1991) John *et al.* (1991) investigated the role of parental smoking before and during pregnancy and the risk of childhood cancer in a population-based case-control study conducted in Colorado. The study included incident childhood cancers, diagnosed between 1976 and 1983 among children 14 years old or younger. Controls were selected by random-digit dialing and were individually matched to cases on age (±3 years), sex, and telephone exchange area. Of the 356 eligible cases, 252 (response rate of 70.8 percent) participated in the study compared to 222 controls (response rate of 62.8 percent). Structured interviews were administered to parents of index subjects and included questions on smoking habits of mothers, fathers, and other household members during the index pregnancy. In

addition, questions regarding the mother's cigarette smoking habits at three months prior to the index's conception and during each trimester of the pregnancy were asked. Questions on father's smoking included use of cigarettes, cigars, and pipes. Information on other smokers in the household was derived based on questions regarding the number of regular smokers at each residence from conception to the time of the child's diagnosis. The definition of nonexposed in this study is "not exposed to smoking by either parent or by other household members from the period starting 1 year before birth through the time of diagnosis." Data on the number of cases and controls who were exposed to other household members only (but not to parents' smoking) were not presented.

For all cancers combined, there was a small increased risk associated with exposure to mothers or fathers' smoking. The RRs for all cancers were 1.3 (95% CI = 0.8-2.0), 1.5 (95% CI = 1.0-2.5), and 1.4 (95% CI = 0.9-2.4), respectively, in relation to mothers who smoked during the 3 months prior to conception, the first trimester, and all three trimesters of the pregnancy. The OR for all cancers combined was 1.3 (95% CI = 0.9-2.0) in relation to any tobacco use by the father. The ORs for all cancers combined in association with mothers' smoking in the absence of father's smoking, fathers' smoking in the absence of others' smoking, and the combined effect of mothers' and fathers' smoking were 1.7 (95% CI = 0.7-4.3), 1.4 (95% CI = 0.9-2.3), and 1.5 (95% CI = 0.9-2.6), respectively. The data suggest an increasing trend in risk with increasing amounts smoked by mothers, but not by fathers. The positive association between ETS exposure and risk of all cancers is largely due to its effect on risk for acute lymphoblastic leukemia, lymphoma, and brain tumors. Father's education was a potential confounder in this study. The OR for all childhood cancers in relation to fathers' and mothers' smoking was 1.5 (95% CI = 0.9-2.6); this OR was reduced to 1.2 (95% CI = 0.7-2.1) when father's education was accounted for in the analysis.

7.1.2.4 Summary While in some studies increased risks overall in childhood cancers were observed, in others no such increases were seen. There are several limitations in both the studies finding an association and those finding no association between ETS exposure and risk of childhood cancers. The cohort study of Pershagen *et al.* (1992) is limited in that it can only examine the effect of ETS exposure on tumors diagnosed up to 5 years of age, whereas all the other studies included cancers up to 10 or 16 years of age. Causes of childhood cancers in very young children may differ from those of older children. The two large case-control studies which found no association with maternal smoking were collaborative studies of childhood cancers conducted in the United Kingdom (McKinney and Stiller, 1986) and the U.S. (Buckley *et al.*, 1986). Selection bias of cases cannot be ruled out in these studies. Childhood cancer patients admitted to academic institutions were enrolled in these studies and may be unrepresentative of all childhood cancers in the population (*e.g.,* higher social class). The denominator of childhood cancers was not presented, and thus participation rates could not be calculated. Because of the association between social class/education and smoking habits, selection bias associated with social class/education

cannot be precluded. Prevalence of smoking habits of mothers/fathers was not presented in these two studies. On the other hand, the strongest positive finding reported in the case-cohort study by Golding *et al.* (1990) was based on a small number of cases and classification of mother's smoking as less than five versus greater than five cigarettes/day. The choice of the less than five cigarettes/day as the baseline category was not explained, and it is unclear whether this cut-off was an *a priori* decision. Presenting the results using nonsmoking mothers as the baseline group would have been a useful comparison to other studies. The results by Stjernfeldt *et al.* (1986a & b) have also been questioned because of the choice of controls (children with diabetes). Finally, there is some suggestion that inadequate adjustment for paternal education (as a surrogate for social class) may have produced an association between parental smoking and risk of childhood cancer that is artificially strengthened (John *et al.*, 1991).

In summary, the evidence for a role of parental smoking and childhood cancers is inconclusive. One (Neutel and Buck, 1971) of two cohort studies reported an elevated risk which is not statistically significant (OR = 1.3, 95% CI = 0.8-2.2). Two (Stjernfeldt *et al.*, 1986; Golding *et al.*, 1990) of five recent case-control studies (conducted in the 1980s) reported significant associations between mother's smoking during pregnancy and risk of childhood cancers. A third case-control study (John *et al.*, 1991) which reported elevated risks that were not statistically significant was the only study in which fathers' smoking during pregnancy in the absence of mothers' smoking was evaluated; the investigators found a statistically nonsignificant increased risk associated with fathers' smoking alone (OR = 1.4, 95% CI = 0.9-2.3). The positive findings are due largely to the significant association between maternal smoking and acute lymphoblastic leukemia in these studies. No other cancer site appeared to be significantly affected by maternal or paternal smoking.

7.2 ETS AND LUNG CANCER

Active smoking is firmly established as a causal factor for lung cancer. The Surgeon General (U.S. DHHS, 1986), National Research Council (NRC, 1986), and U.S. EPA (1992) have reviewed epidemiologic studies investigating the role of ETS exposure as a cause of lung cancer in nonsmokers. Our review focuses on studies published since the latest review—three large U.S. population-based case-control studies (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1991 and 1994), a fourth, considerably smaller, hospital-based case-control study (Kabat *et al.*, 1995), and a recent U.S. cohort study (Cardenas *et al.*, 1997).

7.2.1 Epidemiologic Studies Published Prior to 1991

In 1981, the first epidemiological studies of ETS exposure and lung cancer were published (Hirayama, 1981; Trichopoulos *et al.*, 1981). These studies found that nonsmokers married to smokers showed a significantly higher risk of lung cancer than nonsmokers married to nonsmokers. Some 30 epidemiological studies have since been published. Most of the individual studies found a small increased risk, and a few found statistically significant results; however, all the studies published in the 1980s had small sample sizes which lacked statistical power to detect small associations. The Surgeon General (U.S. DHHS, 1986), NRC (1986), and U.S. EPA (1992) conducted compre-

hensive reviews of the epidemiological literature and concluded that ETS exposure was causally associated with lung cancer. Their conclusions were based on the total weight of evidence and not on any individual study.

The U.S. EPA (1992) report reviewed a total of 30 epidemiologic studies (four prospective follow-up and 26 case-control studies) from eight countries. All the studies examined the risk of lung cancer in nonsmokers in relation to spousal smoking habits. Each study was examined in detail and then the studies were examined collectively. Because none of the studies were exactly alike, and the individual studies had different methodologic strengths and weaknesses, the U.S. EPA report ranked the studies in four tiers and gave special consideration to the 15 studies in the two highest tiers. The U.S. EPA report concluded that ETS is responsible for approximately 3,000 lung cancer deaths per year in U.S. nonsmokers.

In order to gain a more accurate estimate of the association between ETS exposure and lung cancer, a meta-analysis approach has been used to pool results of comparable studies. Numerous meta-analyses have been published on this subject (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992; Fleiss and Gross, 1991; Arundel *et al.*, 1987; Kilpatrick, 1992; Pershagen, 1992; Vainio and Partensen, 1989; Repace and Lowry, 1990; Spizer *et al.*, 1990; Wells *et al.*, 1991; Wells, 1993). A widely disseminated and reviewed meta-analysis was conducted by the U.S. EPA (U.S. EPA, 1992; Farland *et al.*, 1994; Jinot and Bayard, 1994). Despite careful considerations of many methodologic issues of concern in the meta-analysis of ETS exposure and lung cancer (*e.g.*, measurement of ETS exposure, misclassification bias of nonsmoker status and disease status, adjustment for potential confounders), the U.S. EPA report was criticized (LeVois and Layard, 1994; Gori, 1994a & b). Some of the concerns centered around issues that were specific to the study of ETS exposure and lung cancer, including misclassification bias of smokers as nonsmokers and the extent of such misclassification. On the other hand, other issues were generic to meta-analysis techniques, and they include possible publication bias of positive studies and the difficulty in obtaining adjusted risk estimates (Gori, 1994a & b) for meta-analysis. The issue of publication bias has been reviewed in detail by Bero *et al.* (1994), who concluded that there is no publication bias against statistically nonsignificant results on ETS in the peer-reviewed literature.

The U.S. EPA's (1992) reporting of 90 percent confidence intervals has gained much attention and is worth addressing here. The U.S. EPA report uses a one-tailed test of statistical significance (with $p = 0.05$) and reports the corresponding 90 percent confidence intervals, consistent with the one-tailed test. Use of a one-tailed statistical test could be considered to increase the probability of accepting an association (for an individual study) that occurs by chance. A one-tailed test is a standard statistical methodology used when there is prior evidence that the effect of an agent is likely to be in one specific direction. In this case, the Surgeon General (U.S. DHHS, 1986), NRC (1986), and an International Agency for Research on Cancer work group (IARC, 1986) all previously concluded that ETS exposure increased lung cancer risk. The established causal association between active smoking and lung cancer and the chemical similarity between main-

stream smoke and ETS were considered by the U.S. EPA (1992) to provide prior evidence that any effect of ETS on lung cancer would be likely to be positive (*i.e.*, to increase the risk); thus, the one-tailed significance test was the appropriate method for evaluating the hypothesis of an effect of ETS on lung cancer risk (U.S. EPA, 1994). Had the EPA used a two-tailed statistical significance test (with corresponding 95 percent confidence intervals) instead of a one-tailed test (with 90 percent confidence intervals), the overall conclusions regarding causality and degree of risk would have been the same (U.S. EPA, 1994).

7.2.2 Case-Control Studies Published Since 1991

Three large U.S. population-based case-control studies designed specifically to investigate the association between ETS exposure and lung cancer have been published since 1991; they confirm and extend the results of the pooled U.S. studies presented in the U.S. EPA report. These studies were conducted in Florida (Stockwell *et al.*, 1992), Missouri (Brownson *et al.*, 1992), and in five geographic areas of the U.S.—New Orleans, Louisiana; Atlanta, Georgia; Houston, Texas; Los Angeles County, California; and San Francisco Bay Area, California—referred to as the U.S. multicenter study (Fontham *et al.*, 1991 and 1994). Preliminary findings from the U.S. multicenter study (Fontham *et al.*, 1991) were included in the U.S. EPA (1992) report. A fourth study, which is a considerably smaller, hospital-based case-control study, was published in 1995 (Kabat *et al.*, 1995). In addition, three other studies which provide some information on ETS exposure as part of investigations of lung cancer and indoor air pollution in Guangzhou, China (Liu *et al.*, 1993), familial risk factors in Detroit (Schwartz *et al.*, 1996), and various suspected risk factors in Kaohsiung, Taiwan (Ko *et al.*, 1997) are also briefly reviewed in this section.

The case-control studies will be reviewed, and their respective study designs and the main findings will be described. In the evaluation of the methodologic issues related to the study of ETS exposure, the focus will be on the sources of cases and controls, the methods used to obtain information on the exposures of interest, the verification of the exposures of interest and of the diagnosis of lung cancer, and the consideration of potential confounding variables in the analysis of ETS exposure.

To minimize confusion, the ORs and confidence intervals will be cited exactly as theywere reported in the original papers. This means that some numbers are reported to one decimal place whereas others are reported to two decimal places. Odds ratios that had to be calculated for this review are labeled as such in the text and tables—*e.g.*, "calculated odds ratio"—and these estimates are referred to as "crude odds ratios." In some instances, the numbers of cases and controls (presented in the tables) by various intensity of ETS exposure (*i.e.*, pack-years, years of exposure) did not add up to the total numbers of subjects included in the individual studies, and it is assumed that these differences in numbers are due to missing information on specific parameters of intensity of ETS exposure or on the covariates included in the adjustments (the variables that were adjusted for in the different analyses are described as footnotes in the various tables). The meas-

ures of intensity of exposure were generally in terms of years (or smoke-years) or pack-years of exposure, number of cigarettes (or tobacco products) smoked per day, or the number of smokers in the household.

7.2.2.1 Four U.S. Case-Control Studies of ETS and Lung Cancer

Stockwell et al. (1992)

Stockwell *et al.* (1992) conducted a population-based case-control study of women in 28 counties in central Florida (Table 7.4). Eligible cases included women diagnosed with a histologically confirmed primary lung cancer between April 1, 1987, and February 28, 1991, and were identified through the Florida Statewide Cancer Registry and the tumor registries of area hospitals. Age criteria for the study subjects were not specified. Population controls were selected by random-digit dialing; it is unclear whether cases and controls were frequency-matched on any criteria. All cases and control subjects were lifetime nonsmokers, defined as having smoked for a total of less than 6 months or less than 100 cigarettes in their lifetime. The nonsmoking status of the study subjects was verified by checking medical records and checking with physicians' offices (for cases) and by inquiry at the time the subjects were contacted to set up the interview as well as at the beginning of the interview (for cases and controls). The response rate for lung cancer cases was 83 percent; it was not specified for controls.

A combination of telephone (51 percent for cases; 46 percent for controls) and in-person (41 percent for cases; 54 percent for controls) interviews and mailed questionnaires (8 percent for cases; 0.3 percent for controls) were used to obtain information from study subjects. Interviews of surrogate respondents (primarily husbands and children) were necessary for 66.7 percent of the case patients who were too ill to be interviewed or were deceased. Information was obtained on a total of 210 lung cancer patients and 301 controls.

Subjects were asked about their exposure to ETS from husbands, mothers, fathers, siblings, and other household members and at the workplace. Compared to unexposed individuals who had no household ETS exposure, women who were exposed to husbands' smoking had ORs of 1.6 (95% CI = 0.8-3.0) for those who had ever been exposed and 2.2 (95% CI = 1.0-4.9) for those with 40 or more smoke-years of exposure after adjustment for age, race, and education. Similar odds ratios were observed for exposure to smoking by husbands and other household members in adult life (Table 7.5). Exposure to ETS from mothers, fathers, and siblings was associated with an increased risk of lung cancer, although none of the individual increases in risks were statistically significant. Stockwell *et al.* (1992) also considered ETS exposure from different sources during childhood/adolescence in terms of years of exposure. Women who experienced 22 years or more of ETS exposure from all household members combined during childhood/adolescence showed a significantly elevated OR for lung cancer (2.4, 95% CI = 1.1-5.4) (Table 7.6). When ETS exposures from both childhood/adolescence and adulthood (*i.e.*, from husbands and other household members) were considered jointly, women who reported 40 or more years of exposure experienced an elevated risk of lung cancer (OR = 2.3, 95% CI = 1.1-4.6) compared to women who had fewer than 22 years of

exposure (data not shown). These investigators noted that there was no statistically significant association in this study between ETS exposure at work or during social activities and risk of lung cancer (actual results were not presented in Stockwell *et al.*, 1992).

The elevated risks associated with ETS exposure (during childhood/adolescence, adulthood, and all lifetime combined) were observed for all lung cancer cell types; the risk was stronger for cell types other than adenocarcinoma of the lung. Analysis by respondent type showed that the risk estimates for ETS exposure varied by the source of case information. For example, ETS exposure from husbands was a stronger risk factor for lung cancer when the respondents were the case patients (OR = 3.1, 95% CI = 0.9-10.6) or their husbands (OR = 3.1, 95% CI = 0.7-13.7). When the surrogate respondent was a family member other than the patient's husband, ETS exposure was not associated with elevated risk (OR = 0.9, 95% CI = 0.4-1.9).

It should be noted that the distribution of study subjects by ETS exposure was not presented; only the odds ratios were presented. The "unexposed" reference category was comprised of individuals with no household ETS; presumably this same reference category was used in all analyses for cases and controls.

Brownson et al. (1992) Brownson *et al.* (1992) conducted a population-based case-control study of women in Missouri (Table 7.4). Females aged 30 to 84 years who were diagnosed with primary lung cancer between January 1986 and June 1991, and were identified from the Missouri Cancer Registry, were considered eligible. Population controls were identified from a sample of the state driver's license files and Health Care Finance Administration listings. The case group included both lifetime nonsmokers and ex-smokers who had stopped smoking at least 15 years before diagnosis or who had smoked less than 1 pack-year. The definition of lifetime nonsmokers was not specified explicitly. The control group was matched by age group to case patients at about a two to one ratio. Tissue slides were reviewed to confirm the histologic classification for 468 (76 percent) of the 618 lung cancer cases.

The response rate was 95 percent for cases and 75 percent for controls, nonsmokers and ex-smokers combined. Information was collected on a total of 618 lung cancer cases of whom 432 were lifetime nonsmokers and 186 were ex-smokers. Of the lung cancer patients, 402 interviews were conducted with surrogate respondents and 216 interviews were with the lung cancer patients themselves. A total of 1,400 control subjects were interviewed, all of whom were self-respondents; 1,166 controls were lifetime nonsmokers.

All case and control interviews were conducted by telephone at which time the nonsmoking status was verified. Questions on ETS exposure pertained to exposures in both childhood (17 years and younger) and adult life (18 years and older). For each time period, respondents were questioned about the source of exposure (*e.g.*, a parent or spouse) including both household and workplace exposure. After an individual source was deter-

Table 7.4
Study Characteristics of the Four U.S. Case-Control Studies of Lung Cancer and ETS Published Since 1991

	Stockwell *et al.* (1992)	**Brownson *et al.* (1992)**	**Fontham *et al.* (1994)**	**Kabat *et al.* (1995)**
Area	Central Florida	Missouri	5 U.S. metro-politan areas	4 U.S. cities
Accrual period	1987-1991	1986-1991	1985-1991	1983-1990
Sample size[1]				
cases	210 (F)	432 (F)	653 (F)	69 (F), 41 (M)
controls	301 (F)	1166 (F)	1253 (F)	187 (F), 117 (M)
Ages	NA (% by birth year groupings provided)	30-84	20-79	not specified
Source of cases	Florida Cancer Registry	Missouri Cancer Registry	All hospital/regis-tries in specific geographic areas	6 hospitals in the 4 cities
Source of controls	RDD	DMV, HCFA	RDD, HCFA	other hospital patients
Matching variables of lifetime non-smoking controls	NA	age	age, area, & race	age, race, hospital, date of interview
Percent of self-respondents				
cases	33	34*	63	100
controls	100	100	100	100
Mode of data collection	in-person, tele-phone, mailed questionnaires	telephone	in-person	in-person
% Histologic confirmation	100%	76%**	100%**	100%
% adenocarcinoma	61%	66%	76%	NA
Definition of lifetime nonsmoker	smoked for a total of <6 months or <100 cigarettes in their lifetime	not described	<100 cigarettes, no use of other tobacco for >6 mos	<365 cigarettes over lifetime
Verification of nonsmoking status	multistep-medical record, physician, at initial contact & interview	at interview	multistep-medical record, physician, at initial contact & interview	at interview
Biological markers	none	none	urinary cotinine***	none

[1] *Sample size of lifetime nonsmokers in study*
* *Presented for nonsmokers and ex-smokers combined*
** *Confirmed by independent histologic review*
*** *On 81% of self-respondent cases and 85% of controls*
Abbreviations: F-females, M-males, NA-not available, RDD-random digit dialing, DMV-Department of Motor Vehicle, HCFA-Health Care Financing Administration

Table 7.5
Association Between Risk of Lung Cancer in Lifetime Nonsmoking Females and Exposure to Spousal Smoking

Study	Exposure Status			Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse			Odds Ratio (95% CI) for yrs. exp./amt. smoked by spouse
Stockwell *et al.* (1992)	Spouse smoked[a]			AOR[a]	Smoke-years in adult household (spouse and others)[a]			AOR[a]
	no			1.0	<22			1.6 (0.8-3.2)
	yes			1.6 (0.8-3.0)	23-39			1.4 (0.7-2.9)
					40+			2.4 (1.1-5.3)
Brownson *et al.* (1992)	Spouse smoked	Cases*	Controls*	AOR[b]	Cigarette pack-years	cases	controls	AOR[b]
	never	213	568	1.0	0	213	568	1.0
	ever	218	598	1.0 (0.8-1.2)	0-15	32	128	0.7 (0.5-1.1)
					15-40	54	200	0.7 (0.5-1.0)
					40+	110	216	1.3 (1.0-1.7)

Table 7.5 (Continued)

Study	Exposure Status			Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse			Odds Ratio (95% CI) for yrs. exp./amt. smoked by spouse
Fontham *et al.* (1994)	Spouse smoked	cases exposed/ total cases	controls exp/ total controls	AOR[c]	By pack-years of exposure to spouses	cases*	controls*	AOR[c]
	any type				0	267	562	1.00
	tobacco	433/651	766/1,253	1.29 (1.04-1.60)	<15.0	146	300	1.08 (0.86-1.39)
	cigarettes	366/648	691/1,253	1.18 (0.96-1.46)	15.1-39.9	92	190	1.04 (0.76-1.42)
	cigars	85/641	138/1,253	1.25 (0.92-1.71)	40.0-79.9	80	126	1.36 (0.97-1.91)
	pipes	86/640	158/1,253	1.19 (0.88-1.60)	80.0+	24	27	1.79 (0.99-3.25)
Kabat *et al.* (1995)	**Males**				**Males**			
	Spouse smoked:	cases/controls*		AOR[d]	Spouse smoked:	cases/controls*		AOR[d]
	no	28/79		1.0	1-10 cigs/day	5 / 17		0.74 (0.24-2.23)
	yes	11/19		1.60 (0.67-3.82)	11+ cigs/day	5 / 2		7.48 (1.35-41.36)
	Females				**Females**			
	Spouse smoked:	cases/controls*			Spouse smoked:	cases/controls*		
	no	26/ 71		1.0	1-10 cigs/day	17 / 50		0.82 (0.42-1.61)
	yes	41/102		1.08 (0.60-1.94	11+ cigs/day	12 / 28		1.06 (0.49-2.30)

[a] *Distribution of cases and controls was not presented; ORs adjusted for age, race, and education; ORs are from Table 2 of Stockwell et al. (1992).*
[b] *Adjusted for age, previous lung disease; ORs are from Table 2 of Brownson et al. (1992).*
[c] *Adjusted for age, race, study area, education, fruits & vegetables & supplemental vitamin index, dietary cholesterol, family history of lung cancer, and employment in high-risk occupations; ORs are from Table 3 of Fontham et al. (1994).*
[d] *Adjusted for age, years of education, and type of hospital; ORs are from Table 4 of Kabat et al. (1995).*
* *The number of cases and controls by intensity of exposure may not add up to the total numbers of subjects due to missing values.*

Table 7.5b
Risk of Lung Cancer in Nonsmoking Women and Men: a Cohort Analysis

Study	Exposure Status	No. of Lung Cancer Deaths	Multivariate RR[a]	Multivariate CI
Cardenas *et al.* (1997)	Among women			
	-- who never smoked	54	--	
	-- husband ever smoked	96	1.0	0.8-1.6
	-- current smoker	44	1.2	0.8-1.8
	-- former smoker	52	1.1	0.8-1.6
	By cigarettes per day smoked by husbands			
	never	30	1.0	--
	1 to 19	9	1.1	0.5-2.2
	20 to 39	22	1.2	0.7-2.2
	40+	13	1.9	1.0-3.6
	By years in marriage to smoker			
	0	30	1.0	--
	1-17	13	1.5	0.8-2.9
	18-29	14	1.5	0.8-2.8
	30+	17	1.1	0.6-2.1
	By pack-years of exposure			
	0	30	1.0	--
	1-16	10	1.0	0.5-2.1
	17-35	16	1.5	0.8-2.7
	36+	18	1.5	0.8-2.6
	Among men			
	-- who never smoked	79	1.0	
	-- wives ever smoked	18	1.1	0.6-1.8
	-- current smoker	8	1.0	0.5-2.0
	-- former smoker	10	1.1	0.6-2.2

[a] *Adjusted for age, race, education, dietary intake of vegetables and total fat, occupation, and history of lung disease.*

Table 7.6
Association Between Risk of Lung Cancer and ETS Exposure from Parents and Other Household Members

Study & Study area	Sex	ETS exposure	Cases/	Controls	Odds Ratio (95% CI) for exposed
STUDIES CONDUCTED IN THE UNITED STATES					
Janerich *et al.* (1990) New York	M, F	Smoker-years in childhood/adolescence			
		0	57	68	1.0
		1-24	82	94	1.09 (0.68-1.73)
		25+	52	29	2.07 (1.16-3.68)
Stockwell *et al.* (1992) Central Florida	F	(Distributions by exposure not presented)	210	301	
		mother			1.6 (0.6-4.3)
		father			1.2 (0.6-2.3)
		siblings			1.7 (0.8-3.9)
		During childhood/adolescence from parents and siblings			
		(in yrs) <18			1.6 (0.7-3.6)
		18-21			1.1 (0.5-2.6)
		22+			2.4 (1.1-5.4)
Brownson *et al.* (1992) Missouri	F	During childhood from parents			
		never	357	877	1.0
		ever	74	289	0.7 (0.5-0.9)
		During childhood from any household members			
		never	323	802	1.0
		ever	108	364	0.8 (0.6-1.1)
Fontham *et al.* (1994) Five U.S. areas	F	During childhood			
		father			
		no	304	669	1.00
		yes	299	556	0.83 (0.67-1.02)
		mother			
		no	76	161	1.00
		yes	548	1,079	0.86 (0.62-1.18)
		Childhood household exposure			
		(in yrs.) 0	148	444	1.00
		1-17	95	291	0.99 (0.73-1.35)
		18+	146	485	0.88 (0.67-1.16)

Table 7.6 (Continued)

Study & Study area	Sex	ETS exposure	Cases/	Controls	Odds Ratio (95% CI) for exposed
Kabat *et al.* (1995) Four U.S. cities		Childhood exposure			
	M	no	15	41	1.00
		yes	25	76	0.90 (0.43-1.89)
		#smokers: 1	18	53	1.12 (0.46-2.70)
		#smokers: 2+	7	22	1.13 (0.34-3.75)
	F	no	22	81	1.00
		yes	47	106	1.55 (0.95-2.79)
		#smokers: 1	39	82	1.75 (0.91-3.35)
		#smokers: 2+	8	23	1.27 (0.43-3.78)
		Adulthood household exposure			
	M	no	28	83	1.00
		yes	13	34	1.13 (0.53-2.45)
		#smokers: 1	6	28	0.64 (0.19-2.13)
		#smokers: 2+	7	5	4.15 (1.34-12.87)
	F	no	26	68	1.00
		yes	43	119	0.95 (0.53-1.67)
		#smokers: 1	34	93	0.96 (0.50-1.84)
		#smokers: 2+	9	25	0.94 (0.34-2.63)
Wu *et al.* (1985) Los Angeles	F	Parents smoked			
		no	18	29	1.0
		yes	11	33	0.6 (0.2-1.7)
Kabat and Wynder (1984) U.S.A.		Current ETS exposure at home			
	M	no	19	20	1.00
		yes	6	5	1.26 (0.33-4.83)*
	F	no	37	36	1.00
		yes	16	17	0.92 (0.40-2.08)*
STUDIES CONDUCTED IN ASIA					
Sobue (1990) Japan	F	During childhood			
		father			
		no	35	143	1.00
		yes	109	588	0.79 (0.52-1.21)
		mother			
		no	127	668	1.00
		yes	17	63	1.33 (0.74-2.37)
		Other household member			
		no	113	587	1.00
		yes	31	114	1.18 (0.76-1.84)

Table 7.6 (Continued)

Study & Study area	Sex	ETS exposure	Cases/ Controls		Odds Ratio (95% CI) for exposed
Shimizu *et al.* (1988) Japan	F	During childhood and/or adult life (distribution of exposure presented for controls)			
		father			1.1[a]
		mother			4.0 ($p < 0.05$)
		father-in-law			3.2 ($p < 0.05$)
		mother-in-law			0.8
		brother(s) or sister(s)			0.8
		son(s) or daughter(s)			0.8
Gao *et al.* (1987) Shanghai	F	Lived with a smoker during childhood			1.1 (0.7-1.7)
Koo *et al.* (1987) Hong Kong	F	# cohabitants who smoked (included spouse, parents, in-laws, children, or other cohabitants)			
		0	27	49	1.0
		1	48	68	1.73 (0.6-6.4)
		2+	13	20	1.35 (0.6-5.0)
Wu-Williams *et al.* (1990a) North China	F	father smoked			
		no	235	352	1.0
		yes	182	250	1.1 (0.8-1.4)*
		mother smoked			
		no	298	410	1.0
		yes	119	192	0.9 (0.6-1.1)*
STUDIES CONDUCTED IN EUROPE					
Pershagen *et al.* (1987) Sweden	F	parental smoking			
		neither parent smoked	38	NA[b]	1.0
		one or both parents smoked	9	NA	1.0 (0.4-2.3)[b]
Svensson *et al.* (1989) Sweden	F	father smoked			
		no	19	98	1.0
		yes	12	71	0.9 (0.4-2.3)
		mother smoked			
		no	19	98	1.0
		yes	3	5	3.3 (0.5-18.8)

* *Calculated from data provided in the study publication*

[a] *Shimizu et al. reported p-values for findings, but did not report confidence intervals, and confidence intervals could not be calculated from the reported information.*

[b] *The numbers presented are shown in Table 5 of Pershagen et al. (1987). Although the numbers (and %) of cases and controls with at least one parent who smoked are shown in Table 2 of Pershagen et al. (1987), we cannot reproduce the OR of 1.0 shown in their Table 5 if we impute the number of controls by parental smoking habits.*

mined, a series of detailed questions were asked on the type of tobacco used, duration of exposure, intensity of exposure, and average number of hours per day exposed. In the analyses restricted to lifetime nonsmokers, adjustment included age and history of previous lung diseases. Although initially examined, adjustment was not made for dietary beta-carotene and dietary fat because these factors did not confound the associations in this study.

In an analysis restricted to lifetime nonsmokers, there was no increase in risk associated with "ever-exposed" to spousal ETS (adjusted OR = 1.0, 95% CI = 0.8-1.2) or exposure to fewer than 40 pack-years (see Table 7.5). However, analysis of the highest category of exposure to spouses' smoking (greater than 40 pack-years) yielded an OR of 1.3 (95% CI = 1.0-1.7) (Table 7.5). Analyses by histologic type showed the largest increase in risk for other/mixed-cell types and for small-cell carcinomas, but these results were for lifetime nonsmokers and ex-smokers combined. Results were not presented separately for self-respondents and surrogate respondents. There was no association between risk of lung cancer and ETS exposure from parents (adjusted OR = 0.7, 95% CI = 0.5-0.9) or other household members (adjusted OR = 0.8, 95% CI = 0.6-1.1) during childhood (Table 7.6). These investigators also noted that there was no overall elevated lung-cancer risk in this study associated with any ETS exposure in the workplace. However, lifetime nonsmokers showed an increase in risk at the highest quartile of workplace ETS exposure (OR = 1.2, 95% CI = 0.9-1.7) (Table 7.7). Although the extent of exposure among the highest quartile of workplace was not specified, this OR is similar to the U.S. EPA report's risk estimate for spousal smoking obtained from the meta-analysis.

Fontham et al. (1991 and 1994) Fontham *et al.* (1991 and 1994) conducted a population-based case-control study of women in five geographic areas in the U.S.—New Orleans, Louisiana; Atlanta, Georgia; Houston, Texas; Los Angeles County, California; and San Francisco Bay Area, California—referred to as the U.S. multicenter study (Table 7.4). Eligible cases included women with microscopically confirmed primary carcinoma of the lung that were diagnosed between December 1, 1986, and November 30, 1988, among residents of Atlanta and Houston, and during 2 additional years—1989 and 1990—among residents of New Orleans, Los Angeles County, and San Francisco Bay Area. Additional eligibility criteria included age at diagnosis (20 to 79 years), language (English, Spanish, Chinese), history of previous cancer (none), and lifetime non-tobacco use (fewer than 100 cigarettes smoked and no use of any other form of tobacco for more than 5 months). One pathologist independently reviewed and confirmed histologic classification of 85 percent of the lung tumors in this study.

A population-based control group was selected by random-digit dialing and supplemented by random sampling from the U.S. Health Care Financing Administration files for women 65 years and older. Controls were frequency matched to cases on race and age in a two to one ratio of controls to cases and met the same residence, language, and tobacco-use criteria as cases. In-person interviews were completed for 665 of 800 incident lung cancer cases and 1,278 of 1,826 population controls; the respec-

tive response rate was 83 percent and 70 percent. The proportion of interviews conducted with self-respondents was 63 percent for lung cancer patients and 100 percent for controls. The considerably higher percentage of self-respondents in this study compared to the studies conducted by Stockwell *et al.* (1992) and Brownson *et al.* (1992) may be due to the more rapid identification of patients and thus contact of lung cancer cases in this multicenter study.

The lifetime nonsmoking status of study subjects was confirmed using a multistep procedure which included checking: 1) medical records, 2) with physicians' offices, 3) at the time of contact to set up the interview, and 4) at the beginning of the interview. In addition, the subjects' current nonsmoking status was corroborated by measurement of urinary cotinine levels. Cotinine, a sensitive and specific biologic marker of recent tobacco exposure (Haley *et al.*, 1983) was measured on 81 percent of self-respondent cases and 83 percent of controls. Levels of urinary cotinine/creatinine exceeding 100 ng/mg were found in 0.6 percent of cases and 2.3 percent of controls, indicating a low percentage of misclassification of smokers as nonsmokers (Fontham *et al.*, 1994).

The in-person interviews followed an extensive structured questionnaire designed to obtain information on household, occupational, and other exposures to ETS during each subject's lifetime, as well as other exposures associated with lung cancer. Exposure to ETS was examined by source during childhood (father, mother, and other household members who lived in the home for at least 6 months) and during adult life (spouse, other household members, occupational, and social exposures).

Spousal smoking was associated with a statistically significant increased risk of lung cancer; adjusted ORs of 1.29 (95% CI = 1.04-1.60) for ever exposed to spouses' smoking and 1.79 (95% CI = 0.99-3.25) (p for trend = 0.03) for 80 or more pack-years of exposure to spouses' smoking were observed (Table 7.5). Exposure to other sources of ETS during adult life was also associated with an increased risk of lung cancer. Adjusted ORs of 1.39 (95% CI = 1.11-1.74) for ever exposed to ETS at the workplace and 1.86 (95% CI = 1.24-2.78) for 31 or more years of exposure at the workplace were observed (Table 7.7). In addition, increased risks were associated with ETS exposure in social settings (see section 7.2.4.3). When all sources of ETS exposure during adult life were considered jointly as years of exposure, women with 48 years or more of exposure showed an OR of 1.74 (95% CI = 1.14-2.65) compared with women with no ETS exposure (data not shown). The increased risks associated with ETS exposure from spouses, at the workplace, and other social settings were observed for adenocarcinomas as well as other histologic types of lung cancer.

The findings for ETS exposure were similar when the analysis was restricted to self-respondents only. For example, among self-respondents only, an OR of 1.67 (95% CI = 1.03-2.70) was found for women with 48 years or more of exposure for all sources combined in adult life compared with women with no exposure (the OR was 1.74 for all respondents combined—data not shown). These results for ETS exposure were observed after

Table 7.7
Studies on ETS Exposure at the Workplace and Lung Cancer Among Lifetime Nonsmoking Subjects

Study/ Year of study	Questions on ETS exposure	#unexposed/ #exposed cases	#unexposed/ #exposed controls	OR (95% CI) for exposed
STUDIES IN THE UNITED STATES				
Kabat & Wynder (1984) 1961-1980	current or last job			
	males	7/18	14/11	3.3 (1.0-10.4)
	females	27/26	22/31	0.7 (0.3-1.5)
Garfinkel *et al.* (1985) 1971-1981	#hrs/day exposed to smoke of others at work: Past 5 years	80/14	262/52	0.88 (0.7-1.2)
	Past 25 years	42/34	135/118	0.93 (0.7-1.2)
Wu *et al.* (1985) 1981-1982	# years exposed at each job	13/16	31/31	1.3 (0.5-3.3)
Janerich *et al.* (1990) 1982-1984	# smokers at work (lifetime), amount of time working with smokers	NA	NA	no association 0.9 (0.8-1.04)
Brownson *et al.* (1992) 1986-1991	current/most recent job, exposed to other's smoke	NA	NA	no association overall 1.2 (0.9-1.7)[a]
Stockwell *et al.* (1992) 1987-1991	not described	NA	NA	no association
Fontham *et al.* (1994) 1985-1991	# years exposed at each job (lifetime years of exposure at work)	224/385	491/756	1.39 (1.1-1.7)[b]
	By years of exposure	cases	controls	
	0	224	491	1.00[c]
	1-15	213	450	1.30 (1.01-1.67)
	16-30	118	223	1.40 (1.04-1.88)
	31+	54	83	1.86 (1.24-2.78)[b]
Kabat *et al.* (1995) 1983-1990	four (4) jobs that lasted 1 year or more			
	males	18/23	52/65	1.02 (0.50-2.09)
	females	23/35	64/85	1.15 (0.62-2.13)

Table 7.7 (Continued)

Study/ Year of study	Questions on ETS exposure	#unexposed/ #exposed cases	#unexposed/ #exposed controls	OR (95% CI) for exposed
STUDIES IN THE UNITED KINGDOM AND GREECE				
Lee *et al.* (1986) 1977-1982	timing of job not specified, exposure as no, little, a lot			
	males	3/7	40/57	1.61 (0.4-6.6)
	females	12/3	113/47	0.63 (0.2-2.3)
Kalandidi *et al.* (1990) 1987-1989	#smokers at work current/last job:	24/65	40/78	1.39 (0.8-2.5)[d]
STUDIES IN ASIA				
Koo *et al.* (1984) 1981-1983	any ETS exposure at work (all jobs)	NA	NA	0.91 (0.15-5.37)
Shimizu *et al.* (1988) 1982-1985	most recent/current job, any smokers at work	NA	NA	1.2
Wu-Williams *et al.* (1990) 1985-1987	exposure at each job	187/228	301/301	1.2 (0.9-1.6)[e] 1.06 (0.8-1.4)[f]

[a] *For highest quartile of exposure*
[b] *$p < 0.01$*
[c] *Trend, $p = 0.001$*
[d] *Calculated from entries on exposure at work in Table 2 of publication*
[e] *Adjusted for center, age, and education*
[f] *Adjusted for center, age, education, previous lung disease, and heating practices*

adjustment for age, race, study area, education, intake of fruits and vegetables and use of supplemental vitamins, dietary cholesterol, family history of lung cancer, and employment in high-risk occupations.

In this study, ETS exposure during childhood/adolescence from father, mother, or other household members was not associated with risk of lung cancer. The OR for any childhood exposure to ETS (*i.e.*, any household member) was 0.89 (95% CI = 0.72-1.10) (Table 7.6) (data from table 4 of Fontham *et al*. (1994)). However, there was some suggestion that the risk associated with adult ETS exposure varied according to childhood ETS exposure. Significantly elevated risks associated with adult ETS exposures were observed in women with and without childhood exposures. The elevations in risk for women exposed during childhood were twice as high as for those

without childhood exposures. For example, at the highest level of ETS exposure (48 adult smoke-years or more), the authors reported an adjusted OR of 3.25 (95% CI = 1.42-7.46) among women reporting childhood exposures compared to 1.77 (95% CI = 0.98-3.19) for those reporting no childhood exposure (data not shown).

Kabat et al. (1995) Kabat *et al.* (1995) conducted a hospital-based case-control study of women and men between 1983 and 1990 as part of a long-standing study of tobacco-related cancers. This study was carried out in six hospitals located in four U.S. cities (New York City, New York; Chicago, Illinois; Detroit, Michigan; and Philadelphia, Pennsylvania). Newly diagnosed, histologically confirmed cases of primary cancer of the lung were ascertained in the collaborating hospitals. For each case enrolled, up to three control patients who were lifetime nonsmokers matched on age (±5 years), sex, race, hospital, and date of interview (within 2 months) were interviewed. Control patients were admitted for various cancer and noncancer outcomes. About 30 percent of the controls were diagnosed with cancer of the stomach/intestine, genitourinary tract, or lymphatic and hematopoietic system, cancer sites which may be positively associated with tobacco use (see Sections 7.3.3, 7.4.2, and 7.4.4). Thus, the ETS exposure among some controls may be higher than the general population, leading to a bias towards the null.

Subjects were considered lifetime nonsmokers if they had never consumed as much as one cigarette per day for a year, or had smoked fewer than 365 cigarettes over their lifetime. In the structured interview, detailed questions regarding the initiation of smoking early in life were included and provided a basis for excluding ex-smokers who quit decades prior to diagnosis but had smoked more than this minimum amount. The proportion of never-smokers among all lung cancer cases in this study was 3 percent in males and 8 percent in females.

All subjects were interviewed in person in the hospital. The questionnaire included a detailed history of exposure to ETS, during childhood and adult life. Questions were also asked about adult ETS exposures inside and outside the home (at work, in cars and other forms of transportation, and in social settings). Interviews were conducted with 41 male and 69 female never-smoking lung cancer cases and 117 male and 187 female never-smoking controls.

There were no significant associations between spouses' smoking and risk of lung cancer in male (OR = 1.60, 95% CI = 0.67-3.82) or female (OR = 1.08, 95% CI = 0.60-1.94) subjects (Table 7.5). The calculated OR for lung cancer in males and females combined was calculated to be 1.19 (95% CI = 0.76-1.87) in association with spousal ETS exposure. Wives' smoking 11+ cigarettes/day was associated with a significant increased risk (OR = 7.48, 95% CI = 1.35-41.36) of lung cancer in men (Table 7.5). However, this result was based on small numbers and thus unstable, and a similar result was not observed in women associated with their husbands' smoking. For males and females combined, the calculated OR for having a spouse who smoked 11+ cigarettes/day was 1.57 (95% CI = 0.81-3.07). The OR for lung cancer

associated with spouses who smoked in the bedroom was slightly higher than that associated with any smoking by spouses, but this association was not statistically significant in males (OR = 5.02, 95% CI = 0.72-35.01) or females (OR = 1.09, 95% CI = 0.49-2.42) (data not shown)(the crude OR for males and females combined was 1.20, 95% CI = 0.6-2.4).

Results for any household ETS exposure during adult life were similar to the results described above for spousal ETS exposure; household exposure was not significantly associated with risk of lung cancer (Table 7.6). The exception was that, among males, there was a statistically significant increased risk (OR = 4.15, 95% CI = 1.34-12.87) of lung cancer associated with two or more smokers in the adult household, but this was not observed among females (OR = 0.94, 95% CI = 0.34-2.63).

Sources of ETS exposure outside of the home during adult life were also evaluated, including ETS exposure at the workplace, in social situations, and inside cars. Workplace ETS exposure was not associated with increased risk of lung cancer in males or females (Table 7.7) in this study. There were small increased risks for lung cancer associated with ETS exposures in social situations and inside cars (see 7.2.4.3). The elevated risk associated with ETS exposure inside cars was statistically significant in an analysis which combined male and female subjects (see 7.2.5.3).

Exposure to ETS during childhood was not associated with any increased risk in males (OR = 0.90, 95% CI = 0.43-1.89), but in females it was associated with an increased risk which was of borderline statistical significance (OR = 1.55, 95% CI = 0.95-2.79) (Table 7.6). There were no significant dose-response relationships between number of smokers in childhood households and risk of lung cancer in male or female subjects in this study.

7.2.2.2 Other Case-Control Studies Providing Information on ETS and Lung Cancer

Liu et al. (1993)

Liu *et al.* (1993) present the results of a hospital-based case-control study of indoor air pollution and lung cancer in Guangzhou, China. Newly diagnosed cases of primary lung cancer selected from eight major hospitals over a one-year period were included. Controls were individually matched to cases on age, sex, residential district, and date of diagnosis or hospital admission. Six of the eight hospitals (excluding the Tumor Hospital and Chest Hospital) which provided cases also provided controls for this study. Patients with certain diseases were excluded as eligible controls, but the diagnoses of controls included in the study were not presented. Of the 327 lung cancer cases identified, a total of 224 male and 92 female incident lung cancer cases and an equal number of individually matched male and female hospital controls were interviewed.

The main objective of the study was to investigate the role of indoor air pollution and ventilation on risk of lung cancer in smokers and nonsmokers. Questions on spouse's smoking habits were also asked. An unmatched analysis was conducted to examine the effect of ETS exposure among the 38 female cases and 69 female controls who had never smoked. Compared to nonsmoking women who were not exposed to husbands' smoking, women exposed to 1-19 and 20+ cigarettes per day of husbands' smoking showed

ORs of 0.7 and 2.9, respectively (*p* for trend = 0.03) after adjusting for education, occupation, and living area. Risk of lung cancer was increased in association with living in a house with poor air circulation. The crude OR comparing women ever exposed to those with no exposure to husbands' smoking was 1.66 (95% CI = 0.73-3.78). No air circulation and lack of a separate kitchen were other significant risk factors for lung cancer in this study. There is no discussion of whether the analysis of ETS exposure in nonsmokers considered air circulation or presence of a separate kitchen as adjustment variables.

Schwartz et al. (1996) The main objective of this case-control study was to investigate the role of familial risk factors in the etiology of lung cancer. Cases and controls in this study had previously participated in the Occupational Cancer Incidence Surveillance Study (OCISS). OCISS subjects were identified among metropolitan Detroit area residents with specific cancers which included lung cancers. Population controls (without cancers) selected by random digit dialing were identified for the original OCISS study. For this analysis, all lung cancer cases who did not smoke cigarettes, cigars, and/or pipes (it was, however, never specified whether they were lifetime nonsmokers) were eligible. Controls represented a random sample, approximately one-third of all eligible nonsmoking controls, and they were frequency-matched to nonsmoking lung cancer cases by 5-year age group, sex, race, and county of residence. The final eligible sample included 314 cases and 345 controls, of whom 257 case and 277 control interviews were obtained. Some 72 percent of the case and 64 percent of the control subjects were females.

Telephone interviews were conducted. Because of the high case fatality associated with lung cancer, 83 percent of the case interviews had to be conducted with proxies which included spouses, siblings, offspring, or parents. In contrast, 22 percent of the control interviews were completed with proxies. After adjustment for age, race, and sex, exposure to ETS at home was not a significant risk factor for lung cancer (OR = 1.1, 95% CI = 0.8-1.60), while exposure to ETS at work was of borderline statistical significance (OR = 1.5, 95% CI = 1.0-2.2). However, it is unclear whether ETS exposure at home included exposures during childhood and/or adult life. It was also not specified whether ETS exposure at all jobs or the most current or longest job was asked. Limitations of this study include the fact that almost all the information on cases was obtained from proxy interviews and that relevant details regarding ETS exposure variables were not described. This study was not designed to investigate the role of ETS exposure in the etiology of lung cancer in nonsmokers.

Ko et al. (1997) This was a hospital-based case-control study conducted in Kaohsiung, Taiwan, a heavily industrialized city. All eligible lung cancers were identified during a 2-year period in a leading teaching hospital in this study area. Of the 128 eligible female lung cancer patients identified, 117 were interviewed while they were in the hospital. Control women were ophthalmic patients (*n* = 62) or women admitted for a health check (*n* = 55), and they were matched to cases on age and date of interview. The study was designed to investigate various suspected risk factors for lung

cancer including active and passive smoking, previous lung diseases, cooking practices, and indoor environment. Questions on ETS exposure asked about smoking habits of parents, husbands, cohabitants and coworkers. There were 11 cases and 3 controls who were active smokers. The analysis on ETS exposure was conducted among the 105 case-control pairs of nonsmokers. In matched analyses adjusted for socioeconomic status, residential area, and education, risk of lung cancer in nonsmoking women was not associated with ETS exposure from parents (OR = 0.8; 95% CI = 0.4-1.6), cohabitants (OR = 1.0; 95% CI = 0.4-2.3), or coworkers (OR = 1.1; 95% CI = 0.4-3.0), but there was a small nonsignificant increased risk associated with ETS exposure from spouses (OR = 1.3; 95% CI = 0.7-2.5). It was not specified whether exposure from parents and other cohabitants covered exposures during both childhood and adult life. It was also not specified whether exposure from coworkers covered all jobs or the last or longest job. ETS exposure was one of several sources of indoor air pollution investigated in this study. It is not clear whether information on extent (*i.e.*, duration or amount) of ETS exposure was obtained.

7.2.3 A U.S. Cohort Study Published Since 1991

Cardenas et al. (1997)

The analysis by Cardenas *et al.* (1997) utilized data from the CPS-II, which enrolled approximately 1.2 million men and women in 1982. By December 1989, 91.2 percent (1,080,689) were still living, 8.6 percent (101,519) had died, and the remainder had unknown vital status. Death certificates were obtained for 96.8 percent of subjects known to have died.

Among never-smokers in this study, two analyses on ETS exposure and risk of lung cancer were conducted. The main and more complete analysis on long-term ETS exposure was based on information on active smoking habits of spouses obtained directly from spouses who were linked to the index never-smoker. With less than 2 percent of subjects excluded due to missing data, a total of 150 lung-cancer deaths in 192,234 never-smoker women and 97 lung-cancer deaths in 96,542 never-smoker men were available for this analysis. In approximately half of the never-smoker women, information on amount smoked by husbands and years in marriage to husbands who smoked was also available (*i.e.*, for 74 lung-cancer deaths in 92,222 never-smoker women). A second and less complete analysis was based on self reporting of current ETS exposure at home, at work, or in other areas. Thirteen percent of male to 30 percent of female subjects had missing information in one of the three questions on sources of recent ETS exposure. Based on the assumption that individuals with missing data on one of the sources of ETS exposure had no exposure from that source, these analyses included 246 lung cancer deaths in 281,536 never smoking women and 116 lung cancer deaths in 110,687 never smoking men. The analyses were conducted with adjustment for the main confounders which included age, race, years of education, occupation, dietary intake of various fruits, vegetables and fat, and history of previous lung diseases.

In the analyses based on spousal smoking habits (Table 7.5b), never-smoking women married to smokers showed a small increased risk of lung cancer (RR = 1.20, 95% CI = 0.8-1.6); the risk was 1.2 (95% CI = 0.8-1.8)

associated with husbands who were current smokers and 1.1 (95% CI = 0.6-1.6) for husbands who were former smokers. There was an increasing trend of risk associated with number of cigarettes smoked by spouses; the ORs were 1.0, 1.1, 1.2, and 1.9, respectively, for 0, 1-19, 20-39, and 40+ cigarettes smoked per day (*p* for trend = 0.03). Similarly, there was an increasing trend of risk with increasing pack-years smoked by spouse (*p* for trend = 0.10). There was, however, not a smooth trend of increasing risk with increasing years of ETS exposure. The ORs were 1.0, 1.5, and 1.1, respectively, associated with 0, 1-17, 18-29, and 30+ years of exposure (*p* for trend = 0.5). Based on fewer lung-cancer deaths in men and a lower prevalence of men married to smokers, the risk of lung cancer among never smoking men married to smokers was 1.1 (95% CI = 0.6-1.8); the risk was 1.0 (95% CI = 0.5-2.0) associated with wives who were current smokers and 1.1 (95% CI = 0.6-2.2) for wives who were former smokers.

Cardenas *et al.* (1997) reported that none of the self-reported current ETS exposure measures (any exposure or total hours of exposure) was associated with increased lung cancer risk. The multivariate RRs among women who reported 0, 1-2, 3-5, or 6+ hours of ETS per day in all settings were 1.0, 0.8, 0.7, and 1.1, respectively. The corresponding RRs in men were 1.0, 0.6, 1.0, and 1.3.

There are several notable advantages of this cohort study. Possible selective recall bias and information bias with the use of surrogate respondents, concerns raised by some regarding case-control studies, are avoided. Because the main analysis identified only married couples, this precluded any bias introduced as a result of married and unmarried persons describing ETS exposure differently. Moreover, this cohort analysis has an added advantage compared to previous cohort studies in that a large number of potential confounders were accounted for in the analysis and an association with ETS exposure from spouses was present.

The main limitations of this study are the relatively small number of lung cancer deaths available for analysis. In addition, information on amount smoked by husbands and years of marriage to smokers was available on approximately half of the never-smoker women. These investigators calculated that approximately 1,000 expected cases are needed to achieve 80 percent statistical power (assuming an RR of 1.2, alpha of 0.05, 2-sided, and an ETS exposure rate of 60 percent). A second limitation is that spousal ETS exposure was based on the smoking habits of current spouse and that information on ETS exposure from previous marriages or from other household members was not available. Even for current spouses, information on amount smoked and duration of smoking was available on only about half of the never-smokers in this study.

7.2.4 ETS Exposure from Spouses

The results from the recent U.S. studies are compatible with the pooled estimate of the U.S. EPA (1992) report, which found a summary OR of 1.19 (90% CI = 1.04-1.35) for ever exposed to ETS from spouses (for U.S. studies). Results from the largest population-based study, the U.S. multicenter study (OR = 1.29, 95% CI = 1.04-1.60, for ever exposed) (Fontham *et al.*, 1994) were closest to the pooled estimate from

the U.S. EPA report. Of the two other population-based studies, the association found in the Florida study (Stockwell *et al.*, 1992) was stronger (OR = 1.6, 95% CI = 0.8-3.0; although it did not achieve statistical significance except for the highest exposure category: OR = 2.4, 95% CI = 1.1-5.3), and that from the Missouri study (Brownson *et al.*, 1992) was weaker (overall OR = 1.0, 95% CI = 0.8-1.2; for highest exposure category of spousal smoking, OR = 1.3, 95% CI = 1.0-1.7) than the pooled estimate result. Although the authors of the fourth study—the hospital-based case-control study (Kabat *et al.*, 1995)—reported their findings as unsupportive of an association between ETS exposure and risk of lung cancer, the odds ratio were elevated for males (OR = 1.60, 95% CI = 0.67-3.82) and females (OR = 1.08, 95%CI = 0.60-1.94), though not statistically significant, and the results of this small study do not contradict an increased risk on the order of 20 percent. The cohort study by Cardenas *et al.* (1997) also showed a small increased risk of lung cancer (RR = 1.2, 95% CI = 0.8-1.6) associated with being married to a smoker. In addition, positive increasing trends in risk of lung cancer in nonsmokers were observed for increasing ETS exposure indices in all three of the population-based studies (Table 7.5) and in the U.S. cohort study (Table 7.5a). The concordance in these study results gives further credibility to the finding of a causal association between spousal ETS exposure and risk of lung cancer described in the U.S. EPA (1992) report.

The sample sizes of the three population-based U.S. studies (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1994) were considerably larger than previously published case-control studies in the U.S. (Correa *et al.*, 1983; Buffler *et al.*, 1984; Kabat and Wynder 1984; Dalager *et al.*, 1986; Wu *et al.*, 1985; Garfinkel *et al.*, 1985; Humble *et al.*, 1987; Brownson *et al.*, 1987; Janerich *et al.*, 1990). Spousal ETS exposure was not associated with a significant increased risk of lung cancer in males and females in the Kabat *et al.* (1995) study. However, this study was considerably smaller than the other three U.S. studies published in the 1990s and had limited statistical power to detect a significant association. The recent cohort study (Cardenas *et al.*, 1997) was limited by the relatively small number of lung cancer deaths available for analysis.

Another important feature of the post-1991 studies is that they addressed many of the criticisms (Mantel, 1983; Lee, 1986 and 1989; Katzenstein, 1992) directed at previous studies of ETS exposure and lung cancer. Although the extent to which these criticisms were addressed in each of the four case-control studies varied, the concerns were addressed collectively in these studies. Specifically, concerns regarding selection bias, misclassification bias of smokers as lifetime nonsmokers, misclassification of some non-lung cancers as lung cancers, misclassification of ETS exposure, and the lack of adjustment for potential confounders were addressed. Concerns regarding possible selective recall bias and information bias of case-control studies are avoided in the cohort study by Cardenas *et al.* (1997). Moreover, because the main analysis included only married couples who reported their own smoking habits, misclassification of ETS exposure due to reporting bias is also avoided.

The three population-based studies were careful to minimize the possibility of selection and misclassification biases. Selection bias associated with cases from selected hospitals is eliminated since, in all three population-based studies, lung cancer patients were identified from the cancer registries and hospitals covering a specific study area. The use of population-based controls instead of other patients as controls is also advantageous, since ETS exposure of patients with certain diagnoses may be higher and not representative of the exposure distribution of the source population from which cases were drawn. In addition, the U.S. multicenter study (Fontham *et al.*, 1991) examined the issue of differential recall between lung cancer cases and controls by interviewing colon cancer patients as a second control group during the first three years of the study. The findings on ETS exposure were comparable when lung cancer patients were compared to population controls and to colon cancer controls, suggesting that recall bias resulting from having a diagnosis of cancer could not explain the observed association with ETS.

Another source of misclassification bias that is of concern (Wald *et al.*, 1986; Lee, 1989) pertains to the misclassification of smokers as nonsmokers. In two of the four case-control studies (Fontham *et al.*, 1994; Stockwell *et al.*, 1992), the definition of lifetime nonsmokers was limited to individuals who had smoked fewer than 100 cigarettes and had no more than 6 months of tobacco use in their lifetime. In one study (Kabat *et al.*, 1995), subjects were considered lifetime nonsmokers if they had never consumed as much as one cigarette per day for a year, or had smoked fewer than 365 cigarettes over their lifetime. Both the U.S. multicenter study (Fontham *et al.*, 1994) and the Florida study (Stockwell *et al.*, 1992) used multiple sources of information to verify the lifetime nonsmokers' status. In addition, the U.S. multicenter study corroborated the subjects' self-reported current nonsmoking status using the urinary cotinine level. These results showed a very low percentage of cases (0.6 percent) and controls (2.3 percent) had levels of urinary cotinine exceeding 100 ng/mg, suggesting minimal misclassification of smokers as nonsmokers (Fontham *et al.*, 1994). Although the urinary cotinine/creatinine concentration only assesses current smoking (there are currently no biomarkers that allow assessment of past tobacco exposure), these results provided an additional verification of the current nonsmoking status.

Misclassification of lung cancer is also minimized by the requirement of microscopic diagnosis (Stockwell *et al.*, 1992; Fontham *et al.*, 1994; Kabat *et al.*, 1995) and an independent review of diagnostic material (Brownson *et al.*, 1992; Fontham *et al.*, 1994). In the three population-based studies with data by cell type (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1994), adenocarcinoma of the lung was the predominant cell type of lung cancer in nonsmoking women, accounting for over 60 percent of the lung tumors.

Because of the high fatality rate of lung cancer, all three U.S. population-based studies interviewed surrogate respondents to obtain information on a percentage of lung cancer cases who could not participate because they were too ill or were deceased. In all three studies, controls were self-

respondents. The percentage of lung cancer self-respondents was considerably higher for the U.S. multicenter study (63 percent) compared with the other two U.S. studies (33 percent for the Florida and 34 percent for the Missouri study). Since a surrogate's knowledge of the ETS exposure of an index subject is variable and dependent on their relationship and the exposure period of interest, it is likely that the quality of information on ETS exposure is higher in studies in which a high percentage of interview is conducted with self-respondents. On the other hand, the use of surrogate respondents was avoided in the U.S. hospital-based study since all interviews were conducted with the lung cancer cases and hospital patient controls while the subjects were still in the hospital (Kabat *et al.*, 1995).

Another criticism of previous studies of ETS exposure and lung cancer is that a small increased risk associated with ETS exposure may be due to lack of adjustment for potential confounding factors. In particular, it has been suggested that nonsmokers living with smokers have lower dietary intakes of specific micronutrients (Koo *et al.*, 1988; Hebert and Kabat, 1990; Sidney *et al.*, 1989; Le Marchand *et al.*, 1991; Matanoski *et al.*, 1995), including beta-carotene, which may be protective for lung cancer. However, there is little evidence of confounding by dietary factors in the U.S. multicenter study (Fontham *et al.*, 1994) or in a study conducted in Greece (Kalandidi *et al.*, 1990). In fact, similar trends of increased risk of lung cancer associated with increasing duration of exposure were observed at all levels of dietary factors (including intake of fruits and vegetables, supplemental vitamin use, and dietary cholesterol) (Fontham *et al.*, 1994). Other factors including employment in high-risk occupations (Fontham *et al.*, 1994) and previous lung diseases (Brownson *et al.*, 1992; Wu *et al.*, 1995) were examined, and they did not confound the association of ETS exposure and lung cancer. Thus, the recent large, well-conducted study (Fontham *et al.*, 1994) assessed all potential confounders that should be considered in evaluating the association of ETS with lung cancer in nonsmokers; the association was observed with adjustment for these potential confounders.

7.2.5 Other Sources of ETS Exposure

Because of the importance of obtaining a comprehensive measure of lifetime ETS exposure (Cummings *et al.*, 1989), all four U.S. case-control studies included questions to assess ETS exposure at home (from spouses, parents, and other household members during childhood and adult life), at the workplace and in other social settings. However, the exact questions asked and the level of detail obtained varied in these studies. Only a subset of the studies published prior to 1991 included questions on ETS exposures from sources other than spouses.

7.2.5.1 ETS Exposure From Parents and Other Household Members (Other Than Spouses)

Table 7.6 summarizes the case-control studies conducted since 1981 in the U.S. (n = 7) and outside of the U.S. (n = 7) that included questions on ETS exposure from household members other than spouses—represented mainly by exposure from parents during childhood—but also including other household members during childhood and adult life. The study by Akiba *et al.* (1986), which reported "no association," was not included in Table 7.6 since no information on the association or the distribution of subjects by exposure status was provided.

Among the U.S. studies, the strongest evidence for an effect of parental smoking is from studies conducted by Janerich *et al.* (1990) and Stockwell *et al.* (1992). In the study by Janerich *et al.* (1990), exposure during childhood up to age 21 accounted for about one-third of the lifetime duration (expressed in smoker-years) of ETS exposure. The highest level of childhood exposure (25 or more smoker-years) was associated with a statistically significant increased risk (OR = 2.07, 95% CI = 1.16-3.68), although there was no statistically significant elevated risk with 1-24 years of exposure. In the study by Stockwell *et al.* (1992), exposure to ETS from mothers, fathers, and siblings during childhood/adolescence was associated with a 10 to 70 percent increase in risk. Women who experienced 22 years or more of exposure to ETS from all household members combined during childhood/adolescence showed a significantly elevated risk of 2.4 (95% CI = 1.1-5.4) (Table 7.6). On the other hand, risk of lung cancer in nonsmokers was not associated with ETS exposure during childhood in the U.S. multicenter study (Fontham *et al.*, 1994), the Missouri study (Brownson *et al.*, 1992), the U.S. hospital-based study (Kabat *et al.*, 1995), or a small study conducted in Los Angeles County (Wu *et al.*, 1985). However, in the U.S. multicenter study, subjects who were exposed to ETS exposure during both childhood and adult life showed the highest increase in risk of lung cancer (Fontham *et al.*, 1994). In a hospital-based study conducted in the 1970's (Kabat and Wynder, 1984) and a subsequent one conducted in the 1980's (Kabat *et al.*, 1995), smoking by family members during adult life was not associated with risk of lung cancer in nonsmoking males and females.

In two studies conducted in Japan (Shimizu *et al.*, 1988; Sobue, 1990), an increased risk of lung cancer was associated with mothers' smoking; the result was statistically significant in one study (Shimuzu *et al.*, 1988) but not the other (Sobue, 1990). A significantly increased risk of lung cancer was also associated with smoking by the father-in-law in one Japanese study (Shimizu *et al.*, 1988). In Shanghai, China (Gao *et al.*, 1987) and in Northern China (Wu-Williams *et al.*, 1990), exposure to ETS during childhood did not differ significantly between lung cancer cases and controls. In a study conducted in Hong Kong, risk of lung cancer in nonsmokers was increased in households with smokers, although there was not a smooth trend of increasing risks with increasing number of smokers in the household (Koo *et al.*, 1987). In Sweden, no association between parents' smoking and risk of lung cancer was reported in one study (Pershagen *et al.*, 1987), whereas in another study, a statistically nonsignificant 3-fold increased risk of lung cancer was found for mothers' smoking (Svensson *et al.*, 1989).

Quality of information on parents' smoking (or other household members) during childhood may be compromised in some studies, particularly those in which this information is provided by surrogate respondents. Although there is generally good agreement of responses on ETS exposure when subjects themselves were asked on two different occasions whether specific household members smoked, the level of agreement diminished on quantitative aspects of smoking by household members (Pron *et al.*, 1988; Coultas *et al.*, 1989; Brownson *et al.*, 1993a). Studies which show high

concordance on the reporting of exposure to ETS during childhood and parents' smoking habits (Coultas *et al.*, 1989; Brownson *et al.*, 1993a) were based on responses obtained from the subjects themselves. The degree of agreement when the responses on smoking habits of the other household members are provided by surrogate respondents is not known. The fact that exposures from household members other than spouses are reported less reliably may partially explain the inconsistent results regarding the association between the risk of lung cancer and ETS exposure from these household members (*i.e.*, other than spouses); it may also explain the failure of most studies to observe stronger associations with exposure from household members other than from spouses.

7.2.5.2 Workplace ETS Exposure Table 7.7 summarizes case-control studies which included questions on ETS exposure at the workplace. Indicators of workplace ETS exposure varied (the actual questions asked were not provided). In some studies, the indicators of workplace ETS exposure were limited to the most recent job or the last job (Kabat and Wynder, 1984; Shimizu, 1988; Kalandidi *et al.*, 1990; Brownson *et al.*, 1992), at other specific times (Garfinkel *et al.*, 1985), or the timing of the question was not specified (Lee *et al.*, 1986; Stockwell *et al.*, 1992). In one study, number of smokers at work (lifetime) and amount of time working with smokers was assessed (Janerich *et al.*, 1990). In other studies, questions were asked regarding ETS exposure at each workplace of at least 3 months (Koo *et al.*, 1987) or the last four jobs of at least 1 year duration (Kabat *et al.*, 1995). In three other studies, lifetime occupational history was obtained and exposure to ETS was assessed for each job (Wu *et al.*, 1985; Wu-Williams *et al.*, 1990; Fontham *et al.*, 1994).

Studies in which the assessment of workplace exposure to ETS was complete (covering all jobs) with considerable ETS exposure of subjects in the studies are generally supportive of an association between workplace ETS exposure and risk of lung cancer (Wu *et al.*, 1985; Wu-Williams *et al.*, 1990; Fontham *et al.*, 1994). In particular, results from the U.S. multicenter study (Fontham *et al.*, 1994) suggested a trend of increasing risks with increasing duration of ETS exposure at the workplace. Compared to women who had no ETS exposure at the workplace, women who reported exposure for 1-15, 16-30, and 30 or more years showed adjusted odds ratios of 1.30, 1.40, and 1.86, respectively (p for trend = 0.001) (Table 7.7). In a subsequent analysis that selected workers only and adjusted for other adult ETS exposure sources, the RRs associated with workplace exposure were modestly enhanced (Reynolds *et al.*, 1996). The overall odds ratios associated with any reported workplace exposure increased from 1.39 in the earlier analysis to 1.56 (95% CI = 1.21-2.02) and the corresponding point estimates for 1-15, 16-30, and 30 or more years of exposure were likewise elevated; the adjusted odds ratios were 1.46, 1.58, and 2.08, respectively. Occupational exposure to carcinogens is an important confounder for lung cancer in nonsmokers, and the U.S. multicenter study (Fontham *et al.*, 1994) is the only one which adjusted for such exposures.

In addition to the incomplete assessment of exposure to ETS at the workplace in some studies, respondents, particularly surrogate respondents, may be less able to provide information on the subjects' exposure to ETS at the workplace. In a study in which a test-retest design was used to examine the reliability of passive smoke histories reported in personal interviews, self-respondents more reliably reported residential exposure than exposure at work (Pron *et al.*, 1988). This may be a particularly important problem in studies in which the proportion of surrogate respondents was high (Brownson *et al.*, 1992; Stockwell *et al.*, 1992).

Despite some of the above-mentioned difficulties in obtaining histories of lifetime ETS exposure at the workplace, there is reason to believe this source of ETS exposure also increases the risk of lung cancer, as does ETS exposure from spouses. The workplace has been a major source of ETS exposure outside the home (Cummings *et al.*, 1989 and 1990; Emmons *et al.*, 1992; Siegel, 1993), although the relative importance of workplace ETS exposure may be declining in California as the result of increasing restrictions on smoking in the workplace. In the International Agency for Research on Cancer (IARC) ten-country, collaborative study which correlated urinary cotinine levels to self-reported recent exposure to ETS at home (from spouses), in the workplace, and other social settings, Riboli *et al.* (1990) found that exposure to ETS at the workplace was a significant predictor of cotinine levels, similar to ETS exposure from spouses.

7.2.5.3 ETS Exposure in Other Settings Two of the four U.S. case-control studies published since 1991 (Fontham *et al.*, 1994; Kabat *et al.*, 1995) also asked questions about ETS exposure in social settings (other than the workplace) or in modes of transportation. In the U.S. multicenter study, increased risks were associated with ETS exposure in social settings. Women who were exposed for 1-15, 16-30, and >30 years at other social settings compared to no exposure showed adjusted ORs of 1.45, 1.59, and 1.54, respectively (p for trend = 0.002) (Table 6 of Fontham *et al.*, 1994). In the U.S. hospital-based study, associations with ETS exposure in social situations and risk of lung cancer were not statistically significant in males (OR = 1.39, 95% CI = 0.67-2.86) or females (OR = 1.22, 95% CI = 0.69-2.15) (Table 2 of Kabat *et al.* (1995)); the calculated OR for males and females combined was 1.26 (95% CI = 0.81-1.95). ETS exposure in cars was associated with non-significant increased risks of lung cancer in both males (OR = 1.55, 95% CI = 0.63-3.78) and females (OR = 1.84, 95% CI = 0.96-3.53) in the Kabat *et al.* (1995) study. Although the risks for males and females considered separately were not significantly different from controls, the calculated risk for males and females combined was significantly elevated (OR = 1.73 (95% CI = 1.03-2.92). No male cases were exposed to ETS in other modes of transportation, whereas there was a significant excess of female cases compared to female controls who reported such exposures (OR = 5.17, 95% CI = 1.46-18.24). ETS exposure in other modes of transportation was associated with an OR of 2.23 (95% CI = 0.83-5.99) for lung cancer in males and females combined in the Kabat *et al.* (1995) study.

7.2.6 Summary Despite the compelling biologic plausibility of an effect of ETS exposure on risk of lung cancer, detection of an effect has been difficult because a small excess in risk is difficult to establish in a single epidemiologic study. The U.S. EPA (1992), NRC (1986), and Surgeon General (U.S. DHHS, 1986) all undertook comprehensive reviews of the literature and determined on the basis of the overall evidence that ETS exposure causes lung cancer. Since the publication of the most recent authoritative review of lung cancer and ETS exposure (U.S. EPA, 1992), three large U.S. population-based studies (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1991 and 1994), a smaller hospital-based case-control study (Kabat *et al.*, 1995), and a cohort study (Cardenas *et al.*, 1997) have been published. The three population-based studies were designed to and have successfully addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized (*i.e.*, small sample size, possible selection bias, possible misclassification biases, inadequate adjustment for potential confounders). Results from these studies and the cohort study are consistent with the conclusions of the U.S. EPA (1992), NRC (1986), and Surgeon General (U.S. DHHS, 1986) reports. Each of the three population-based studies shows a statistically significant increased risk of lung cancer in nonsmokers associated with long term exposure to ETS as well as increasing risk with increasing ETS exposure. The smaller hospital-based study lacked the statistical power to find the effect observed in the other studies. The results of the cohort study, though not statistically significant, were similar to the risk estimated by the U.S. EPA. Taken together, the recent studies provide additional evidence that ETS exposure is causally associated with lung cancer. The consistency of the findings in the five recent studies and the meta-analysis result of the U.S. EPA indicate about a 20 percent increased risk of lung cancer in nonsmokers.

7.3 ETS AND CANCER SITES OTHER THAN LUNG THAT ARE ASSOCIATED WITH ACTIVE SMOKING: NASAL SINUS, CERVICAL AND BLADDER

Active smoking is firmly established as a causal factor for cancers of the lung, larynx, oral cavity, esophagus, bladder, and nasal sinus cavity; in addition, evidence exists which suggests that smokers are at increased risk for kidney and cervical cancer. As reviewed above, the role of ETS exposure and risk of cancers in nonsmokers has been investigated mainly for lung cancer (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992). There are some data on the role of ETS for other cancer sites, including cancers of nasal sinus cavity, cervix, and bladder (U.S. DHHS, 1982 and 1989; IARC, 1986).

7.3.1 Nasal Sinus Cancer

7.3.1.1 Active Smoking and Nasal Sinus Cancer

Cancers of the nasal cavity and paranasal sinuses are extremely rare, accounting for 0.2 percent of all invasive incident cancers and 1.4 percent of all newly diagnosed respiratory cancers in the U.S. Use of tobacco products, various occupational exposures (*e.g.*, wood dust), and history of nasal polyps, have been implicated as risk factors for these tumors (Elwood *et al.*, 1981; Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992). Although the risk associated with any use of tobacco is modest (OR about 1.5), up to a 5-fold increased risk has been observed with

heavy smoking (Elwood *et al.*, 1981). The evidence suggests that the effect of smoking, particularly current or recent tobacco use, is stronger for squamous cell carcinoma than for other cell types (mainly adenocarcinomas) of nasal sinus cancer (Elwood *et al.*, 1981; Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992). The proportion of squamous cell nasal sinus cancers included in the different studies may influence the overall strength of the relationship between active smoking and all nasal sinus cancers combined. Studies which did not find a significant association between active smoking and nasal sinus cancer were generally small studies (*i.e.*, <50 cases and controls) (Tola *et al.*, 1980; Merler *et al.*, 1986), or had included few squamous cell carcinomas of the nasal sinus. For example, the study by Merler *et al.* (1986) included less than 20 percent squamous cell carcinomas compared to at least 40 percent of this cell type in other studies finding a positive association with smoking (Elwood *et al.*, 1981; Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Tola *et al.*, 1980; Zheng *et al.*, 1992).

7.3.1.2 ETS and Nasal Sinus Cancer The role of ETS exposure in the etiology of nasal sinus cancer in nonsmokers has been investigated in one cohort and two case-control studies (Table 7.8).

Hirayama (1983 and 1984) Using data from a Japanese prospective study (see Section 7.1 for detailed description), Hirayama (1983 and 1984) reported an increased risk of para-nasal sinus cancer (based on 28 nasal sinus cancer deaths) among nonsmoking women exposed to husbands' smoking. Relative risks increased with amount husbands smoked: compared to women married to nonsmokers, the RR was 1.7 (95% CI = 0.7-4.2), 2.0 (95% CI = 0.6-6.3), and 2.6 (95% CI = 1.0-6.3, $p \leq 0.05$), for women whose husbands smoked 1-14, 15-19, and 20+ cigarettes per day respectively, when husbands' age and occupation were adjusted for. The dose-dependent increase in risk was statistically significant ($p < 0.03$). Active smoking was not associated with nasal sinus cancer in this study; the OR was 0.9 (90% CI = 0.5-1.4) for males and females combined (Hirayama, 1990). Cell type distribution of nasal sinus cancer in nonsmokers and smokers was not available in this Japanese cohort study.

Fukuda and Shibata (1988 and 1990) The second study was conducted by Fukuda and Shibata (1988 and 1990) in Japan using a case-control study design. The 1988 report presented preliminary findings, and the 1990 report included results on 169 (125 men and 44 women) squamous cell maxillary sinus cancer cases and 338 controls (250 men and 88 women). Controls were selected from the general population. All subjects were interviewed directly. Nine of 125 male cases and 48 of 250 male controls had never smoked. Active smoking was a significant risk factor in men; the RR was 4.6 for smoking >39 cigarettes per day compared to nonsmokers. Based on a small number of nonsmoking men, exposure to ETS was associated with a small, nonsignificant increased risk of nasal cancer. Most of the female cases and controls in this study were nonsmokers (35 of 44 cases and 74 of 88 controls had never smoked). Active smoking was associated with a nonsignificant increased risk of nasal cancer in women. Among nonsmoking

Table 7.8
Association Between Passive Smoke Exposure and Risk of Nasal Sinus Cancer in Nonsmokers

Studies	Exposure to Passive Smoking		Relative Risk (95% CI)	
Cohort Studies				
Hirayama (1984)	Spouse's smoking in cig/day:			
	No	(5)[a]	1.0	
	Ex-smoker or Smokers			
	1-14	(9)	1.7	(0.7-4.2)
	15-19	(4)	2.0	(0.6-6.3)
	20+	(10)	2.6	(1.0-6.3)
Case-Control Studies				
Fukuda and Shibata (1990)	# Smokers in household			
	0	(11/35)[b]	1.0	
	1	(15/34)	1.4	(0.6-3.5)
	2+	(9/5)	5.7[c]	(1.7-19.4)
	1+	(24/39)	2.0	(0.8-4.5)
Zheng et al. (1993)	Ever exposed[d]			
	No		1.0	
	Yes		3.0	(1.0-8.9)

[a] *Number of nasal sinus cancer deaths.*
[b] *Number of cases/controls.*
[c] *p for trend = 0.02.*
[d] *Number of cases/controls by exposure category was not presented.*

women, domestic exposure to ETS, represented by the number of smokers in the household, was a significant risk factor. Compared to nonsmoking women with no reported ETS exposure, nonsmoking women who reported one, and two or more smokers in the household showed RRs of 1.4 and 5.7, respectively (95% CIs = 0.6-1.5 and 1.7-19.4; *p* for trend = 0.02). The OR associated with any passive smoke exposure (*i.e.*, none versus any exposure) is 1.96 (95% CI = 0.8-4.5). Information on duration or intensity of ETS exposure was not reported. The effect associated with passive smoking persisted with adjustment for other risk factors including sinusitis and/or polyps, nasal trauma, and woodworking.

Zheng et al. (1993) The third study was a case-control analysis of cancer of the nasal cavity and sinuses among white men in the U.S. using data from the 1986 National Mortality Followback Survey (Zheng *et al.*, 1993). The study included a total of 147 cases (76 maxillary sinus, 11 nasal cavity, 4 auditory

and middle ear, 56 other accessory sinuses cancer) and 449 controls who died of other causes. All information was obtained from a surrogate who responded to a mailed questionnaire. There was an increased risk of nasal cancer among cigarette smokers, with a nearly 2-fold increased risk among heavy or long-term smokers for all nasal cancer sites. Compared to nonsmokers, heavy smokers showed an OR of 2.7 (95% CI = 1.2-6.4) for maxillary sinus cancers and an OR of 1.3 for other nasal cancer (95% CI = 0.5-3.3). Twenty-eight cases and 99 controls had never smoked. Among nonsmokers, more cases than controls had a wife who smoked cigarettes (OR = 3.0, 95% CI = 1.0-8.9, $p \leq 0.05$), but the authors stated there was not a smooth trend of increasing risks as the number of cigarettes smoked by the spouse increased (data on dose-response were not presented). The 3-fold risk associated with having a wife who smoked is somewhat surprising since more than half (15 of 28) of the tumors in nonsmokers were other nasal sinus cancer and this subgroup was less strongly associated with active smoking. However, the histologic cell type of nasal sinus cancer among smokers and nonsmokers was not available in this study, making it difficult to make direct comparisons of findings in smokers and nonsmokers.

7.3.1.3 Summary Existing studies consistently show a significant positive association between exposure to ETS and nasal sinus cancer in nonsmokers, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. The results have been observed in studies in white American males and Japanese females, in cohort and case-control study designs, and with some adjustment for possible confounders. The risks associated with ETS exposure ranged from 1.7 to 3.0.

Future studies need to confirm the magnitude of risk associated with ETS exposure, to characterize the risk by the source of ETS exposure (*i.e.*, spouse, other household members, coworkers) and by timing of ETS exposure (current versus past exposure), and to establish the dose-response relationship. It is also important that future studies examine the association between ETS and nasal sinus cancer by histologic type and subsite of nasal sinus cancers, and the role of other potential confounders in the association. Studies designed to investigate the mechanism(s) of action of active smoking and ETS exposure will help to elucidate their respective roles in the development of nasal sinus cancer.

7.3.2 Cervical Cancer

7.3.2.1 Active Smoking and Cervical Cancer

Numerous epidemiologic studies conducted in different populations of varying age groups exhibiting different degrees of cervical lesions have provided supportive evidence that women who smoke cigarettes are more likely to develop cervical cancer than women who do not (Winkelstein, 1990). The statistical association between active smoking and cervical cancer is reduced with adjustment for sexual activity variables (*e.g.*, number of partners, age at first intercourse) or infection with human papilloma virus (HPV), which has been accepted as the sexually transmitted etiological factor in cervical cancer (Brinton, 1990; Schiffman *et al.*, 1993; Munoz *et al.*, 1994; zur Hausen, 1986). However, an association between smoking and cervical cancer/intraepithelial neoplasia (CIN) has been found in case-con-

trol studies that have been able to control for these behavioral risk factors (Buckley *et al.*, 1981; Hellberg *et al.*, 1983; Brinton *et al.*, 1986; Clarke *et al.*, 1982; La Vecchia *et al.*, 1986; Becker *et al.*, 1994).

In most studies, the excess risk of cervical cancer for smokers is about 2-fold, with the highest risks generally observed for heavy or current smokers, suggesting that tobacco smoke may have a late-stage effect on cervical cancer development. The data also suggest that tobacco smoke may be a cofactor in the development of particularly high-grade CIN (Brinton and Hoover, 1992; Schiffman *et al.*, 1993) by acting with or enhancing other infectious agents, such as cervical HPV (zur Hausen, 1986; Burger *et al.*, 1993) in the promotion of cervical neoplasia. A possible mode of action of tobacco smoke is to compromise immune function (Barton *et al.*, 1988).

In addition to the epidemiological evidence, an association between smoking and cervical cancer is biologically plausible since carcinogens in tobacco smoke can be absorbed in the lung and transported to distant sites by the blood. Tobacco constituents, including cotinine and nicotine, have been detected in the cervical mucus of smokers (see below). Higher levels of DNA adducts in cervical biopsies of smokers compared to nonsmokers have also been reported (Simons, 1994, see below). Among women with cervical dysplasia, higher levels of mutagenicity in the cervical mucus of smokers compared to nonsmokers have been found (Holly *et al.*, 1986), although this result has not been observed in studies of women without cervical dysplasia (Schiffman *et al.*, 1987; Holly *et al.*, 1993).

7.3.2.2 ETS Exposure and Cervical Cancer

The relationship between ETS exposure and cervical cancer was investigated in one cohort and three case-control studies (Table 7.9).

Hirayama (1981)

As part of the Japanese cohort study, Hirayama (1981) presented results on risk of cervical cancer in women by husbands' smoking habits. Based on 250 cervical cancer deaths in nonsmokers, the RRs were 1.15, and 1.14 for women whose husbands were ex-smokers or smoked 1-19 cigarettes/day, and >20 cigarettes/day, respectively, compared to women whose husbands were nonsmokers (*p* value for trend = 0.25). In the same study, women who ever smoked showed a high risk of cervical cancer compared to nonsmokers (RR = 1.6, 90% CI = 1.3-1.9), and there was some suggestion of increasing risks with increasing amounts smoked (the RRs associated with smoking 1-9, 10-19, and 20+ cigarettes/day were 1.7 (90% CI = 1.3-2.2), 1.3 (90% CI = 1.0-1.8) and 2.4 (90% CI = 1.4-3.9), respectively (Hirayama, 1990)). The findings on active smoking and passive smoking were not adjusted for potential confounders including subjects' or husbands' sexual activity.

Sandler (1985a)

A case-control study which provided some data on the role of ETS exposure and risk of cervical cancer in nonsmokers (see Section 7.1.1 for details) was a study on childhood and adult life ETS exposure and risk of various cancer outcomes (Sandler, 1985a). Because this study included different cancer outcomes, information typically obtained in studies of a specific cancer site (*e.g.*, sexual activity in studies of cervical cancer) was not

Table 7.9
Relationship Between Active and Passive Smoke Exposure and Risk of Cervical Cancer

Study	# Cases/# Controls Cervical Cytology (among cases)	Active Smoking			Passive Smoking (Among Never Smokers)		
				Adj. OR[a]			Adj. OR[a]
Hirayama (1981, 1990)	Total number of cervical cancer deaths was 589; number of cervical cancers in never smokers was 250	Ever smoked		1.6 (1.3-1.9)	NS		1.0
		1-9 cigarettes/day		1.7 (1.3-2.3)	Ex/1-19/day		1.15
		10-19		1.3 (1.0-1.8)	≥20/day		1.14[b]
		20+		2.4 (1.4-3.9)			
Sandler *et al.* (1985a & b)	56 cervical cases among nonsmokers -data on nonsmoking controls not presented (there were a total of 330 female controls)				Exposed to Spouse's smoking	CA/CO NA	2.1 ($p < 0.05$)
					Mother smoking	no 37/196[c]	1.0
						yes 3/24	0.7 (0.2-2.3)
					Father smoking	no 15/120	1.0
						yes 19/91	1.7 (0.8-3.4)
			CA/CO	Adj. OR[d]	Hrs/day[e]	CA/CO	Adj. OR[d]
Slattery *et al.* (1989)	266 cases/408 controls (cases: 78% carcinoma *in situ*, 22% invasive cancer)	Never	81/305	1.0	None	NA	1.0
		Ex-smoker	37/48	1.4 (0.8-2.5)	0.1-0.9	NA	1.1 (0.5-2.9)
		Current			1.0-2.9	NA	1.6 (0.5-4.7)
		smoker	148/55	3.4 (2.1-5.6)	≥3.0	NA	3.4 (1.2-9.5)

Table 7.9 (Continued)

Study	# Cases/# Controls Cervical Cytology (among cases)	Active Smoking			Passive Smoking (Among Never Smokers)		
			CA/CO	Adj. OR[f]	At Home Yrs Exposure	CA/CO	Adj. OR[f]
Coker *et al.* (1992)	103 cases/268 controls (All biopsy-confirmed cervical intraepithelial neoplasia, class II or III)	Never	37/170	1.0	Not exposed	9/49	1.0
		Ever smoked	66/96	1.7 (0.9-3.3)	<17 yrs	18/52	1.5 (0.5-4.0)
		Current smoker	66/49	3.4 (1.7-7.0)	≥18 yrs	9/69	0.4 (0.1-1.3)
					At Work Yrs Exposure	CA/CO	Adj. OR
					Not exposed	28/132	1.0
					1-4 yrs	6/21	1.7 (0.5-5.1)
					≥5 yrs	2/16	0.4 (0.1-2.5)

[a] *90% CI.*
[b] *p value was 0.25.*
[c] *Number of cases and controls was calculated from Table 4 of Sandler et al., 1985e.*
[d] *Adjusted for age, church attendance, education, and number of sexual partners of the women.*
[e] *Number of hours of exposure per day inside and outside of the home.*
[f] *Adjusted for age, years of education, race, number of pap smears, number of partners, and genital warts.*

Abbreviations: NA = not available, CA/CO = cases/controls, OR = odds ratio.

collected. There were a total of 518 cancer patients; 101 had cervical cancers, of which 56 occurred in women who had never smoked. The 56 nonsmokers with cervical cancer were compared to 235 nonsmoking control women. Spouses' smoking habits were associated with an increased risk of cervical cancer in nonsmokers (OR = 2.1, 95% CI = 1.2-3.9) after adjustment for age, race, education, and smoking habits of parents. In the same study, husbands' smoking also increased risk of cervical cancer in women who were smokers (OR = 2.0, 95% CI = 0.9-4.1); the effect was observed after adjustment for the above-mentioned variables as well as personal smoking habits of women. Sandler *et al.* (1985b) also examined the association between parental smoking during childhood and risk of cervical cancer. Maternal smoking was not associated with risk of cervical cancer (OR = 0.66, 95% CI = 0.19-2.29) whereas paternal smoking was associated with a statistically nonsignificant increased risk (OR = 1.67, 95% CI = 0.81-3.45). The difference in results for mothers' versus fathers' smoking is likely due to chance; among controls the prevalence of mothers who smoked was low (11 percent) compared to fathers who smoked (43 percent).

Slattery et al. (1989) A second case-control study on this subject was designed to investigate the role of active smoking and passive smoking in the etiology of cervical cancer. This study included 266 women with cervical cancer and 408 population controls, selected by random-digit dialing in Utah (Slattery *et al.*, 1989). Eighty-one cases and 305 controls had never smoked. Women were asked whether they were exposed to "a lot, some, a little, or no" tobacco smoke inside or outside their homes and the number of hours of exposure per day, during the 5 years before interview. Among nonsmokers, ETS exposure inside and outside of the home was associated with a significantly increased risk with adjustment for potential confounders which included age, education, church attendance, and number of sexual partners of the woman. A 3-fold increased risk (OR = 3.4, 95% CI = 1.2-9.5) was observed for three or more hours of exposure per day. The increased risks associated with ETS exposure among nonsmoking women were comparable to the risks associated with active smoking in this study (Table 7.5). Although specific information on HPV infection and partners' sexual activity was not available, the effect of active smoking was strongest among women who had a few (none to one) sexual partners (OR = 14.2, 95% CI = 9.2-38.9) and weakest for women with four or more partners (the highest category of partners in this study, OR = 2.3, 95% CI = 1.4-3.9). The authors interpreted this finding to suggest that cigarette smoking, and presumably ETS exposure, as risk factors for cervical cancer may be more important among women who have not experienced other major risk factors for this cancer (*i.e.*, HPV infection).

Coker et al. (1992) Another case-control study which was designed to examine the role of active and passive smoking included 103 CIN cases (40 percent CIN II, 60 percent CIN III) and 268 controls; 37 CIN cases and 170 controls had never smoked (Coker *et al.*, 1992) (Table 7.9). All subjects had attended a family practice clinic, and controls were women with normal cervical cytology at enrollment. Subjects were asked about tobacco smoke exposure at the workplace and whether they had ever lived with a smoker who had

smoked for at least 1 year. The total number of years of exposure and the relationship of the smoker to the index subject were also asked. For nonsmokers, after adjusting for potential confounders, there was no significant or consistent association between ETS exposure at work or at home and risk of CIN. Analysis by source of ETS exposure showed no association with parents' smoking (OR = 0.4, 95% CI = 0.1-1.2), a positive association with husbands' smoking (OR = 1.5, 95% CI = 0.3-6.2) or others' smoking (OR = 1.8, 95% CI = 0.4-8.4) after adjustment for age, education, race, number of Pap smears, number of partners, and genital warts. The crude OR was calculated for any smoking by husbands (*i.e.*, combine smoking of husband only and of parent) is 2.2 (95% CI = 0.9-5.7); the crude OR for any parents' smoking (*i.e.*, combine smoking of parents only and of parent and husband) is 0.9 (95% CI = 0.4-2.1) (calculated based on Table 5 of Coker *et al.*, 1992). In this study, active smoking was a risk factor irrespective of HPV status; its effect was stronger among women classified as HPV-negative than those classified as HPV-positive.

Additional epidemiological information on cervical cancer Data from several other studies on cervical cancer show that husbands of women with cervical cancer are more likely to be smokers than husbands of control women, although the effect of husband's smoking generally diminished with adjustment for a woman's smoking. In a study conducted by Buckley *et al.* (1981), husbands' smoking was associated with an increased risk even after adjustment for wives' smoking habits although its effect diminished. There were too few nonsmoking women to evaluate the role of husbands' smoking in this subgroup. In a study by Hellberg *et al.* (1983 and 1986), the effect of husbands' smoking diminished and was no longer statistically significant after adjustment for wives' smoking habits, whereas the effect of wives' smoking persisted with adjustment for husbands' smoking. There was, however, a statistically nonsignificant excess of husbands who smoked among nonsmoking wives (Hellberg *et al.*, 1986). In a third study, Zunzunegui *et al.* (1986) reported an excess of husbands who smoked. Although this excess risk was not adjusted for wives' smoking habits, the authors argued that there was a deficit of smokers among wives and thus wives' smoking is an unlikely explanation for the finding on husbands' smoking.

Two case-control studies of cervical cancer, one conducted in Spain, a low risk area (Bosch *et al.*, 1996) and one conducted in Cali, Columbia, a high risk area (Munoz *et al.*, 1996) offered some additional information on the role of husbands' smoking in the etiology of wives' risk of cervical cancer. The study in Spain included 306 cases and 327 controls, while the study in Cali included 210 cases and 262 controls. Prevalence of active smoking among cervical cancer cases and controls was not presented in either study. In the study conducted in Spain, in all women, after adjustment for the woman's own active smoking habits, there was a significant trend of increasing risk in association with spouse's smoking. The ORs for cervical cancer were 1.0, 1.8, 2.1, and 2.5 associated with no, 0.1-3.2, 13.3-26.1, ≥26.2 pack-years of spouse's smoking (Bosch *et al.*, 1996). In the Cali study, although husbands' smoking was also associated with an increased risk of cervical cancer in wives, this result was not statistically significant

after adjustment for wives' smoking habits (Munoz *et al.*, 1996). Both studies are limited in that they did not present results on nonsmoker controls and nonsmoker cervical cancer patients.

7.3.2.3 Biomarkers of Cervical ETS Exposure

In addition to questionnaire-based data, several small studies have been conducted to determine whether there are measurable levels of tobacco-smoke constituents in cervical epithelial cells of nonsmokers. Detectable levels of nicotine and cotinine were found in the cervical mucus of nonsmokers; the levels ranged from <1 to about 6 percent of those of active smokers (Sasson *et al.*, 1985; Hellberg *et al.*, 1988; Jones *et al.*, 1991; McCann *et al.*, 1992, see Table 7.10). In three of these studies (Hellberg *et al.*, 1988; Jones *et al.*, 1991; McCann *et al.*, 1992), data were presented separately for nonsmokers exposed to ETS and those with no reported exposure to ETS. In two studies (Hellberg *et al.*, 1988; McCann *et al.*, 1992), levels of nicotine/cotinine in cervical mucus were not distinguishable between nonsmokers with and without ETS exposure, whereas in a third study, higher levels of nicotine were found in women with ETS exposure compared to those with no reported exposure (Jones *et al.*, 1991) (Table 7.10). None of the studies on cervical cancer has examined risk of cancer in relation to presence or absence of nicotine/cotinine in the cervical mucus, but this evidence from cross-sectional clinical studies supports the hypothesis that cervical exposure to tobacco constituents occurs from exposure to tobacco smoke.

The presence of carcinogen-DNA adducts in human tissues has been used as evidence of smoking-induced DNA damage. Using ^{32}P-postlabelling techniques, a linear relationship between cigarette consumption and levels of aromatic DNA adducts has been demonstrated in human bronchial epithelium (Phillips *et al.*, 1990a) and other tobacco-related sites, including the cervical epithelium (Phillips *et al.*, 1990b; Cuzick *et al.*, 1990). Recently, Simons (1993) measured levels of DNA adducts in cervical biopsies of 39 women admitted for hysterectomy for benign disease or colposcopy. In this group, 18 were smokers (11 current, 4 ex-smokers who stopped in the last 6 months, 3 longer-term ex-smokers) and 21 had never smoked. Of the nonsmokers, 75 percent (n = 16) reported exposure to ETS at work or in the home. Urinary cotinine/creatinine levels were also available on these subjects; a ratio of 0.06 or greater was used to indicate active smoking in the previous 24-48 hours.

The median DNA adduct level (per 10^8 nucleotides) was 4.62 in self-reported smokers, which was significantly higher than that in self-reported nonsmokers (3.47). Seven self-reported nonsmokers showed a urinary cotinine/creatinine ratio of 0.06 or greater, and they were reclassified as smokers (n = 25). The median DNA adduct level in self-reported and reclassified smokers was 4.45 compared to 3.52 (p = 0.07) in confirmed nonsmokers (*i.e.*, urinary cotinine/creatinine <0.06). The presence of adducts in cervical epithelium and the correlation with smoking habits strongly suggest that the adducts are a consequence of exposure to tobacco constituents. These results provide direct biochemical evidence that potentially carcinogenic agents may affect the DNA of cervical epithelial cells. It is notable that all

Table 7.10
Nicotine and Cotinine Measured in the Cervical Mucus of Smokers, Passive Smokers and Nonsmokers

Study	Levels (ng/ml) of Nicotine	Levels (ng/ml) of Cotinine
Sasson *et al.*, 1985[a]		
Smokers (*n* = 10)	740	316
Nonsmokers (*n* = 8)	16	3
Hellberg *et al.*, 1988[a]		
Smokers (*n* = 17)	1,056	1,061
Nonsmokers with ETS exposure		
Yes[b] (*n* = 4)	20	51
No (*n* = 14)	43	78

	Levels of Nicotine (ng/ml) Mean	Median	Range
Jones *et al.*, 1991[c]			
Smokers (*n* = 31)	34.3	11.8	2.8-383.4
Nonsmokers with ETS exposure[d]			
at home (*n* = 32)	0.1	0.8	<0.2-8.2
outside of home (*n* = 42)	NA[f]	0.4	<0.2-5.2
none (*n* = 70)	NA	0.2	<0.2-3.8
McCann *et al.*, 1992[c]			
Smokers (*n* = 25)	107.2	56	4-358
Nonsmokers with ETS exposure[d]			
Yes[e] (*n* = 12)	3.6	3.5	<0.2-12
No (*n* = 12)	3.9	3.5[g]	<0.2-14

[a] *Cervical mucus collected using aspiration methods.*
[b] *Exposed at home or work, time of passive smoke exposure relative to specimen collection not specified.*
[c] *Cervical mucus collected using cervical flush techniques.*
[d] *Passive smoke exposure in the last 24 hours.*
[e] *Nonsmokers with ETS exposure at home or at work.*
[f] *NA = not available.*
[g] *Excluded one outlier who was usually exposed to passive smoking several hours/day, but had no exposure within the last 24 hours.*

the women in the study had detectable proportions of DNA adducts regardless of their smoking status. The relatively high DNA adduct levels in nonsmokers may reflect exposure to ETS, reported by 75 percent of nonsmokers in this study. Future studies on DNA adduct levels by self-reported exposure to ETS in nonsmokers are needed to confirm these suggestive results.

7.3.2.4 Summary There is supportive evidence from epidemiological and biochemical studies implicating a role for ETS exposure in the etiology of cervical cancer in nonsmokers. A positive, but nonsignificant association was reported in one cohort study (Hirayama, 1981) and a significant, positive association was observed in two (Sandler *et al.*, 1985a; Slattery *et al.*, 1989) of three case-control studies. In the third case-control study, conducted by Coker *et al.* (1992), spousal ETS was associated with an increased the risk of cervical cancer/intraepithelial neoplasia in nonsmokers although the result was of borderline statistical significance. Any exposure to ETS (*i.e.*, parents and spouses combined) was not a risk factor in the study by Coker *et al.* (1992); this finding is not too surprising since risk of cervical cancer appears to be most affected by current tobacco use. In one of three biochemical studies, levels of nicotine in the cervical mucus of nonsmokers exposed to ETS were reported to be higher than levels in those with no exposure. Demonstration of detectable levels of nicotine and cotinine in cervical mucus of nonsmokers suggests that constituents of cigarette smoke may reach more distant sites such as the cervix and play a direct mutagenic role in the etiology of cervical cancer. In addition, the presence of DNA adduct levels in the cervical epithelium of nonsmokers supports the hypothesis that carcinogenic constituents of tobacco smoke may adversely effect the cervical epithelium.

Little is known about the transport of nicotine and cotinine throughout the body and about its metabolism in distant organ sites. Mutagenicity of semen due to smoking is plausible, and direct cervical contact with semen of smoking partners may represent another source of exposure to tobacco constituents. It is important to confirm these findings, to determine the importance of recent exposure to ETS (*i.e.*, within recent 5 years) versus lifetime exposure to ETS, and to determine the effect of exposure from spouses versus other household members or coworkers. It is also important to evaluate the effect of passive smoking by stage of cervical cancer (*e.g.*, invasive and pre-invasive), and by history of potential confounding factors, including HPV infection. Measurement of levels of cotinine/nicotine in cervical mucus as well as DNA adducts in cervical epithelium of nonsmokers will complement the epidemiological findings from questionnaires, although such measurements may not be available for cervical cancer cases who are enrolled in studies after surgical treatment for their cancers.

7.3.3 Bladder Cancer

7.3.3.1 Active Smoking and Bladder Cancer

Active smoking is firmly established as a cause of bladder cancer; the relative risks for active smoking ranged from 2 to 10 in different studies (IARC, 1986). The estimated attributable risk for bladder cancer due to smoking is 47 percent in men and 38 percent in women (Shopland *et al.*, 1991). The range in relative risk estimates has been explained partly by the different types of tobacco smoked in different countries and the differences in carcinogenicity of tobacco types. Black tobacco products, commonly smoked in countries such as Italy and Argentina, are associated with higher risks of bladder cancer (Vineis *et al.*, 1984; Iscovich *et al.*, 1987) than blond tobacco products, smoked in the U.S. and Canada (Hartge *et al.*, 1990; Burch *et al.*, 1989). Black tobacco, compared to blond tobacco, contains higher concen-

trations of various aromatic amines, including 4-aminobiphenyl, an established bladder carcinogen (Patrianakos and Hoffmann, 1979; IARC, 1972).

7.3.3.2 ETS and Bladder Cancer

Risk of bladder cancer in nonsmokers in relation to ETS exposure was evaluated in two studies (Table 7.11).

Kabat et al. (1986)

The first study was conducted by Kabat *et al.* (1986) as part of a large on-going case-control study of smoking and cancer. Between 1976 and 1983, a total of 948 bladder cancer cases (751 male and 197 female) were interviewed, 152 of whom (76 male and 76 female) were lifetime nonsmokers (*i.e.*, smoked less than one cigarette, cigar, or pipe per day for 1 year). Hospital controls who were also lifetime nonsmokers were matched to each case on age, sex, race, hospital, and year of interview. There were a total of 492 nonsmoking controls (238 male and 254 female). Questions on ETS exposure were added to the questionnaire in 1979; this information was available on only 40 of 152 cases and 75 of 492 controls interviewed. Questions were asked regarding exposure to ETS inside the home, represented by spouses' smoking, and exposure outside of the home, including exposure at work or in transportation. Results were presented in terms of hours of ETS exposure per week.

The findings on the relationship between ETS exposure and bladder cancer were inconsistent by gender and by source of exposure. For nonsmoking males, there was a nonsignificant increased risk of bladder cancer associated with ETS exposure at home but not at work, whereas among nonsmoking females, a nonsignificant increased risk was observed for ETS exposure at work but not at home (Table 7.11). This study has several limitations, however. The most serious ones include the small sample size of nonsmokers and the fact that controls were selected from among hospital patients. Although controls were diagnosed with presumably non-tobacco-related diseases (specific diagnoses were not specified), many malignant and non-malignant diseases are causally related to tobacco smoke. Hence, it is quite conceivable that hospital controls may be more likely to be exposed to ETS than the general population.

Burch et al. (1989)

A second study was conducted by Burch *et al.* (1989) in Canada between 1979 and 1982. This study included 826 histologically-confirmed bladder cancers and 792 randomly selected controls (Table 7.11). Of these, 142 cases and 217 controls were nonsmokers (defined as having smoked fewer than 185 cigarettes in total). Subjects were asked about their exposure to the tobacco smoke of others at home and at work. For all subjects and for nonsmokers, there was no association between risk of bladder cancer and ETS exposure at home or at work. The authors suggested that because of the modest risk associated with active smoking (RR = 2.7) in this study, any association between ETS and bladder cancer in nonsmokers may be too weak to be detectable in questionnaire-based epidemiologic studies.

7.3.3.3 Biomarkers of Exposure to Bladder Carcinogens from ETS Exposure

Aside from questionnaire-based epidemiologic studies, some data are available from biochemical measurement studies which evaluated the effect of ETS and risk of bladder cancer in nonsmokers. These studies measured hemoglobin (Hb) adducts of 4- or 3-aminobiphenyl (4-ABP or 3-ABP) which are

Table 7.11
Passive Smoking and Bladder Cancer Among Nonsmokers

Study	Males		Females	
	# Exposed Cases/Controls	OR (95% CI)	# Exposed Cases/Controls	OR (95% CI)
Kabat *et al.* (1986)[a]				
Exposed to passive smoking				
At home	6/10	1.5 (0.5-4.5)	6/13	0.6 (0.5-1.2)
At work or in transportation	11/25	0.7 (0.2-1.8)	6/5	2.5 (0.6-10.1)
Burch *et al.* (1989)[b]				
Exposed to passive smoking				
At home	37/72	0.9 (0.5-2.0)	66/90	0.8 (0.3-1.7)
At work	25/45	1.0 (0.5-1.9)	26/38	0.9 (0.5-1.8)

[a] *Total number of nonsmokers were: males-23 cases, 44 controls; females-17 cases, 28 controls.*
[b] *Total number of nonsmokers were: males-61 cases, 112 controls; females-81 cases, 105 controls.*

formed over the 120-day lifespan of the erythrocyte and therefore may serve as dosimeters of average exposure over the previous 4 months. As mentioned above, the aromatic 4-ABP is a potent human bladder carcinogen (IARC, 1972).

In one study, concentrations of adducts of 4- and 3-ABP were measured in 57 nonsmokers. Subjects who reported exposure to ETS and had detectable serum cotinine levels showed higher median and mean levels of both adducts than subjects who reported no exposure to ETS and had no detectable cotinine levels. The result was of borderline significance for 4-ABP-Hb and was statistically significant for 3-ABP-Hb (MacClure *et al.*, 1989) (Table 7.12). In a second study, Barstch *et al.* (1990) extended the investigation of 4-ABP-Hb levels in smokers and nonsmokers by N-acetylation phenotype, a marker of susceptibility for bladder cancer (Table 7.13). It has been established that at the same level of exposure to active smoking and other exposures to xenobiotics, slow acetylators are at higher risk of bladder cancer than fast acetylators (Cartwright *et al.*, 1982; Vineis *et al.*, 1990). Among nonsmokers in this study, those with ETS exposure showed higher levels of ABP adducts than those with no ETS exposure. However, the relative increase in ABP adducts differed for “slow” and “fast” acetylators. Among nonsmokers with no ETS exposure, the ABP levels were at least two times higher among “slow” than “fast” acetylators. However, the ABP levels among nonsmokers with ETS exposure were comparable for “fast” and “slow” acetylators. Thus, the increase in ABP levels in relation to ETS exposure was more apparent for “fast” than “slow” acetylators (Table 7.13). It is of note that in both studies, nonsmokers showed levels of hemoglobin adducts of 4-ABP that were 28-35 percent of those of smokers, and the levels of 4-ABP were somewhat higher in nonsmokers exposed to

ETS than those not exposed. Levels of 4-ABP were 7 percent higher in nonsmokers exposed to ETS compared to nonsmokers not exposed in one study (MacClure *et al.*, 1989). In a second study, 4-ABP levels were 14 percent higher in nonsmokers exposed than nonsmokers not exposed among "slow" acetylators, and were almost two times higher among exposed "fast" acetylators compared to non-exposed "fast acetylators."

Future studies need to confirm and better characterize the relationship between levels of hemoglobin adducts in nonsmokers and their exposure to ETS by acetylator status.

7.3.3.4 Summary In summary, the evidence from questionnaire-based epidemiologic studies of ETS and bladder cancer is inadequate. There have been two case-control studies to date, both showed no significant increased risk associated with ETS exposure. These studies, however, had serious limitations including small sample sizes and crude assessment of exposure to ETS. On the other hand, the evidence from two biochemical studies is suggestive. In both studies, nonsmokers exposed to ETS showed higher levels of hemoglobin adducts of an established bladder carcinogen than nonsmokers not exposed to ETS, providing supporting evidence that nonsmokers exposed to ETS may be at increased risk of bladder cancer.

7.4 ETS AND CANCER SITES WHERE EVIDENCE FOR THE ROLE OF ACTIVE SMOKING IS EQUIVOCAL

7.4.1 Breast Cancer

7.4.1.1 Active Smoking and Breast Cancer

A large number of epidemiologic studies have investigated the association of active smoking and risk of breast cancer (Baron, 1984; MacMahon, 1990; Palmer and Rosenberg, 1993; Calle *et al.*, 1994; Baron *et al.*, 1996), and the results are inconclusive. A few case-control (Williams and Horm, 1977; Vessey *et al.*, 1983; O'Connell *et al.*, 1987) and cohort studies (Hammond, 1966) have found a protective effect associated with smoking. However, the majority of studies have found no association (Smith *et al.*, 1984; Adami *et al.*, 1988; Baron *et al.*, 1986; Rosenberg *et al.*, 1984; Porter and Jick, 1983; Brinton *et al.*, 1986; London *et al.*, 1989; Schechter *et al.*, 1989; Vatten and Kvinnsland, 1990; Field *et al.*, 1992) or a weak positive association with smoking (Le *et al.*, 1984; Rohan and Baron, 1989; Palmer *et al.*, 1991; Schechter *et al.*, 1985; Brownson *et al.*, 1988; Stockwell and Lyman, 1987; Calle *et al.*, 1994). The case-control studies which have found an increased risk with smoking tended to have selected cases and controls from cancer screening programs (Schechter *et al.*, 1985; Brownson *et al.*, 1988) or have found the increased risk among premenopausal women (Schechter *et al.*, 1985; Rohan and Baron, 1989; Brownson *et al.*, 1988); other studies found effects for selective smoking variables such as starting at an early age (Brinton *et al.*, 1986; Palmer *et al.*, 1991) or among former smokers (Hiatt *et al.*, 1988; Baron *et al.*, 1996). Meara *et al.* (1989) showed that bias in selection of cases and controls in hospital-based series would spuriously show a decreased risk of breast cancer with increasing amounts smoked. On the other hand, bias associated with selecting subjects from a cancer-screening population would spuriously produce an increased risk of breast cancer with increasing amounts smoked.

In the one prospective study which found a small, significant increased risk of fatal breast cancer with current smoking, the authors hypothesized that these findings could reflect either a poorer prognosis among breast cancer cases who smoke or a delayed diagnosis among current smokers (Calle *et al.*, 1994).

The above epidemiologic studies investigated the risk of breast cancer in active smokers compared to all nonsmokers in the baseline group. A recent study (Morabia *et al.*, 1996) investigated the effect of active smoking compared to nonsmokers not exposed to ETS. Data were also presented which allowed comparison of the effect of active smoking compared to all nonsmokers and to nonsmokers not exposed to ETS. We calculate that compared to all nonsmokers (126 cases and 621 controls), the crude ORs associated with ever smoking 1-9, 10-19, and 20+ cigarettes per day were 1.1, 1.5, and 1.6, respectively (p trend = 0.007). The corresponding adjusted ORs when compared to nonsmokers not exposed to ETS (28 cases and 241 controls) were 2.4, 3.6, and 3.7 (p trend = 0.09; from Table 2 of Morabia *et al.*, 1996). Similar results were obtained when current active smokers were compared to all nonsmokers and to nonsmokers not exposed to ETS.

7.4.1.2 ETS and Breast Cancer

A role of passive smoking in the etiology of breast cancer was first hypothesized by Horton (1988), who noted that countries with high mortality rates of lung cancer in males generally had high rates of breast cancer, whereas countries with low rates of lung cancer had low rates of breast cancer. Based on this observation, Horton then (1988 and 1992) tested the hypothesis and found that passive smoking (using male lung cancer rates as a proxy variable) is a risk factor for female breast cancer. There was, however, little support for this hypothesis in another correlational study which investigated the relationship between female breast cancer and male lung cancer within five countries (Williams and Lloyd, 1989). Deleterious effects of smoking on the breast are plausible since carcinogens in smoke (*e.g.*, 3-4 benzo[a]pyrene) or their metabolites are absorbed systemically (Kotin *et al.*, 1959), and have been detected in nipple aspirates of non-lactating women (Petrakis *et al.*, 1980).

Four analytic epidemiologic (one cohort and three case-control) studies have investigated the association between ETS exposure and risk of breast cancer among nonsmokers. Known risk factors for breast cancer (*i.e.*, reproductive factors, alcohol intake, social class) were not accounted for in the analysis of ETS exposure in the first two studies (Hirayama, 1984; Sandler *et al.*, 1985a) but they were accounted for in the two recent studies (Smith *et al.*, 1994; Morabia *et al.*, 1996). Only one study (Morabia *et al.*, 1996) was designed specifically to investigate the role of ETS and breast cancer.

Hirayama (1984) The first study was a Japanese cohort study (Hirayama, 1984) which included 115 breast cancer deaths in never-smoking women. Nonsmoking women whose husbands smoked showed a small, nonsignificant increased risk of breast cancer (RR = 1.3, 95% CI = 0.8-2.0).

Sandler et al. (1985a) In a case-control study conducted in North Carolina, husbands' smoking was associated with an increased risk of breast cancer (RR = 1.9, 95% CI = 0.9-4.2). The association was observed among pre-

Table 7.12
Mean Levels of Hemoglobin Adducts of 4- AND 3- Aminobiphenyls in nonsmokers

Population	4-ABP (pg/g Hb)	3-ABP (pg/g Hb)
Ex-smokers (at baseline)	130.4	16.0
Ex-smokers (after stopping smoking for two months)	33.3	1.7
Nonsmokers		
ETS exposure (-)[a] and Cotinine level (-)	45.9	1.2
ETS exposure (+)[b] and Cotinine level (+)	49.2	1.9

Reference: Maclure et al. (1989)
[a] *Based on 44 subjects-15 subjects had low levels of self-reported ETS exposure and no detectable cotinine levels; 29 subjects had no reported ETS exposure and no detectable cotinine levels.*
[b] *Based on 13 subjects-7 subjects had low levels of self-reported ETS exposure and detectable cotinine levels, 6 subjects had high levels of self-reported ETS exposure and detectable cotinine levels. The 6 subjects who reported high exposure to ETS showed the highest mean levels of 4-ABP (54 pg/g) and 3-ABP (2.4 pg/g) and median levels of 4-ABP (48 pg/g) and 3-ABP (2.6 pg/g).*

Table 7.13
Mean Levels of 4-ABP Hemoglobin Adducts (PG/G of Hemoglobin) Among Smokers and Nonsmokers by Acetylator Phenotype

Population	Acetylator Phenotype Slow	Fast
Black-tobacco smokers (*n* = 16)	175.0	117.5
Blond-tobacco smokers (*n* = 31)	111.8	86.4
Nonsmokers (*n* = 50)	31.7	19.4
Exposed to ETS		
No (*n* = 35)	30.4	12.3
Yes (*n* = 15)	34.8	33.6

Reference: Bartsch et al. (1990)

menopausal women (RR = 7.1, 95% CI = 1.6-31.3), but not among post-menopausal women (RR = 0.9, 95% CI = 0.4-2.2) (Sandler *et al.*, 1985a; Wells, 1991). In a further analysis of the case-control data from North Carolina, Wells (1992) reported that compared to nonsmoking women married to never-smokers, the age-adjusted RRs were 1.62 among nonsmoking women married to smokers, 0.64 among smoking women married to nonsmokers, and 1.51 among smoking women married to smokers.

Smith et al. (1994) The role of active and passive smoking was investigated in a case-control study conducted among young (diagnosed before the age of 36) breast cancer patients who were diagnosed between 1982 and 1985 and were residents in one of 11 health regions in the UK (Smith *et al.*, 1994). This study was designed specifically to study the role of reproductive factors, oral contraceptives, active smoking, and use of alcohol and caffeine. Questions on passive smoking were added and were administered to respondents who resided in three of the 11 participating health regions. In this study, one control was matched to each case interviewed. Each case/control pair were patients of the same general practitioner; the control was randomly selected from the list of patients of the general practitioner who cared for the case and was matched to the case on age (date of birth within 6 months). A mailed questionnaire was used to gather information on passive smoking exposure after the subjects had already participated in an in-person interview for the main study. The main study included a total of 755 breast cancer cases and an equal number of controls. A subset of 409 women (208 breast cancer cases and 201 controls) of whom 94 cases and 99 controls were nonsmokers, provided information on ETS exposure.

Active smoking was not associated with risk of breast cancer in this study; the crude OR for having ever smoked was 1.04, and the adjusted OR was 1.01 (adjustment included age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history, use of oral contraceptives, alcohol use, and biopsy for benign breast disease). Based on calculations that 114 of the 208 cases and 102 of the 201 controls who responded to questions on ETS exposure had ever smoked, the effect of active smoking was similar in the subset of subjects who responded to questions on passive smoke exposure (crude OR = 1.18 for women who had ever smoked) and for all subjects combined (*i.e.*, OR = 1.04).

Results on the association between passive smoking and risk of breast cancer were presented for smokers and nonsmokers combined. There was some suggestion that risk was highest among individuals who were exposed to ETS during both childhood and adult life. Compared to women who were not exposed to ETS, exposure during childhood only, adult life only, and during both childhood and adult life were associated with ORs of 1.98 (95% CI = 0.35-11.36), 2.65 (95% CI = 0.80-8.83), and 3.13 (95% CI = 1.05-9.38), respectively. Although there was an increased risk of breast cancer associated with childhood ETS exposure, adult exposure to ETS from partners, from other smokers at home and at work, and total lifetime exposure, there was no consistent dose trend of increasing risks with increasing levels of any of these sources of ETS exposure. However, the investigators noted

that the passive smoking findings among nonsmokers were similar to those for smokers and nonsmokers combined. The relative risks were consistently elevated, but again there was no evidence of a significant dose response for any exposure variable.

Morabia et al. (1996) A population case-control study conducted in Geneva, Switzerland (Morabia *et al.*, 1996) offered additional information on the role of active smoking and passive smoking in the etiology of breast cancer. In this study, 244 of 344 breast cancer patients aged less than 75 and diagnosed over a 2-year period consented to an in-person interview. Using an age-stratified random sampling scheme, population controls were identified from a listing which included all residents in Geneva. A total of 1,032 of the 1,473 eligible controls participated in this study.

All participants were asked specific questions on active and passive smoking including passive smoke exposure at home, at work, and during leisure time. Active and passive smoking exposure were recorded year by year, between the age of 10 years and the date of the interview. An episode of exposure is defined as at least 6 months of exposure when the woman was passively or actively exposed to tobacco smoke. For each episode of exposure, the woman was asked the age at which she was exposed and the corresponding calendar years. The number of hours per week of each passive smoking episode was recorded. An active smoker had smoked at least 100 cigarettes in her lifetime. Passive smokers were women who reported having been exposed to passive smoke at least 1 hour per day for at least 12 consecutive months during their lifetime.

Of the 244 breast cancer patients and 1,032 controls who were interviewed, 126 cases (51 percent) and 621 (60 percent) controls were lifetime nonsmokers. We calculate that compared to nonsmokers, the crude RRs for breast cancer associated with being a former smoker and a current smoker were 1.78 and 1.15, respectively. Among the 126 nonsmoking cases and 621 nonsmoking controls, 28 cases and 241 controls reported no ETS exposure. This group of nonsmokers with no ETS exposure comprised the baseline comparison group in the analyses reported by Morabia *et al.* (1996). Risk of breast cancer was elevated in nonsmokers who were exposed to ETS exposure from spouses and from all sources combined (*i.e.*, including from spouses). Compared to nonsmoking women who were not exposed to any ETS, the OR was 2.6 (95% CI = 1.6-4.3) for women who were exposed to passive smoking from spouses and 2.3 (95% CI = 1.5-3.7) for women who were ever exposed to passive smoking from all sources combined. The OR associated with high exposure (>50 hours/day-years) from spouses (OR = 2.7, 95% CI = 1.5-4.7) was essentially the same as lower exposure (1-50 hours/day-years) from spouses (OR = 2.3, 95% CI = 1.3-5.0). The OR associated with high exposure (>50 hours/day-years) from all sources combined (OR = 2.5, 95% CI = 1.5-4.2) was also similar to that associated with lower exposure (1-50 hours/day-years, OR = 2.2, 95% CI = 1.3-3.7).

Using nonsmokers never exposed to passive smoking as the baseline group, the magnitude of risks associated with ETS exposure were similar to the risks associated with active smoking. The risk of breast cancer was

increased among active smokers who smoked <20 pack-years (OR = 2.2, 95% CI = 1.2-4.3) and 20+ pack-years (OR = 3.2, 95% CI = 1.8-5.9). These findings on ETS exposure and active smoking were adjusted for age, education, body mass index, age at menarche, age at first birth, oral contraceptive use, and family history of breast cancer.

7.4.1.3 Summary All four studies on ETS exposure and breast cancer suggest that exposure to ETS is associated with an increased risk of breast cancer. Despite the consistency of this apparent observation, these results cannot be considered conclusive and must be interpreted cautiously for several reasons. In two studies, the associations with ETS exposure were present in select subgroups, younger women in one study (Hirayama, 1984) and premenopausal women in another study (Sandler *et al.*, 1985a; Wells, 1992). In three studies (Wells, 1992; Smith *et al.*, 1994; Morabia *et al.*, 1996), there is either no association between active smoking and risk of breast cancer or the effect of active smoking is weaker or comparable to the effect of passive smoking. Given that active smokers are also passively exposed to tobacco smoke, these findings on ETS exposure need to be reconciled. Moreover, in all the studies, there is no indication of increasing risk of breast cancer with increasing dose or measures of intensity of passive smoking. The apparent findings may be due to a deficit of cases who reported they had never been exposed or an excess of controls who reported they had been exposed to passive smoking, but at this time, there are also no obvious explanations why this would have occurred in each of the four studies. Results from a recent study suggest that tobacco smoke may influence the risk of breast cancer only in certain susceptible groups of women (Ambrosone *et al.*, 1995 and 1996).

7.4.2 Stomach Cancers The epidemiological evidence in support of active smoking as a risk factor for stomach cancer is equivocal. The 1982 Surgeon General's Report (U.S. DHHS, 1982) and the 1986 IARC report (IARC, 1986) concluded that tobacco smoke is associated with an increased risk of stomach cancer, but it is uncertain whether the relationship is causal. The hypothesis that tobacco smoke is a causal risk factor for stomach cancer is biologically plausible, since high concentrations of N-nitroso compounds are found in both mainstream and sidestream smoke. Exposure to N-nitroso compounds has been established as important in the development of stomach cancers (Preston-Martin and Correa, 1989).

Results from a cohort study conducted in Japan (Hirayama, 1984) are not supportive of an association between ETS exposure and risk of stomach cancer in nonsmokers. In this study, the risk of stomach cancer in nonsmokers married to nonsmoking husbands was similar to that of nonsmokers married to husbands who were ex-smokers or smoked 1-19 cigarettes/day (RR = 1.03) and those married to husbands who smoked greater than 20 cigarettes/day (RR = 1.05). The RR for stomach cancer in relation to active smoking in the same cohort was 1.3 for females and 1.6 for males (Hirayama, 1979). However, these associations with active smoking were not adjusted for dietary or other risk factors of stomach cancer. In

summary, thus far there is no epidemiologic evidence for an association between ETS exposure and stomach cancer, but research on this issue has been extremely limited.

7.4.3 Brain Tumors The age-incidence curve for brain tumors displays a bimodal distribution, peaking at ages 5 and 60. Brain tumors are a heterogeneous disease with different types of tumor occurring in the cranial cavity or in the spinal canal. The most common types of brain tumors are gliomas and meningiomas. Causes of brain tumors are not known, but exposure to N-nitroso compounds and certain occupations have been suspected (Preston-Martin and Correa, 1989). The hypothesis that ETS exposure increases the risk of brain tumors in adults and children is biologically plausible, since precursors of endogenously formed N-nitroso compounds are present in ETS. Moreover, in animal studies, neurogenic as well as other tumors were induced after transplacental exposure to a number of compounds present in tobacco smoke, including several nitrosamines (Preston-Martin and Correa, 1989). Some data suggest that active smoking may be related to brain tumors in adults, but the evidence is not consistent (Burch *et al.*, 1987).

7.4.3.1 In Adults A possible role of passive smoking in the etiology of brain tumors was first suggested in a prospective study conducted in Japan (Hirayama, 1984) (see Section 7.1.1 for study details). Based on 34 brain tumor deaths, there was an increased risk associated with ETS exposure. Nonsmoking women married to men who smoked 1-14, 15-19, and 20+ cigarettes per day showed RRs of 3.0 (95% CI = 1.1-8.6), 6.3 (95% CI = 2.0-19.4), and 4.3 (95% CI = 1.5-12.2), respectively, when the age and occupations of husbands were adjusted for in the analysis. Smokers showed a statistically nonsignificant increased risk of brain tumors compared to nonsmokers (RR = 1.2, 90% CI = 0.80-1.9) risk estimates by amount smoked were not presented (Hirayama, 1990).

In a case-control study which included all cancer outcomes, Sandler *et al.* (1985b) investigated the association between parental smoking and risk of brain tumors in adults (ages 15-59 years). Based on 11 cases among nonsmokers, there was a nonsignificant increased risk associated with father's smoking (OR = 1.65, 95% CI = 0.44-6.24), but not with mother's smoking (OR = 0.82, 95% CI = 0.10-6.64).

Ryan *et al.* (1992) published a case-control study on meningiomas and gliomas. This Australian study was one of 10 studies on adult brain tumors coordinated by the IARC. Classification of ETS exposure status was based on whether subjects were regularly exposed to smoking of parents, spouses, or coworkers. The authors reported an effect due to ETS, particularly for meningiomas. However, it is difficult to interpret these results because the analysis included all subjects who were not exposed to ETS in the baseline group, irrespective of the subject's active smoking habits. Thus, although there was an increased risk associated with ETS exposure for meningioma (RR = 2.5, 95% CI = 1.0-6.1) and for glioma (RR = 1.3, 95% CI = 0.6-2.7), it is not possible to rule out the effect of active smoking among those exposed to ETS.

7.4.3.2 In Children/ Young Adults

The effect of passive smoking and risk of brain/nervous system tumors in children has been evaluated in ten studies (Table 7.14). Five studies were designed specifically to identify risk factors for all brain tumors combined (Gold *et al.*, 1979; Preston-Martin *et al.*, 1982; Howe *et al.*, 1989; Gold *et al.*, 1993; McCredie *et al.*, 1994), one study was focused on astrocytoma (Kuijten *et al.*, 1990), and four studies included all childhood cancers and results were presented for cancers of the brain or nervous system (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; John *et al.*, 1991; Pershagen *et al.*, 1992) (see Section 7.1.2 for study details).

Findings from four studies on childhood brain tumors (Preston-Martin *et al.*, 1982; Howe *et al.*, 1989; John *et al.*, 1991; McCredie *et al.*, 1994) show a small increased risk in relation to paternal smoking (Table 7.14); results were statistically significant in two studies (Preston-Martin *et al.*, 1982; McCredie *et al.*, 1994). Each of the four studies shows no association between maternal smoking during pregnancy and risk of childhood brain cancers.

Gold et al. (1979) Gold *et al.* (1979) conducted a hospital-based case-control study in Baltimore, MD which included all children under the age of 20 years, diagnosed with primary malignant brain tumors during the period 1965-1975. Children with brain tumors were compared to two types of controls; normal controls selected from birth certificates and controls with malignancies other than brain tumors. Each control was individually matched to children with brain tumors on sex, date of birth (plus or minus 1 year), race, and age at diagnosis (for cancer controls only). The response rate was 66 percent for brain tumor cases, 63 percent for cancer controls, and 21 percent for normal controls. There were a total of 73 matched-pairs of children with brain tumors and normal controls and 78 matched pairs of children with brain tumors and other cancer controls. Parents of cases and controls were interviewed. Maternal smoking prior to the index pregnancy did not differ between mothers of children with brain tumors and mothers of control children. However, mothers of children with brain tumors were more likely to have continued to smoke during the pregnancy compared to mothers in either control group (RR = 5.0, $p = 0.22$ for normal controls; RR = ∞, $p = 0.13$ for cancer controls). This finding, however, was not confirmed in a later study by the same investigators (Gold *et al.*, 1993, see below). Neither study presented data on the percentage of mothers who stopped smoking during pregnancy, and there is no apparent explanation for the discrepancy in findings.

Preston-Martin et al. (1982) Preston-Martin *et al.* (1982) conducted a population-based case-control study of brain tumors in Los Angeles County. Eligible subjects had a histologically confirmed brain tumor, diagnosed at or under 25 years of age between 1972 and 1977. Of the 317 eligible cases identified, mothers of 226 patients were interviewed. For each case interviewed, a friend ($n = 153$) or a neighborhood control ($n = 56$) was interviewed. Case and control mothers did not differ significantly in consumption of cigarettes during the index pregnancy (OR = 1.1, $p = 0.42$). However, there was a significant excess of case mothers who lived in a household with someone else who smoked (OR = 1.5, $p = 0.03$) compared to controls.

Howe et al. (1989) Howe *et al.* (1989) conducted a hospital-based case-control study of childhood brain tumors in southern Ontario between 1977 and 1983. Eligible cases consisted of all cases of brain tumors diagnosed in children under age 20 at two main hospitals in Toronto. Of the 123 cases identified, 74 were interviewed (60 percent). Up to two randomly selected controls, matched to each case by sex, date of birth (within 2 years), and area of residence, were identified from population lists maintained by the Ontario government. The study included a total of 74 cases and 138 controls. Maternal (OR = 1.42, $p = 0.36$) and paternal smoking (OR = 1.13, $p = 0.69$) during index pregnancy was associated with a small, nonsignificant increased risk of brain tumor.

Gold et al. (1993) Gold *et al.* (1993) conducted a large multi-centered population-based case-control study on childhood brain tumors. Cases were identified from eight population-based registries under the Surveillance, Epidemiology, and End Results (SEER) program; cases were 18 years of age or younger at the time of diagnosis of a histologically confirmed brain tumor between January 1977 and December 1981, and they resided in the catchment areas of the registries at the time of diagnosis. Three control children, selected mainly by random-digit dialing, were matched to each case by age, sex, and mother's racial/ethnic classification, as well as by area code and telephone prefix. In-person, structured interviews were conducted with parents of 361 cases and 1,083 controls. The participation rate was 85 percent for both cases and controls. Smoking habits of mothers and fathers during preconception, prenatal, and early postnatal periods were available. Most of the paternal information was supplied directly by the fathers (71 percent of interviews) and the remainder was supplied by the mothers (26 percent). In addition, information on various potential confounders (*e.g.*, intake of alcohol, coffee and tea, parental educational level), histologic type, and location of tumor were obtained.

There was no association between risk of childhood brain tumor and maternal or paternal smoking at any time, specifically during the year the index child was born, or in the 2 years before the index child was born (Table 7.14). Compared to children whose parents were both nonsmokers, the ORs for brain tumors was 0.95 (95% CI = 0.66-1.36) when both parents smoked, 0.94 (95% CI = 0.66-1.33) when only fathers smoked, and 1.06 (95% CI = 0.82-1.37) when only mothers smoked. The results were unchanged when analyses were stratified by histologic type of tumor (astrocytoma, medulloblastoma, other) and location of tumor (supratentorial, infratentorial, other), or when adjustment was made for potential confounders. Information on parental smoking before, during, and after the index pregnancy was obtained—there was no increase or decrease in the percentage of case and control parents who did not smoke in the year during which the index subject was born compared to the two previous years, and only minor changes in the percentage of case and control fathers and mothers who smoked less than a pack/day versus greater than a pack/day during these two time periods. Smoking habits during the early postnatal periods were not presented separately but were included as part of the year the index child was born. Thus, the effects of maternal or paternal smoking before, during, or after the index pregnancy could not be distinguished.

Table 7.14
Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother	Father
		continued smoking during pregnancy[a]	
Gold *et al.*, 1979 (Age < 20)	84/73 (population) 84/78 (hospital)	5.0 ∞	No data
		During pregnancy	During pregnancy
Preston-Martin *et al.*, 1982 (Age < 25)	209/209	1.1	1.5[a]
		# cig/day during pregnancy 0 1-9 10+ cig/day	
Stjernfeldt *et al.*, 1986 (Age ≤ 16)	43/340	1.0 1.0 0.9	No data
		# cig/day during pregnancy 0 1-9 10+ cig/day	
McKinney and Stiller, 1986 (Age ≤ 15)	78/156	1.0 1.1 1.0	No data
		During pregnancy	During pregnancy
Howe *et al.*, 1989 (Age ≤ 20)	74/132	1.4	1.1
		During first trimester	12 months prior to birth
John *et al.*, 1991 (Age ≤ 14)	48/196	1.0	1.4
		Mother's smoking alone	Father's smoking alone
		*	1.9 (0.9-4.2)
		at 2-3 mos of pregnancy 0 <10 10+ cig/day	
Pershagen *et al.*, 1992 (Age ≤ 5)	81[b]	1.0 0.9 1.1	No data
McCredie *et al.*, 1994 (Age ≤ 14)	82/104	During pregnancy 1.3	During pregnancy 2.2[a] 4.2[c] 1.1[d]
Kuijten *et al.*, 1990 (Age ≤ 14)	163[e]/163	During pregnancy 1.0	During pregnancy 0.8

Table 7.14 (Continued)

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother	OR for Smoking Habits of Father
Gold *et al.*, 1993 (Age ≤ 18)	361/1083	Ever smoked 0.9	Ever smoked 1.1
		During yr of birth 0 <1 pack/day pack/day 1.0 0.8 1.0	During yr of birth 0 <1 pack/day pack/day 1.0 0.7 1.1
		2 yrs before birth 0 <1 pack/day pack/day 1.0 0.8 1.0	2 yrs before birth 0 <1 pack/day pack/day 1.0 0.9 1.2
		Mother's smoking alone 1.1	Father's smoking alone 0.9

[a] *p < 0.05*
[b] *cohort study*
[c] *OR if data obtained from mother*
[d] *OR if data obtained from father*
[e] *Cases restricted to astrocytoma*
* *0 exposed cases, 8 exposed controls*

McCredie et al. (1994) McCredie *et al.* (1994) conducted a population-based case-control study of incident primary malignant brain tumors diagnosed in children aged 0-14 years in New South Wales, Australia from 1985 to 1989. Each case was aged matched (±3 to 12 months of age) to two controls selected from electoral rolls. The response rate was 85 percent for cases and 60 percent for controls, resulting in completed personal interviews with mothers of 82 cases and 164 controls. Most of the information was provided by the mothers of cases and controls. In addition, fathers of 45 cases and 60 controls were also present at the interview or were interviewed directly about themselves over the telephone. Based on the smoking habits presented for mothers and fathers, and compared to subjects whose parents were both nonsmokers, increased risks were found in relation to smoking by either parent (OR = 1.61, 95% CI = 0.94-2.75) and to mothers' smoking (OR = 1.33, 95% CI = 0.72-2.46). A significant increased risk of brain tumors was associated with fathers' smoking (OR = 2.19, 95% CI = 1.25-3.85). Fathers' smoking is presumed to explain the association with mothers' smoking which, when examined alone, was not associated with an increased risk (OR = 0.4, 95% CI = 0.1-1.3). Risk of brain tumors was significantly increased if fathers' smoked before pregnancy (OR = 2.0, 95% CI = 1.0-4.1) or if mothers' reported they were exposed to fathers' smoking during pregnancy (OR = 2.2, 95% CI = 1.2-3.8).

McCredie *et al.* (1994) interpreted the effect of fathers' smoking to be due to recall bias by mothers. According to the authors

> "no increasing risk was seen with increasing use of cigarettes and after stratification by source of information (father or mother), the increased risk was present in the proxy data (ORs of 5.5 and 4.2, respectively, for the 2 smoking variables just mentioned) but not in those obtained directly from the father (ORs of 1.0 and 1.1). Moreover, no increased risk was found with mother's exposure to tobacco smoke either of other household members (OR = 1.3, 95% CI = 0.6 to 2.8) or at work (OR = 0.4, 95% CI = 0.4-1.4)."

However, based on the data presented, it cannot be determined whether the increased risk associated with fathers' smoking is explained by selective recall by mothers or whether the finding of no association is due to case fathers' denial of their own smoking. The distribution of fathers' smoking by respondent (*i.e.*, mothers or fathers) or by case/control status was not presented. The authors also indicated that control women who were interviewed were of higher social class than the eligible controls who refused to participate, raising the possibility that control fathers who participated may be less likely to smoke because of the inverse association between smoking and social class.

Kuijten et al. (1990) A study conducted by Kuijten *et al.* (1990) was designed to identify risk factors for astrocytoma, the most frequently occurring central nervous system tumors in children. Eligible cases included children diagnosed with this type of brain tumor before age 15 years, between 1980-1986, in one of eight tumor registry hospitals in Pennsylvania, New Jersey, and Delaware. Controls were selected by random-digit dialing and were pair-matched to cases for age (±2 years), race, and telephone exchange. Information was available on mothers of 163 cases and controls, and fathers of 160 cases and controls. Mothers and fathers were interviewed separately by telephone, and presumably each was asked about their own smoking habits. Mothers' smoking (OR = 1.0, 95% CI = 0.6-1.7) and mothers' exposure to sidestream smoke (OR = 0.8, 95% CI = 0.5-1.3) were not associated with risk of astrocytoma (Kuijten *et al.*, 1990).

Other studies' results on brain tumors in children. Data from three (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Pershagen *et al.*, 1992) of the four studies focusing on all childhood cancers showed no association between maternal smoking during pregnancy and risk of cancers of the brain/nervous system. In all three studies, the RRs were close to 1.0 irrespective of the amount smoked by mothers (1-9, 10+ cigarettes/day) (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Pershagen *et al.*, 1992). Information on father's smoking was not available in these studies (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Pershagen *et al.*, 1992; see Table 7.14). In the study by John *et al.* (1991), mothers' smoking was also not associated with risk, but fathers' smoking was associated with an elevated risk (RR = 1.4, 95% CI = 0.7-2.8). The effect of fathers' smoking on brain tumor risk was more apparent in the absence of mothers' smoking (RR = 1.9, 95% CI = 0.9-4.2).

7.4.3.3 Summary In adults, the epidemiologic evidence for an association between ETS exposure and risk of brain tumor is inadequate, but the effect has not been fully researched. Although a cohort (Hirayama, 1984) and a case-control study (Ryan *et al.*, 1992) are suggestive of a positive association in adults, the results were based on small numbers (Hirayama, 1984) and may be confounded by active smoking (Ryan *et al.*, 1992). In a second case-control study (Sandler *et al.*, 1985a & b), a non-significant increase was observed with fathers' but not mothers' smoking.

In children, data from the ten available studies do not support an effect due to mothers' smoking during pregnancy or the year before pregnancy. The only suggestive finding was for mothers who continued to smoke during pregnancy compared to mothers who stopped smoking during pregnancy in one study (Gold *et al.*, 1979), but this finding was not confirmed in a larger study conducted by the same investigators (Gold *et al.*, 1993). Six of the ten studies also collected information on fathers' smoking during the index pregnancy. In four studies, there was an association between paternal smoking and risk of brain tumors (Preston-Martin *et al.*, 1982; Howe *et al.*, 1989; John *et al.*, 1991; McCredie *et al.*, 1994); results were statistically significant in two studies (Preston-Martin *et al.*, 1982; McCredie *et al.*, 1994). In a third study, the effect of fathers' smoking in the absence of mothers' smoking was of borderline statistical significance (John *et al.*, 1991). The range of ORs for paternal smoking in the positive studies was 1.5 to 2.2.

The positive association between paternal smoking and childhood brain tumors reported (Preston-Martin *et al.*, 1982; John *et al.*, 1991; McCredie *et al.*, 1994) and the biologic plausibility of the hypothesis justify further research to clarify the relationship. Given that purported relationships with risk of childhood brain tumors have been reported for electromagnetic field exposures, parental occupation, and radon exposures, future studies on ETS and brain tumors would need to account for the effects of these other suspected risk factors.

7.4.4 Leukemia

There is increasing evidence that cigarette smoking may be causally related to leukemia in adults (Austin and Cole, 1986; Brownson *et al.*, 1993b). Smoking has emerged as a risk factor for leukemia in a number of prospective studies, including the first (Hammond, 1966; Garfinkel and Boffetta, 1990) and second American Cancer Society studies (Garfinkel and Boffetta 1990), the U.S. Veteran cohort study (Kahn, 1966; Rogot and Murray, 1980; Kinlen and Rogot, 1988; McLaughlin *et al.*, 1989), and the Adventist Health study (Mills *et al.*, 1990). In two other cohort studies with small numbers of leukemia deaths (<75 in each study), smoking was associated with statistically nonsignificant increased risks of leukemia (Weir and Dunn, 1970; Linet *et al.*, 1992). Smoking was not a risk factor for leukemia in the British doctors' cohort in which more than 70 percent of the deaths from marrow and reticuloendothelial malignancies were lymphomas and myelomas (Doll and Peto, 1976). Case-control studies which have compared smoking histories of leukemia patients with population controls have

7.4.4.1 Active Smoking and Leukemia

found statistically significant positive associations with tobacco use (Sandler *et al.*, 1993; Brown *et al.*, 1992; Severson, 1987; Severson *et al.*, 1990). Tobacco use was also a significant risk factor in a case-control study in which all leukemia patients diagnosed between 1984 and 1987 in the Missouri Cancer Registry were compared to other cancer patients (excluding lip, oral cavity, esophagus, lung, and bladder) (Brownson, 1989). No association with smoking was found in two U.S. hospital-based case-control studies (Kabat *et al.*, 1988; Spitz *et al.*, 1990) in which selection bias of leukemia cases was likely or in a third study restricted to chronic lymphatic leukemia (Flodin *et al.*, 1988). The association with smoking is most consistent for myeloid leukemias, particularly acute myeloid leukemia, and less consistent for chronic lymphocytic leukemia (Kinlen and Rogot, 1988; McLaughlin *et al.*, 1989; Garfinkel and Boffetta, 1990; Mills *et al.*, 1990; Brownson, 1989).

Cigarette smoke contains many compounds, some of which have been associated with increased risk of leukemia. These include benzene, nitrosamines, urethane, and radioactive compounds (Austin and Cole, 1986). In animal studies, leukemia can also be induced by transplacentally-acting carcinogens, many of which are found in tobacco smoke (Coghlin *et al.*, 1991; Sorsa and Husgafuel-Pursiarnen, 1988).

7.4.4.2 ETS and Risk of Hematopoietic Tumors in Adults

The association between ETS exposure and risk of hematopoietic tumors including leukemia was reported in one study. Among nonsmoking women with tumors of hematopoietic tissues (including Hodgkins disease, non-Hodgkins disease lymphomas, and acute leukemias), Sandler *et al.* (1985b) reported an increased risk in relation to mothers' (OR = 2.18, 95% CI = 0.69-6.92) and fathers' (OR = 2.42, 95% CI = 0.88-6.61) smoking during the childhood years of the index subjects (see Section 7.1.1 for study description). Although smoking habits of husbands were available in the same study, their effect on risk was not reported (Sandler *et al.*, 1985a).

7.4.4.3 ETS and Risk of Leukemia in Children

One of the first studies to investigate the role of parental smoking and risk of leukemia in children was conducted by Manning and Carroll (1957) (see Section 7.1.2 for a detailed description). In this hospital-based study, smoking habits of mothers of 188 children with acute leukemia were compared to those of mothers of controls. Thirty-nine percent of mothers of children with leukemia smoked 10 or more cigarettes a day at interview compared to 38 percent among mothers of children admitted for orthopedic reasons. A second study included 1,416 childhood cancers (677 were leukemia) and an equal number of population controls in the United Kingdom (Stewart *et al.*, 1958) (see Section 7.1.2 for a detailed description). There was little case-control difference in smoking habits of fathers, but there was a slight excess of case mothers who smoked. A third study (Neutel and Buck, 1971) compared rates of leukemia by smoking habits of mothers during pregnancy (see Section 7.1.2 for details). The rate of leukemia in children was higher among mothers who smoked (6.0 per 100,000 child-years) compared to mothers who did not smoke (3.4 per 100,000 child years) (RR = 1.8). However, these results were based on a small number of events (<12 cases of leukemia) among subjects with nonsmoking and smoking mothers.

Since the 1980s, one cohort study and seven case-control studies offer additional information on the possible effect of parental smoking on childhood leukemia (Table 7.15). Three of the studies included only acute lymphocytic leukemia (ALL) (Van Steensel-Moll *et al.*, 1985; Stjernfeldt *et al.*, 1986; Buckley *et al.*, 1986), one study was limited to acute myeloid leukemia (Severson *et al.*, 1993), whereas four studies included all leukemias (McKinney and Stiller, 1986; Magnani *et al.*, 1990; John *et al.*, 1991; Pershagen *et al.*, 1992). In two studies, risk estimates were presented for ALL and non-acute lymphocytic leukemia (non-ALL) separately (Magnani *et al.*, 1990; John *et al.*, 1991).

In the Swedish cohort study (Pershagen *et al.*, 1992) (see Section 7.1.2 for a detailed description), cancer incidence in some 50,000 children born between 1982 and 1987 was determined. Maternal smoking at 2 to 3 months of pregnancy was categorized as none, 1-9 cigarettes/day, and >10 cigarettes/day. There were 129 cancers of the lymphatic and hematopoietic system (84 lymphatic leukemia, 15 myeloid leukemia, 16 reticulosis, and 14 other hematopoietic and lymphatic system). There was no increased risk associated with mothers' smoking during pregnancy for lymphatic leukemia when year and county of birth, birth order of index subject, and maternal age were adjusted for in the analysis (Table 7.14). Mothers' smoking during the entire pregnancy was not available. An association would have been missed only if there was a differential number of case mothers (compared to control mothers) who smoked later in the pregnancy, and if smoking in the second and third trimesters are more likely to be associated with risk. More importantly, the follow-up period only allowed ascertainment of leukemia up to 5 years of age so that associations between risk of leukemia at older ages and maternal smoking could not be evaluated.

Of the case-control studies on childhood leukemia (Van Steensel-Moll *et al.*, 1985; Severson *et al.*, 1993) or childhood cancers which included leukemia (Stjernfeldt *et al.*, 1986a & b; McKinney and Stiller, 1986; Buckley *et al.*, 1986; Magnani *et al.*, 1990; John *et al.*, 1991) (see Section 7.1.2), a significant association between mothers' smoking during the index pregnancy and risk of ALL was observed in two studies (Stjernfeldt *et al.*, 1986a & b; John *et al.*, 1992) (see Section 7.1.2 for study details). Compared to children of nonsmokers, subjects whose mothers smoked 10+ cigarettes/day showed about a 2-fold increased risk in one study (RR = 2.1, 95% CI = 1.3-3.3) (Stjernfeldt *et al.*, 1986a & b) and a 3-fold increased risk in another (RR = 2.9, 95% CI = 1.2-6.8) (John *et al.*, 1991) (Table 7.14). A subsequent report by Stjernfeldt *et al.* (1992) confirmed that the effect of mothers' smoking was independent of the risk associated with diagnostic X-rays. Among subjects whose mothers had not had X-ray exposure during pregnancy, the ORs for ALL were 1.3 and 2.2, respectively if mothers smoked 1-9 and 10+ cigarettes/day compared to children of nonsmokers. The corresponding ORs were 1.8 and 3.6 in the group whose mothers had had X-ray exposure. In the other positive study (John *et al.*, 1991), mothers' and fathers' smoking together was associated with about a 2-fold increased risk (OR = 2.2, 95% CI = 1.0-5.0). The OR for ALL was 2.9 (95% CI = 0.8-10.3) when only mothers smoked and 1.7 (95% CI = 0.7-3.8) when only fathers

smoked. Mothers' smoking prior to conception, during the first trimester of pregnancy, and during the entire pregnancy were all associated with increased risks of ALL, and it was not possible to determine the effect of mothers' smoking prior to versus during pregnancy. The effect of parental smoking was specific to ALL. There was no increased risk of other leukemias in relation to smoking of mothers and fathers (OR = 1.0, 95% CI = 0.2-4.2) (John *et al.*, 1991).

Five case-control studies are not supportive of an association between childhood leukemia risk and ETS exposure. One study was conducted in the Netherlands, using a complete nationwide register of histologically-confirmed childhood leukemia cases diagnosed between 1973 and 1980 (Van Steensel-Moll *et al.*, 1985). Seven hundred and thirteen children, aged less than 15 years, were diagnosed with leukemia during this time period. Using the census lists available by municipality, two controls with the same date of birth (within two months), the same sex, and who lived in the same municipality as the case at the time of diagnosis were randomly selected. The second control served as replacement if the first control did not respond. Between 1981 and 1982, parents of cases and controls were sent a questionnaire which asked about maternal events before and during pregnancy of the index subjects. A total of 625 leukemia patients and 615 controls responded, representing response rates of 90 percent, 70 percent, and 68 percent, respectively, for the parents of leukemic patients, and first and second controls. Analyses were restricted to 519 patients with ALL and 507 controls. Mothers of ALL cases and controls did not differ in their smoking habits in the year before pregnancy (age- and sex-adjusted RR = 1.0, 95% CI = 0.8-1.3) or during pregnancy (age- and sex-adjusted RR = 1.0, 95% CI = 0.7-1.3).

A second study not supportive of an association was reported by McKinney and Stiller (1986) (see Section 7.1.2 for study details). In this study, 93 of the 171 leukemias were non-ALL (McKinney *et al.*, 1987). Thus, if an association between ETS and leukemia is specific for ALL, an analysis including all leukemias combined may have diluted an ETS effect. Another study which did not find an association between ALL and parental smoking during the index pregnancy was reported by Buckley *et al.* (1986) (see Section 7.1.2). This study was published as a letter to the editor, and few details were provided.

No association between parental smoking and risk of leukemia in children was found in a hospital-based case-control study conducted in the main pediatric hospital in Turin, Italy between 1981 and 1984 (Magnani *et al.*, 1990). There were a total of 142 children with ALL, 22 with non-ALL, and 19 with non-Hodgkins lymphoma (NHL). These were compared to 307 controls who were identified by a random sampling of children hospitalized in the medical or surgical wards of the hospital. Data on parental smoking habits, parental occupation, ionizing radiation, and childhood diseases were collected using a standard questionnaire administered to a relative of the child while the child was still in the hospital. After adjusting for socioeconomic status, risk of ALL was not associated with mothers or father's smoking habits up to the birth of index subject (Table 7.15). It is difficult to

interpret results from this study because of several methodologic limitations. Factors such as residence and socioeconomic status may have affected the selection of cases and controls in this hospital-based study. In addition, there were no records of potential hospital controls that were missed because of early discharge during the first two years of this study. Finally, both incident and prevalent cases were included as eligible cases.

A fifth study, restricted to acute myeloid leukemia (AML) also did not find an association with maternal smoking. AML is the most frequently diagnosed leukemia in adults and is the subtype most consistently associated with active smoking (Austin and Cole, 1986; Brownson *et al.*, 1993b). However, AML is less common in children, representing about 15 percent of leukemia in children. This case-control study was a multicentered study conducted as part of the Childrens Cancer Group studies of *in utero* and postnatal exposures. Cases were identified through the registration files of the Children's Cancer Group, a cooperative clinical trials group which included about 100 primary and affiliate institutions throughout North America. Eligible cases in this study included patients newly diagnosed with AML from January 1980 through December 1984 who were 18 years of age or younger at the time of diagnosis. A total of 187 matched case-control pairs were interviewed, representing completion rates of 71 percent among eligible cases (n = 187) and 78 percent among eligible controls (n = 262). The objective was to interview one control per case matched to cases on age, race, and telephone area code and exchange, and selected by random digit dialing.

Mothers and fathers of study subjects were interviewed separately by telephone. As part of the interview, both the mother and the father were asked about cigarette smoking status (current, past, or never) and smoking practices during: a) the month immediately preceding the index pregnancy; b) the index pregnancy; and c) nursing. Detailed information was requested regarding the trimesters in which the parent smoked and the number of cigarettes smoked per day during the pregnancy. Mothers of children with AML were less likely to be current smokers, *i.e.*, smoking cigarettes at the time of interview. However, mothers of children with AML were more likely to have ever smoked (OR = 1.32, 95% CI = 0.85-2.09) or smoked during pregnancy (OR = 1.20, 95% CI = 0.77-1.86) although these results were not statistically significant. The authors indicated that paternal smoking was also not associated with risk of AML (results on paternal smoking were not shown).

7.4.4.4 Summary In adults, the association between ETS exposure and hematopoietic tumors was addressed in only one study. That study (Sandler *et al.,* 1985b) reported increased risk in relation to mothers' and fathers' smoking during childhood. The epidemiologic evidence for parental smoking and risk of leukemia in children is conflicting. No association between ETS exposure and risk of leukemia was found in the only cohort study, and a significant positive association, specifically for ALL was observed in 2 of the 7 case-control studies. In one of the two studies which found an increased risk with mothers' smoking, fathers' smoking was available and appeared to have an independent effect on risk. The range of ORs associated with

Table 7.15
Maternal or Parental Smoking During Pregnancy and Childhood Leukemia

Cohort Studies (Age of Subjects)	**# Cases (Type of Leukemia)**	**Smoking Habits (cig/day)**	**OR (95% CI) Maternal Smoking**	**OR (95% CI) Paternal Smoking**
Pershagen *et al.*, 1992 (Age ≤ 5)	All Leukemia	2-3 mos of pregnancy		
	72	No	1.0	Not available
	18	1-9	0.9 (0.6-1.6)	
	9	10+	0.7 (0.4-1.5)	
	21 (lymphatic)	Yes	0.8 (0.5-1.3)	
	6 (myeloid)	Yes	1.6 (0.6-4.8)	

Case-Control Studies (Age of Subjects)	**# Cases/ # Controls (Type)[a]**	**Smoking Habits (cig/day)**	**OR (95% CI) Maternal Smoking**	**OR (95% CI) Paternal Smoking**
Van Steensel-Moll *et al.*,1985 (Age ≤ 15)	519/507 (ALL)	Yes, yr before Pregnancy	1.0 (0.8-1.3)	Not available
		Yes, during pregnancy	1.0 (0.7-1.3)	
		During pregnancy		
Stjernfeldt *et al.*, 1986 (Age ≤ 16)	132/340 (ALL)	1-9	1.3 (0.7-2.6)	Not available
		10+	2.1 (1.3-3.3)	
		During pregnancy		
McKinney *et al.*, 1986 (Age ≤ 15)	171/342 (78 ALL, 93 non-ALL)	1-10	1.0 (0.6-1.7)	No association
		11+	0.6 (0.4-1.0)	
		During pregnancy		
Buckley *et al.*, 1986 (Age ≤ 15)	742/740 (ALL)	1-9	1.0 (0.6-1.5)	No association
		10+	0.9 (0.7-1.1)	
Magnani *et al.*, 1990 (Not specified)	142/307 (ALL)	Smoking up to child's birth		
		Yes	0.7 (0.5-1.1)	0.9 (0.6-1.5)
		1-15 cig/day	0.6 (0.4-1.0)	0.9 (0.5-1.6)
		16+ cig/day	1.0 (0.4-2.7)	0.9 (0.6-1.5)
	22/307 (non-ALL)	Yes	2.0 (0.8-4.8)	0.9 (0.3-2.1)

Table 7.15 (Continued)

Cohort Studies (Age of Subjects)	# Cases (Type of Leukemia)[a]	Smoking Habits (cig/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
			During 3 trimesters	During pregnancy
John *et al.*, 1991 (Age ≤ 14)	73/196 (ALL)	1-10	2.0 (0.7-5.9)	2.6 (0.9-7.9)
		11-20	2.9 (1.2-6.8)	1.6 (0.7-3.7)
		21+		1.6 (0.7-4.0)
			Parent smoking in absence of other parent	
			2.9 (0.8-10.3)	1.7 (0.7-3.8)
	(non-ALL)		During 3 trimesters	During pregnancy
		Yes	0.6 (0.1-3.0)	0.8 (0.2-2.3)
Severson *et al.*, 1993 (Age ≤ 18)	187/187 (acute myeloid leukemia)		During pregnancy	
		Yes	1.2 (0.8-1.9)	No association

[a] *ALL = Acute lymphocytic leukemias, non-ALL = non acute lymphocytic leukemias.*

mothers' smoking at least 10 cigarettes per day during pregnancy was 2.1 to 2.9 and 1.6 for fathers' smoking at least 10 cigarettes per day. With respect to the relationship of ETS exposure and childhood leukemia, there is no satisfactory explanation for the inconsistent results between the case-control studies not supportive of an association (Van Steensel-Moll *et al.*, 1985; McKinney and Stiller, 1986; Buckley *et al.*, 1986; Magnani *et al.*, 1990; Severson *et al.*, 1993) and those supportive of an association (Stjernfeldt *et al.*, 1986a & b; John *et al.*, 1991).

There are several difficulties in trying to reconcile these different findings. First, most of the studies did not present sufficient information to allow comparison of the prevalence of maternal and paternal smoking in the studies. Second, it is not known whether the age distributions of leukemia or ALL were similar in the studies showing an association and those showing no association. It is conceivable that the effect of ETS on risk of leukemia may vary by age. Risk factors for leukemia diagnosed in children aged 3-4 are likely to differ from those in children diagnosed with leukemia in their teens. Thus, the relative roles of intrauterine ETS exposure, prenatal esposure, and postnatal exposure to ETS may differ depending on the age at onset of leukemia. Third, the source and types of subjects used as controls may be particularly important. Controls selected from general practitioner lists and hospital admissions for minor conditions may be biased with respect to tobacco-smoke exposure since maternal smoking has been associated with various conditions, including nonmalignant lung dis-

eases. Fourth, the role of potential confounders including the effect of socioeconomic status may be especially important. In some studies, adjustment for paternal education level reduced the risks in relation to ETS exposure (John *et al.*, 1991), suggesting that perhaps both paternal and maternal education level should be adjusted for in the analysis.

Despite the fact there are eight studies on ETS exposure and parental smoking, and that most of these studies had relatively large sample sizes, a conclusion regarding the association cannot be reached for the reasons mentioned above. Future studies would need to distinguish between ALL and non-ALL, and to examine the risk pattern by age of diagnosis of leukemia (*e.g.*, ≤5, 6-10, ≥11 years of age). In addition, the studies should be designed to minimize selection bias of cases and controls (*i.e.*, by making sure that factors such as residence, medical coverage, and socioeconomic status do not influence selection into study), to minimize information bias (*i.e.*, by obtaining necessary information on maternal and paternal smoking during, and after the index pregnancy), and to be able to adjust for potential confounders in the analysis.

7.4.5 Lymphomas and Non-Hodgkin's Lymphomas

The effect of ETS exposure and risk of lymphomas and non-Hodgkin's lymphomas (NHL) was examined in six studies of childhood cancers (Table 7.16). In one case-control study with 169 cases of NHL (Buckley *et al.*, 1986), there was no association between maternal smoking during pregnancy and risk (Table 7.15), whereas increased risks were reported in two small studies (less than 20 cases of NHL in each) (Stjernfeldt *et al.*, 1986a & b; Magnani *et al.*, 1990). Two studies offered information on risk of lymphomas and exposure to ETS (McKinney and Stiller, 1986; John *et al.*, 1991). McKinney and Stiller, (1986) found a 90 percent increase in risk of lymphomas in subjects whose mothers' smoked 1-10 cigarettes/day during pregnancy, but there was no increased risk for subjects whose mothers who smoked more. John *et al.* (1991) reported an increased risk of lymphoma in relation to fathers' smoking during the index pregnancy (RR = 1.9, 95% CI = 0.7-4.8) and mothers' smoking during all three trimesters of pregnancy (RR = 1.9, 95% CI = 1.0-7.6). There were, however, too few cases in this study (n = 26) to investigate the association by amount smoked by mothers or fathers. In the cohort analysis by Pershagen *et al.* (1992), maternal smoking was associated with an increased risk for cancers of the hematopoietic and lymphatic system (excluding leukemia). Children whose mothers smoked at 2-3 months of pregnancy showed an elevated risk for reticulosis (RR = 1.7, 95% CI = 0.6-5.0, based on 16 cases) and tumors of other hematopoietic and lymphatic systems (RR = 2.0, 95% CI = 0.7-5.5, based on 14 cases). For this group of cancers combined, the RR was 2.4 (95% CI = 1.0-5.5) for subjects whose mothers' smoked less than 10 cigarettes/day, but an increased risk was not observed for subjects whose mothers smoked more.

In summary, the data on ETS exposure and risk of lymphomas and NHL are inadequate. Although small increased risks have been reported in some studies, the results are difficult to interpret given that they were based on small numbers, with wide confidence limits, and the dose-response trends were largely not smooth.

7.4.6 Other Rare Childhood Cancers

A few epidemiologic studies have examined the potential impact of maternal smoking and ETS exposure on rare childhood cancers. These studies are discussed below.

7.4.6.1 Neuroblastoma

Neuroblastoma is an embryonal tumor of the sympathetic nervous system diagnosed primarily in infancy. Extrinsic factors that influence the risk of neuroblastoma are likely to act while the child is *in utero*, or perhaps upon parental germ cells prior to conception. Thus, the focus of etiologic investigations is on parental exposures during and prior to the prenatal period.

Kramer *et al.* (1987) conducted a case-control study of neuroblastoma focusing on both family medical history and parental medical and drug exposures prior to birth of the index child. Histologically confirmed cases, identified by the Greater Delaware Valley Pediatric Tumor Registry between 1970 and 1979, were included. One population control per case was selected by random-digit dialing. Controls were matched to cases by date of birth (±3 years), race, and cases' telephone number (area code and first five digits). Of the 139 eligible cases (74.8 percent), 104 were successfully interviewed. These cases were compared to 101 of 177 controls who were interviewed (57.1 percent). A small increased risk was observed for mother's smoking during pregnancy (OR = 1.26, 90% CI = 0.76-2.09) and at any time prior to conception of the index child (OR = 1.26, $p = 0.20$). Father's smoking during the 2 years prior to birth of the index child conferred a similar increase in risk (OR = 1.30, 90% CI = 0.83-2.05). The RR for father's smoking was stronger (OR = 1.60, 90% CI = 0.94-2.74) when his smoking habits any time prior to the index child's birth was considered.

7.4.6.2 Wilms' Tumor of the Kidney

Smoking is an established risk factor for cancers of the kidney and renal pelvis in adults (IARC, 1986). Induction of Wilms' tumors in rodents by transplacental N-ethylnitrosourea has been described (Hard, 1985), suggesting that nitrosamines, including tobacco-specific nitrosamines, may have an etiologic role in these tumors.

The role of ETS exposure and risk of Wilms' tumor of the kidney has been evaluated in four studies. One study was designed specifically to identify risk factors for Wilms' tumors (Bunin *et al.*, 1987), whereas in three other studies Wilms' tumors were one of the childhood cancers presented in the analysis (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Buckley *et al.*, 1986).

Bunin *et al.* (1987) conducted a hospital-based case-control study of Wilms' tumor to examine the role of gestational risk factors. Histologically confirmed Wilms' tumor diagnosed among whites aged 15 years or younger between 1970 and 1983 were included. Controls were selected by random-digit dialing and were pair-matched to cases on year of birth (±3 years), race, and telephone area code and exchange. Of the 124 eligible cases, 88 were included and were compared to 88 of the 159 controls identified (participation rates were 71 percent and 55 percent, respectively). The authors reported that there is no association between maternal smoking during pregnancy and risk of Wilms' tumor (data were not presented).

There is no evidence for a role of maternal smoking and risk of Wilms' tumor in the study conducted by McKinney and Stiller (1986). Based on 32 cases of Wilms tumors, the RRs were 0.86 (95% CI = 0.3-2.6) and 1.17 (95% CI = 0.4-3.5), respectively, for subjects whose mothers smoked 1-10, and 11+ cigarettes during pregnancy compared to subjects whose mothers were nonsmokers. However, in two studies, there was some suggestion of a small increased risk in relation to maternal smoking. Buckley *et al.* (1986) (n = 61 kidney cancers) reported RRs of 1.58 (95% CI = 0.60-4.18) and 0.93 (95% CI = 0.47-1.83), respectively, for subjects whose mothers smoked 1-9 and 10+ cigarettes per day during pregnancy compared to children of nonsmokers. In the other study, the corresponding RRs were 0.70 (95% CI = 0.1-5.6) and 2.53 (95% CI = 0.9-7.2) in an analysis which included only 16 cases of kidney cancer (Stjernfeldt *et al.*, 1986a & b).

7.4.6.3 Germ Cell Tumors Germ cell tumors include teratomas, yolk sac tumors, and germinoma. In 1980-1982, the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) interviewed the parents of 555 children with newly diagnosed cancer and the parents of 1,100 control children chosen from hospital admissions and general practitioner lists (see 7.1.2, case-control studies). Two controls were individually matched to each case interviewed. Characteristics of mothers and their exposures during the index pregnancy were compared for 41 children with germ cell tumors and 82 controls (McKinney and Stiller, 1986). Mothers of cases and controls did not differ in their smoking habits during 1 year prior to or 1 month prior to the index pregnancy (44 percent of case mothers smoked compared to 42 percent of control mothers). Smoking patterns of fathers were also comparable (56 percent of case fathers compared to 57 percent of control fathers smoked).

7.4.6.4 Bone and Soft-Tissue Sarcomas Bone and soft tissue sarcomas account for about 10 percent of childhood cancers (Li, 1982). The main types of bone tumors are osteosarcoma and Ewing's tumor, and the main type of soft-tissue sarcoma is rhabdomyosarcoma (RMS).

Grufferman *et al.* (1982) conducted a case-control study of childhood RMS by including the families of 33 cases and 99 controls. All incident cases of childhood RMS diagnosed in North Carolina residents during 1967-1976 were considered eligible (37 were eligible). For each of the cases interviewed, 3 controls of the same age (±2 months), sex, and race were randomly selected from North Carolina birth certificates. Of the 99 controls first selected, 70 were successfully interviewed. Risk of RMS was not related to mothers' smoking at any time (RR = 0.8, 95% CI = 0.3-2.0), or mothers' smoking during the pregnancy of the index subject (RR = 1.0, 95% CI = 0.4-2.4). On the other hand, fathers' smoking was a statistically significant risk factor (RR = 3.9, 95% CI = 1.5-9.6). The point estimate of the risk in relation to fathers' smoking diminished when the analysis accounted for family income and fathers' education and occupation (RR = 2.8, p = 0.07).

As part of the IRESCC study (see 7.1.2, Case-control studies), characteristics of mothers and their prenatal exposures were compared for 43 cases with soft tissue tumors, 30 cases with bone sarcomas, and their 146

Table 7.16
Association Between Exposure to Passive Smoking and Risk of Non-Hodgkins Lymphoma and Lymphoma in Children

Studies	Exposure to Passive Smoking	Relative Risk	95% CI
Stjernfeldt *et al.*, 1986	Non-Hodgkins Lymphoma (*n* = 16)		
	Mother's smoking during pregnancy		
	0 (cig/day)	1.0	
	1-9	1.9	(0.3-6.7)
	10+	2.1	(0.7-6.4)
	Hodgkins Lymphoma (*n* = 15)		
	0 (cig/day)	1.0	
	1-9	1.1	(0.2-4.9)
	10+	0.3	(0.1-2.2)
Buckley *et al.*, 1986	Non-Hodgkins Lymphoma (*n* = 169)		
	Mother's smoking during pregnancy		
	0 (cig/day)	1.0	
	1-9	0.8	(0.3-1.8)
	10+	1.0	(0.7-1.4)
Magnani *et al.*, 1990	Non-Hodgkins Lymphoma (*n* = 19)		
	Mother's smoking up to child's birth	1.7	(0.7-4.5)
	Father's smoking up to child's birth	6.7	(1.0-43.4)
McKinney and Stiller, 1986	Lymphomas (*n* = 74)		
	Mother's smoking during pregnancy		
	0 (cig/day)	1.0	
	1-10	1.9	(0.9-4.0)
	11+	1.0	(0.5-2.1)
John *et al.*, 1991	Lymphoma (*n* = 26)		
	Mother's smoking		
	-Three months prior to conception	1.9	(0.7-5.2)
	-First trimester of pregnancy	2.5	(0.9-7.0)
	-All three trimesters of pregnancy	2.7	(1.0-7.6)
	Father's smoking during pregnancy	1.9	(0.7-4.8)
Pershagen *et al.*, 1992	Hematopoietic and Lymphatic excluding leukemia (*n* = 30)		
	Mother's smoking at 2-3 months of pregnancy		
	0 (cig/day)	1.0	
	1-9	2.4	(1.0-5.5)
	10+	1.1	(0.3-3.6)

matched controls (McKinney and Stiller, 1986; Hartley *et al.*, 1988). Compared to children whose mothers were nonsmokers, children whose mothers smoked 1-10, and 11+ cigarettes/day during pregnancy showed RRs of 1.37 (95% CI = 0.53-3.55) and 1.47 (95% CI = 0.56-3.84) respectively for soft tissue sarcomas. The corresponding RRs were 1.48 (95% CI = 0.46-4.74) and 2.16 (95% CI = 0.68, 6.85) for bone tumors (McKinney and Stiller, 1986). In a more detailed report on risk factors for these two tumor sites, Hartley *et al.* (1988) described that "mothers' and fathers' smoking history before and during the index pregnancy did not show any case excess" and did not elaborate on the findings.

No association between paternal and maternal smoking habits and risk of RMS and non-RMS-soft tissue sarcomas (STS) was reported by Magnani *et al.* (1989). In this hospital-based case-control study conducted in 1983-1984 in Torino and Padova, Italy, there were a total of 36 RMS, 16 non-RMS-STS, and 326 controls. The RRs for fathers' smoking 0, 1-15, and 16+ cigarettes/day up to the index child's birth were 1.0, 0.7 (95% CI = 0.3-2.0), and 0.8 (95% CI = 0.4-1.8), respectively. The corresponding RRs for mothers' smoking were 1.0 (95% CI = 0.4-2.3), and undefined (0 cases and 17 controls) (Magnani *et al.*, 1989).

The role of ETS in the etiology of soft tissue sarcomas is unclear, particularly in the case of RMS. Although the association between RMS and fathers' smoking reported by Grufferman *et al.* (1982) is intriguing, it has not been confirmed. These authors proposed that there may be a direct carcinogenic effect introduced either in a prezygotic manner or by passive inhalation of cigarette smoke by the patients. Evans *et al.* (1981) found morphologic sperm abnormalities in cigarette smokers, in support of a direct mutagenic effect of fathers' cigarette smoking.

7.4.6.5 Summary The epidemiologic evidence on ETS exposure and other rare childhood cancer is inadequate. Given that these are rare events, most of the studies are limited by small sample sizes, and any effect of ETS exposure is not likely to be statistically significant. Thus, it is important to evaluate these studies in terms of the collective evidence, the direction of the risk estimates from individual studies, and possible biases (*i.e.*, confounding by social class, or other antenatal exposures) in explaining the findings.

7.5 CHAPTER SUMMARY AND CONCLUSIONS In studies on all cancers (combined), there is limited evidence (two cohort and one case-control study) that exposure to spousal smoking may increase overall risk of cancer (including lung) in nonsmoking women. However, when cancers of the lung were excluded from the analysis, risk elevations for other cancers were not significant.

With respect to lung cancer, three large U.S. population-based studies and a smaller hospital-based case-control study have been published since the most recent comprehensive review (U.S. EPA, 1992); the three population-based studies were designed to and have successfully addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized. Results from these studies and the smaller case-con-

trol study are compatible with the causal association between ETS exposure and risk of lung cancer in nonsmokers already reported by the U.S. EPA (1992), Surgeon General (U.S. DHHS, 1986) and NRC (1986).

Although there have been only three studies on ETS exposure and nasal sinus cancers, all three studies showed a consistent association between exposure and risk, presenting strong evidence that exposure to ETS increases the risk of nasal sinus cancers in nonsmoking adults. Future studies need to characterize the magnitude of risk between nasal sinus cancer and ETS exposure and the dose-response relationship. The epidemiological and biochemical evidence suggests that exposure to ETS may increase the risk of cervical cancer in nonsmokers. On the other hand, although the biochemical data suggest that ETS is a plausible carcinogen for bladder cancer in nonsmokers, the limited epidemiologic data are not supportive of an association. There is insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and adult cancers of the bladder, breast, stomach, or brain at this time.

In children, the evidence is unclear as to whether paternal smoking increases the risk for all childhood cancers, and specifically acute lymphoblastic leukemia and brain tumors, the two leading cancer sites in children (Li, 1982). The uncertainty about the association between ETS exposure and increased risks in these two tumor sites is due largely to the conflicting results reported and the limitations of the studies finding no association. On the other hand, the association between ETS exposure and other childhood tumors is difficult to study because of the limited number of subjects with the specific cancers in most studies.

Despite the uncertainty in epidemiological data on childhood cancers and ETS exposure, an ETS effect on risk of childhood cancer is a concern due to both transplacental and passive smoke exposure. Studies to date were not designed to distinguish between transplacental exposure (*i.e.*, mother's smoking during pregnancy), prenatal ETS exposure (*i.e.*, father's smoking during pregnancy), and postnatal ETS exposure (*i.e.*, mother's and father's smoking after birth and any other relevant sources of ETS exposure). In fact, most studies only had information on mother's smoking during pregnancy, or mother and father's smoking during pregnancy. However, even if the data were available, it would be a challenge to separate the long-term effects of *in utero* exposure to maternal smoking, and the effects of prenatal and postnatal ETS exposure on the risk of cancer in children. This is because maternal and paternal smoking behavior during pregnancy and after delivery are closely linked. In any case, a transplacental effect or an ETS effect is biologically plausible. The demonstration of a 4-fold higher mean level of carcinogen-hemoglobin adducts in fetuses of smoking mothers as compared to fetuses of nonsmoking mothers, and the approximately 60 percent higher hemoglobin adduct levels in nonsmoking mothers with high levels of ETS exposure compared to those with low exposure, suggest that *in utero* exposure may be more concentrated (Coghlin *et al.*, 1991; Hammond *et al.*, 1993) (see Section 7.1.2; Table 7.2).

The concentrated transplacental exposure, in conjunction with passive smoke exposure prenatally and postnatally, may predispose the child to increased risk of various cancers.

To summarize, ETS exposure is causally associated with cancers of the lung and nasal sinus; the evidence is suggestive of a causal association between ETS exposure and cervical cancer. The relationship between ETS exposure and leukemia, childhood brain cancer, and breast cancer is less clear, and although some studies are indicative of a causal association, the overall evidence is inadequate for forming firm conclusions. Finally, there is currently insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and cancers of the bladder, stomach, hematopoietic system, and lymphatic system.

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Cardiovascular Health Effects

8.0 INTRODUCTION In this chapter, epidemiologic studies and other human data regarding the relationship between coronary heart disease (CHD) and exposure to environmental tobacco smoke (ETS) by nonsmokers are reviewed, and the overall weight of evidence for an association is presented. In addition to the human evidence, there is confirmatory animal evidence (*e.g.*, Glantz and Parmley, 1991 and 1995) which is summarized briefly.

CHD includes a spectrum of clinical manifestations, the major forms of which are myocardial infarction (MI), angina pectoris (AP), and sudden unexpected death (SUD) which occurs in persons with no prior history of CHD. Etiology for the various heart-disease endpoints and their occurrence have been examined in detail (U.S. DHHS, 1983 and 1990; Kannel, 1976). Different terms have been used to represent CHD in the literature, including ischemic heart disease (IHD), and arteriosclerotic heart disease (AHD). For uniformity, CHD will be used throughout this chapter. Results by specific endpoints (*i.e.*, MI, SUD, or AP) or for cardiovascular mortality versus morbidity will be presented separately when such data are available.

8.0.1 Active Smoking A causal association between active smoking and CHD is well established (U.S. DHHS, 1983 and 1990). Evidence from case-control and cohort studies has clearly revealed a higher risk of MI, SUD, and other deaths from CHD in cigarette smokers than in nonsmokers. Although smoking clearly provokes AP (Friedman *et al.*, 1975) and risks of AP are elevated in smokers compared to nonsmokers in some studies (Willett *et al.*, 1987; Beard *et al.*, 1989; Hagman *et al.*, 1987), the association has not been observed consistently, and the association with smoking tends to be weaker for AP than for other heart disease endpoints (Kannel, 1976 and 1981). The excess risk of CHD morbidity and mortality in relation to smoking extends to all age groups, to both genders, and to populations within and outside the U.S. The data are generally supportive of a dose-response relationship in that the risks increase with increasing duration of smoking, increasing number of cigarettes smoked, and with increasing depth of inhalation.

8.0.2 Previous Reviews on Environmental Tobacco Smoke and Coronary Heart Disease in Nonsmokers Since 1984, some 18 studies have examined the association between environmental tobacco smoke (ETS) and risk of CHD in nonsmokers. In 1986, this literature was first reviewed qualitatively in *A Report of the Surgeon General* (U.S. DHHS, 1986) and a report from the National Research Council (NRC, 1986). Available for the 1986 reviews were data from three cohort studies (Hirayama, 1984; Gillis *et al.*, 1984; Garland *et al.*, 1985) and one case-control study (Lee *et al.*, 1986). Both 1986 reviews concluded that an association between ETS and CHD was biologically plausible but the epidemiological evidence was inconclusive. A 1990 review (Wu-Williams and

Samet, 1990) included results from two additional cohort studies (Svendsen *et al.*, 1987; Helsing *et al.*, 1988). These authors concluded that in all "prospective studies, there was an excess of heart disease mortality among nonsmokers with ETS exposure although the exposure-response relationship is not clear."

In addition, five more quantitative reviews have been published: Wells (1988); Glantz and Parmley (1991); Steenland (1992); Wells (1994); Glantz and Parmley (1995). Four of these reviews included a meta-analysis to calculate a pooled relative risk for CHD in relation to ETS exposure (Wells, 1988; Glantz and Parmley, 1991; Wells, 1994; Glantz and Parmley, 1995). The 1988 review by Wells included five cohort studies (Hirayama, 1984; Gillis *et al.*, 1984; Garland *et al.*, 1985; Svendsen *et al.*, 1987; Helsing *et al.*, 1988) and two case-control studies (Lee *et al.*, 1986; Martin *et al.*, 1986 (unpublished)). Based on 1,522 CHD events in females and 443 CHD events in males, Wells (1988) calculated that the odds ratio (OR) for CHD in relation to ETS exposure was 1.23 (95% CI = 1.1-1.4) for females and 1.31 (95% CI = 1.1-1.6) for males.

The subsequent review by Glantz and Parmley (1991a) summarized results from ten studies; four were new studies published between 1989 and 1990, which were not covered in previous reviews (He *et al.*, 1989; Hole *et al.*, 1989; Humble *et al.*, 1990; Butler, 1988). These authors presented results from the individual studies separately for males and females and calculated a significantly elevated pooled risk estimate for males (relative risk (RR) = 1.3, 95% CI = 1.1-1.6), for females (RR = 1.3, 95% CI = 1.2-1.4), and for both genders combined (RR = 1.3, 95% CI = 1.2-1.4). This review also discussed possible mechanisms for an ETS effect on heart disease in nonsmokers. An updated review of this subject was published by the same authors in 1995 (Glantz and Parmley, 1995).

Wells' 1994 review included results from 13 studies; eight of these studies were not included in his 1988 review (Hole *et al.*, 1989; Humble *et al.*, 1990; Butler, 1988; Dobson *et al.*, 1991a; He *et al.*, 1994; La Vecchia *et al.*, 1993; Jackson, 1989; Sandler *et al.*, 1989 (this covered the same study as Helsing *et al.*, 1988)). Pooled risk estimates for CHD morbidity and mortality in relation to ETS exposure were presented for males and females both separately and combined. Risk estimates were presented with and without correction for misclassification bias of smokers as nonsmokers. In women the OR was 1.51 (95% CI = 1.2-2.0) for CHD morbidity and 1.23 (95% CI = 1.11-1.36) for CHD mortality in association with ETS exposure. The corresponding ORs in men were 1.28 (95% CI = 0.91-1.81) and 1.25 (95% CI = 1.03-1.51). The ORs for CHD morbidity and mortality in women and men were almost unchanged after correction for misclassification bias.

Also included in some of these reviews were estimates of the number of CHD deaths in nonsmokers that could be attributed to ETS exposure (Wells, 1988; Steenland, 1992; Wells, 1994). Steenland's review (1992)[1] covered

[1] Steenland's review included a 1991 study (Dobson *et al.*, 1991); excluded the abstract by Butler (1988); and did not cite Gillis *et al.* (1984), who presented preliminary findings on the same study population covered by Hole *et al.* (1989).

essentially the same studies as the review by Glantz and Parmley (1991a), and in addition, estimated the number of CHD deaths in nonsmokers and former smokers that could be attributable to ETS. Steenland concluded that some 28,000 deaths in U.S. never-smokers and 19,500 deaths in U.S. former smokers (who had stopped smoking at least 15 years before the study) could be attributed to ETS exposure. To conduct this analysis, Steenland applied the age- and sex-specific CHD rates for U.S. never-smokers estimated from cohort studies conducted in the 1970s and 1980s; the prevalence of exposure to ETS among nonsmoker controls reported in case-control studies conducted during the same time period; and the relative risk of CHD in nonsmokers associated with ETS exposure from the study by Helsing *et al.* (1988), the largest U.S. study on ETS and risk of CHD in nonsmokers. These results are very similar to those presented by Wells (1988, 1989, 1990) who used somewhat different methods and assumptions in his calculations. In another study, Wells (1994) estimated that 62,000 deaths from ischemic heart disease in the U.S. in 1985 were due to ETS exposure. One possible reason for the considerably higher estimate in the 1994 review is the higher CHD death rates in 1985, both overall and in never-smokers compared to the never-smoker death rates that were used in the earlier risk assessments. Moreover, Wells (1994) assumed that the ETS exposure from background sources (*i.e.*, other than from spouses) was higher than that assumed in the previous reviews and applied methodology that the U.S. EPA (1992) used in estimating the lung cancer burden of ETS exposure.

The conclusions of the reviews by Glantz and Parmley (1991a) and Steenland (1992) were endorsed by the American Heart Association (Taylor and Johnson, 1992). However, critics of the review by Glantz and Parmley (Huber and Brockie, 1991; Simmons, 1991; Holcomb, 1991; Decker, 1991; Mantel, 1992) questioned the reviewers' interpretation of the epidemiological data and the meaningfulness of relative risk estimates that were less than 3.0. They also questioned the authors' method of deriving the pooled risk estimate, and the inclusion of "positive" findings that were not statistically significant. The critics attributed the observed association between ETS and heart disease to biases, including inadequate adjustment or lack of adjustment for potential confounders in some studies. Glantz and Parmley (1991b, 1991c, 1992) discounted these criticisms in their responses. A second line of criticism questioned the fundamental relationship between active smoking and CHD in women (Seltzer, 1991a & b) and whether the magnitude of effect observed between CHD and passive smoking is plausible after asserting that the association with active smoking is relatively weak (Mantel, 1992; Skrabanek, 1992).

8.0.3 Chapter Overview This chapter will include, first, a description of each of the studies on ETS and CHD in terms of the design of study, measures of exposures, information on potential confounders, and the main study findings (Section 8.1). The studies included in this review represent all the published studies on this topic that had been included in either the review by Glantz and Parmley (1991a) or by Steenland (1992), as well as five case control studies (Jackson *et al.*, 1991; He *et al.*, 1994; La Vecchia *et al.*, 1993; Layard, 1995; Muscat and Wynder, 1995), two analyses of the same cohort

data set (LeVois and Layard, 1995; Steenland *et al.*, 1996), and a recent report of a cohort analysis (Kawachi *et al.*, 1997) of the Nurses' Health Study. Second, in Section 8.2 the effect of bias on the risk estimates in these studies will be discussed. The main sources of bias are misclassification of smokers as nonsmokers, the lack of control for potential confounders, and misclassification of ETS exposure. Also in Section 8.2, the biological plausibility of an association between ETS and CHD will be discussed by comparing this link to the association between active smoking and CHD. Finally, in Section 8.3 supportive data, primarily the acute effects of ETS on cardiovascular function in nonsmokers will be presented. These include a discussion of the effects of ETS exposure on internal and common carotid wall thickness, endothelium function, exercise tolerance, lipid profile, platelet function, and fibrogen levels.

8.1 DESCRIPTION OF EPIDEMIOLOGIC STUDIES

The relationship between ETS and CHD in nonsmokers has been examined in ten cohort and eight case-control studies (summarized in Table 8.1). Eight of the cohort studies were conducted in the United States, one in Japan, and one in Scotland. The case-control studies were conducted in the United Kingdom, China, Australia, New Zealand, Italy, and the United States.

8.1.1 Cohort studies

Japanese cohort study (Hirayama, 1981, 1984, 1990)

In the Japanese cohort study (Hirayama, 1984), adults at least 40 years of age who were residents in one of 29 health-center districts in Japan were enrolled in 1965. About 90 percent of the targeted population participated in the study and completed a questionnaire on various lifestyle factors including smoking habits, drinking habits, and occupational history. Mortality of the cohort was monitored by review of the annual census of residents and death certificates. The relationship between CHD mortality and ETS was evaluated in cohort subjects followed between 1966 and 1981.

There were 494 deaths from CHD identified among 91,540 lifetime non-smoking women. Compared to nonsmoking women married to nonsmokers, women married to ex-smokers or smokers of 1-19 cigarettes/day, and to smokers of 20+ cigarettes/day, showed relative risks of 1.10 (90% CI = 0.91-1.33), and 1.31 (90% CI = 1.06-1.63), respectively for CHD (one-sided p for trend = 0.019—Hirayama, 1984). The increase in relative risk of CHD in relation to husband's smoking was observed when the analysis was adjusted for husband's age (40-49, 50-59, 60-69, 70+) and occupation (Table 8.1). A later update (Hirayama, 1990) showed that similar results were observed when adjustment was made for wife's age. Despite the strengths of a large sample size of nonsmoking women and of CHD deaths in this cohort, the study's value is lessened by the lack of information on potential confounders of CHD, which made it impossible to adjust for other heart disease risk factors in the analysis.

Lee (1990a) questioned the results of this study because the analysis based on 14 years of follow-up data (*i.e.*, from 1966-1979) did not yield a statistically significant association, whereas the results based on 16 years of follow-up data (*i.e.*, with an additional 94 CHD deaths between 1980-1981)

Table 8.1
Cohort Studies on ETS Exposure and Heart Disease

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results: Population at Risk	Results: # Events	Results: Relative Risks (95% CI)	Comments
Japan (Hirayama, 1984)	91,540 nonsmoking women.	Husband's smoking habits:				RRs adjusted for husband's age and occupation.
	study conducted in 1966-1981	nonsmoker	21,895	118	1.0	
		ex-smoker or smoked				
	subjects followed for 16 years	1-19 cig/day	44,184	240	1.0 (0.9-1.3)	
		20+ cig/day	25,461	136	1.3 (1.1-1.6)	
	494 coronary heart disease (CHD) deaths					
San Diego (Garland *et al.*, 1985)	695 currently married nonsmoking women.	Husband's smoking habits:				RRs adjusted for age only—95% CI not available.
		never-smoker	203	2	1.0	
	study conducted in 1972-1974	ex-smoker	395	15	3.0	
		current smoker	97	2	2.3	The RR adjusted for age, systolic blood pressure, total plasma cholesterol, obesity, and years of marriage was 2.7 for husbands who were ex- or current smokers compared to husbands who did not smoke.
	subjects followed for 10 years					
	19 CHD deaths					

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results: Person Years	Results: # Events (CHD deaths)	Results: Relative Risks (95% CI)	Comments
Loma Linda, California (Butler, 1988)	Spouse Pair Cohort	Spouse Pair Cohort				Spouse Pair Cohort
	9,785 nonsmoking Seventh-Day Adventists	Husband's smoking:				RRs adjusted for age
		Never	43,053	60	1.00	
		Past	8,092	16	0.96 (0.6-1.7)	
		Current	2,487	4	1.40 (0.5-3.8)	
	followed between 1976 and 1982	AHSMOG Cohort				
						AHSMOG Cohort
	87 CHD deaths in nonsmoking women	Females				
		Lived with a smoker:				RRs adjusted for age
		0	12,826	33	1.00	
	AHSMOG Cohort	1-10 yrs	3,301	9	1.46 (0.7-3.1)	
		11 + yrs	8,215	28	1.53 (0.9-2.5)	
	2,345 males and 4,122 females of whom 1,489 males and 3,488 never smoked	Worked with a smoker:				
		0				
		1-10 yrs	13,870	44	1.0	
		11 + yrs	5,802	13	1.85 (1.0-3.4)	
			4,670	13	1.86 (1.0-3.5)	
	followed between 1976 and 1982	Males				
		Lived with a smoker:				
		0	8,725	62	1.00	
	70 female deaths and 76 male deaths from CHD in never-smokers	1-10 yrs	1,729	3	0.41 (0.1-1.3)	
		11 + yrs	3,126	10	0.61 (0.3-1.2)	
		Worked with a smoker:				
		0	7,999	53	1.00	
		1-10 yrs	3,160	13	1.26 (0.7-2.3)	
		11 + yrs	2,420	9	0.76 (0.4-1.6)	

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results: Population at Risk	Results: # Events	Results: Relative Risks (95% CI)	Comments
18 Cities in the United States (Svendsen, 1987)	1,245 never smoking married men	Wives smoking habits:	(CHD deaths)			RRs presented are adjusted for age, baseline blood pressure, cholesterol, weight, drinks/wk and education.
		never-smoker	959	8	1.0	
		smoker	286	5	2.23 (0.7-6.9)	
	study conducted in 1973		(Fatal and nonfatal CHD)			
		never-smoker	959	48	1.0	
	subjects followed for 7 years, until 1982	smoker	286	21	1.61 (1.0-2.7)	
		Coworkers smoked:	(For CHD deaths)			RRs on coworkers' smoking were adjusted for age and wives' smoking status.
	endpoints included CHD, fatal, and nonfatal events	No	NA	NA	1.0	
		Yes	NA	NA	2.6 (0.5-12.7)	
		Coworkers smoked:	(Fatal and nonfatal CHD)			
		No	NA	NA	1.0	
		Yes	NA	NA	1.4 (0.8-2.5)	

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results: Population at Risk	Results: # Events	Results: Relative Risks (95% CI)	Comments
Washington County, Maryland (Helsing, 1988)	3,454 white men and 12,348 white women who never smoked	Household passive smoking score:				RR adjusted for age, housing quality, schooling, marital status.
		Males:				
		0	2,434	248	1.0	
	study conducted in 1963	1+	1,020	122	1.31 (1.1-1.6)	
		1-5	459	56	1.38 (1.1-1.8)	
		6-12	561	66	1.25 (1.0-1.6)	
	subjects followed through mid-1975	Females:				
		0	4,259	437	1.0	
		1+	8,086	551	1.24 (1.1-1.4)	
	370 CHD deaths in men and 988 CHD deaths in women	1-5	3,412	252	1.20 (1.0-1.4)	
		6-12	4,674	299	1.27 (1.1-1.5)	

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results: Population at Risk	Results: # Events	Results: Relative Risks (95% CI)	Comments
Western Scotland (Hole, 1989)	15,399 residents aged 45-64, completed self-administered questionnaire between 1972 and 1976	Males and females:	Angina			RRs adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol body mass index.
		never-smoker	917	43	1.00	
		passive smoker	1,538	74	1.11 (0.7-1.7)	
	followed for an average of 11.5 years	Males and females:	IHD deaths			
		never-smoker	917	30	1.00	
		passive smoker	1,538	54	2.01 (1.2-3.4)	
	917 never-smokers, 1,538 passive smokers					
	endpoints: heart disease symptoms including angina, and ischemic heart disease (IHD) death					

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results: Population at Risk	Results: # Events	Results: Relative Risks (95% CI)	Comments
Evans County, Georgia (Humble, 1990)	1,127 women, 943 were nonsmokers, 513 were married to never or current smokers	Husband smoker vs. nonsmoker				Women whose husbands were ex-smokers were excluded.
		All subjects	513	76	1.59 (1.0-2.6)	
		Blacks	185	NA	1.78 (0.9-3.7)	Baseline comparison group was women whose husbands never smoked.
	study conducted in 1960-1961	Whites (by social class): high	161	NA	1.97 (0.7-5.3)	
		low	167	NA	0.79 (0.3-2.0)	
	subjects followed for 20 years					RRs adjusted for age, blood pressure, cholesterol, and body mass.
	endpoints included cardiovascular disease death (CVD), smoking related CVD, and all causes					

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Males OR	Males 95% CI	Females OR	Females 95% CI	Comments
United States (Le Vois and Layard, 1995)	CPS-I						ORs presented were adjusted for age and race. Further adjustment for weight, exercise, education, dietary factors, history of hypertension and diabetes did not have any appreciable effect on risks. These ORs were not presented.
		Exposed to:					
	Total of 88,458 male and 247,412 female never-smokers	Any smoking spouse	0.97	0.90-1.05	1.08?	0.98-1.08	
		Former smoker	0.95	0.83-1.09	0.99	0.93-1.06	
		#cigarettes/day					
	CHD deaths:	1-19	0.99	0.89-1.09	1.04	0.97-1.12	
	7,768 in males	20-39	0.98	0.85-1.18	1.06	0.98-1.16	
	7,133 in females	40+	0.96	0.78-1.15	0.96	0.78-1.15	
	CPS-II	Exposed to:					Follow-up period during which these CHD deaths were observed was not described.
		Any smoking spouse	0.97	0.87-1.08	1.00	0.88-1.14	
	108,772 male and 226,067 female never-smokers; smoking status of spouses was known	Former smoker	0.81	0.70-0.98	0.99	0.86-1.13	
		#cigarettes/day					
		1-19	1.36	1.10-1.68	1.14	0.86-1.51	OR's were adjusted for age and race.
		20-39	1.28	1.00-1.58	0.98	0.75-1.29	
		40+	1.13	0.81-2.11	1.27	0.80-2.01	
	CHD deaths: 1,966 in males 1,099 in females						*These analyses utilize the same datasets analyzed by Steenland et al. (1996) (see next page).*

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Males OR	Males 95% CI	Females OR	Females 95% CI	Comments
United States (Steenland *et al.*, 1996)	Analysis 1	Exposed to:					These ORs were adjusted for age, self-reported history of heart disease, hypertension, diabetes, arthritis, body mass index, educational level, aspirin use, diuretic use, liquor consumption (in men), wine intake (in women), employment status, exercise, and estrogen use (in women).
	Spousal cohort of 101,227 male and 208,372 female never-smokers	Current smoker	1.22	1.07-1.40	1.10	0.96-1.27	
		Cigarettes/day					
		<20	1.33	1.09-1.61	1.15	0.90-1.45	
		20	1.17	0.92-1.48	1.07	0.90-1.28	
		21-39	1.09*	0.77-1.63	0.99	0.87-1.47	
		40+			1.04	0.88-1.13	
	CHD deaths: 2,494 men 1,325 women	Former smoker	0.96	0.83-1.11	1.00	0.88-1.13	
	Analysis 2	Exposed to:					
	Spousal subcohort with single marriage and data on amount and duration of exposure to smoking during marriage	Current smoker	1.48	1.21-1.80	1.18	0.91-1.46	
		Former smoker	0.97	0.79-1.20	1.08	0.90-1.29	
		Years exposed to cigarette smoke					
		1-12	1.14	0.80-1.63	0.84	0.59-1.20	*These analyses utilize the same datasets analyzed by LeVois and Layard (1995) (see preceding page)*
		13-21	1.13	0.80-1.69	0.99	0.73-1.39	
		22-29	1.14	0.84-1.56	1.20	0.91-1.59	
	58,530 male and 99,821 female never-smokers	30+	1.25	1.01-1.53	1.20	0.96-1.46	
	CHD deaths: 1,299 men 572 women						

* *For those whose spouses smoke >21 cigarettes per day.*

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Males OR	Males 95% CI	Females OR	Females 95% CI	Comments
United States (Steenland *et al.*, 1996) (Continued)	Analysis 3	Exposed currently	1.23	1.03-1.47	1.19	0.97-1.45	In analysis 4, the number of subjects in the cohort and the number of CHD deaths applied to the analysis for exposure at work. The numbers varied somewhat for the analyses on exposure at home and elsewhere.
	Subjects concordant for both self-reported current exposure to cigarettes and exposure based on spousal report	Self-report:					
		1-2 hours/day	1.23	0.81-1.07	0.70	0.45-1.10	
		3-4 hours/day	1.35	0.95-1.90	1.21	0.85-1.74	
		>4 hours/day	1.13	0.84-1.61	1.28	1.10-1.62	
		Smoking reported by spouse:					
	54,668 male and 80,549 female never-smokers[?]	cigarettes/day					
		<20	1.37	1.04-1.79	1.22	0.88-1.72	
		20	1.15	0.86-1.53	1.14	0.83-1.67	
		21-39	1.12*	0.77-1.83	1.02	0.66-1.60	
	CHD deaths: 1,180 men, 426 women	40+			1.28	0.81-2.01	
	Analysis 4						
	Restricted to those currently employed	Exposed at home	1.15	1.01-1.32	1.07	0.96-1.17	
		Exposed at work	1.03	0.89-1.19	1.06	0.84-1.34	
		Exposed elsewhere	1.03	0.93-1.13	0.91	0.83-1.00	
	76,710 male and 75,237 female never-smokers						
	CHD deaths: 1,751 men 768 women						

* *For those whose spouses smoke >21 cigarettes per day.*

Table 8.1 (Continued)

Geographical Area (Reference)	Cohort-Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Females OR	Females 95% CI	Comments
United States Nurses' Health Study (Kawachi *et al.*, 1997)	121,700 nurses aged 30-55 years enrolled in 1976	Exposure to ETS			All ORs were adjusted for alcohol use, body mass index, history of hypertension, diabetes, hypercholesterolemia, menopausal status, use of hormones, physical activity, intake of Vitamin E and fat, use of aspirin, and family history.
		at home or at work:	Total CHD		
		never	1.00		
		any	1.71	(1.03-2.84)	
	Questions on ETS exposure asked in a follow-up questionnaire in 1982	occasional	1.58	(0.93-2.68)	
		regular	1.81	(1.11-3.28)	
			Nonfatal MI		
		never	1.00		
	32,046 women were never-smokers	any	1.73	(0.99-3.03)	
		occasional	1.64	(0.92-2.93)	
		regular	1.86	(1.04-3.42)	
	follow-up between 1982 and 1992		Fatal CHD		
		never	1.00		
	152 incident CHD (127 nonfatal MI, 25 fatal CHD)	any	1.87	(0.56-8.20)	
		occasional	1.50	(0.42-5.36)	
		regular	2.55	(0.71-9.12)	
		By years of living with smoker in adult life:	Total CHD		
		<1	1.00		
		1-9	1.19	(0.75-1.90)	
		10-19	1.54	(0.99-2.40)	
		20-29	1.11	(0.89-1.77)	
		30+	1.50	(0.97-2.32)	

were statistically significant. This criticism is ill-founded since the results based on 14 years of follow-up (and 410 CHD deaths) showed the same pattern of increased risks—the RRs were 1.05 (90% CI = 0.86-1.29), and 1.21 (90% CI = 0.95-1.53) when husbands were ex-smokers or smoked 1-19 cigarettes/day, and when they smoked 20+ cigarettes/day, respectively, compared to husbands who did not smoke (Hirayama, 1990). However, what is unclear and warrants explanation is the discrepancy in the results based on 14 years of follow-up in Hirayama's first report (1981) and his second report (Hirayama, 1984). In the 1981 report, Hirayama found RRs of 0.97 when husbands were ex-smokers or smoked 1-19 cigarettes/day and 1.03 for 20+ cigarettes/day ($p = 0.39$) (based on 406 CHD deaths).

San Diego study (Garland et al., 1985) A second report on the role of ETS and heart disease utilized data collected in a cohort of predominantly white, upper middle-class subjects in San Diego (Garland *et al.*, 1985). This cohort was established between 1972 and 1974 and successfully enrolled 82 percent of the subjects contacted. A standardized interview was administered and covered cigarette use; past hospitalizations for heart attack, heart failure, or stroke; and duration of marriage. Questions on smoking included smoking status at enrollment (current, former, or never) and among current smokers, the number of cigarettes smoked per day. In addition, blood pressure, weight, height, and plasma cholesterol were measured at study enrollment.

The analysis on ETS and heart disease was based on 695 married nonsmoking women, classified by their husbands' self-reported smoking status at enrollment; it excluded women who had a history of heart disease or stroke and women who had smoked. Vital status of the cohort was determined by annual mailings for 10 years. Follow-up was almost complete and death certificates were obtained for all deaths. After 10 years of follow-up, there were 19 deaths due to CHD (International Classification of Diseases, Adapted (ICDA) 410.0-414.9) among nonsmoking married women. The age-adjusted mortality rates were 1.2, 3.6, and 2.7, respectively, for women married to nonsmokers, ex-smokers, and current smokers (one-sided p for trend, ≤ 0.10). The corresponding RRs for the adjusted mortality rates were 1.0, 3.0, and 2.3. The relative risk for CHD mortality among women married to current or former smokers compared to women married to never-smokers was 2.7 (p value ≤ 0.10) after adjustment for age, systolic blood pressure, total plasma cholesterol, obesity index, and years of marriage (Table 8.1).

Most of the information on CHD risk in this study was based on nonsmoking women married to ex-smokers at study enrollment. A possible explanation for the higher risk among nonsmoking women married to former smokers than to current smokers is that this group of husbands had been very heavy smokers and had stopped smoking for health reasons. Thus, wives of these former smokers may have been heavily exposed. The findings in relation to "any ETS exposure" are only suggestive, given the small numbers of CHD deaths and the fact that the analysis was conducted by husbands' smoking status and not amount smoked by husbands.

MRFIT - 18 cities study (Svendsen et al., 1987) The role of ETS and risk of heart disease was evaluated in a cohort of men aged 35-57 years who were recruited in 18 U.S. cities beginning in 1973 for the Multiple Risk Factor Intervention Trial (MRFIT) (Svendsen *et al.*, 1987). At enrollment, extensive information was collected, including smoking history of the index subjects and of their wives, family members, and coworkers. In addition, markers of exposure to tobacco smoke, including serum thiocyanate and expired air carbon monoxide were measured, and pulmonary function tests were conducted. Pulmonary function tests and measurements of thiocyanate were conducted at entry into the study (baseline) and at each of six annual examinations, whereas expired carbon monoxide was measured at baseline, and at the third and sixth examination.

Cause of death was classified by a committee of three cardiologists who reviewed the hospital/physician records, death certificates, autopsy reports, and next-of-kin interviews. Subjects were followed an average of 7 years and the effect of ETS was investigated for CHD death (including documented MI, SUD, congestive heart failure, and death associated with surgery for CHD) and fatal or nonfatal CHD events combined.

Analyses were conducted for all never-smokers and nonsmokers (*i.e.*, ever-smokers who stopped prior to entry into the study) at entry. Of the 12,866 men, there were 1,245 married men who never smoked, of whom 286 were married to smokers and 959 to nonsmokers. Among men who never smoked, there were 13 deaths due to CHD and 56 nonfatal CHD events (Table 8.1). Compared to men married to nonsmokers, men married to smokers showed a higher risk of death from CHD (adjusted RR = 2.23, 95% CI = 0.72-6.92) and for fatal and nonfatal CHD combined (adjusted RR = 1.61, 95% CI = 0.96-2.71) after adjusting for other risk factors for heart disease (age, blood pressure, cholesterol, weight, drinks per week, and education). The adjusted relative risks were slightly higher than the unadjusted values.

The effect of ETS exposure from wives' smoking was also evaluated among all nonsmoking men. Both men who never smoked and those who stopped smoking prior to entry into the study were included (numbers of subjects and number of CHD events in the latter group were not specified). Nonsmoking men whose wives smoked showed a higher risk of death from CHD (adjusted RR = 1.59, 95% CI = 0.84-3.02) and a higher risk of fatal and nonfatal CHD combined (adjusted RR = 1.32, 95% CI = 0.95-1.84) as compared to men whose wives did not smoke. However, these risk estimates are lower than those presented above for men who never smoked, suggesting that the effect due to ETS exposure may have been diluted substantially by including ex-smokers in the analysis.

In the same study, there is a suggestion of an ETS effect from coworkers' smoking after adjusting for age and wives' smoking habits (these RRs were presumably not adjusted for other CHD risk factors). The adjusted RR was 2.6 (95% CI = 0.5-12.7) for CHD death and 1.4 (95% CI = 0.8-2.5) for fatal or nonfatal CHD combined for men who never smoked but were exposed to coworkers' smoking. The joint effect of ETS exposure from wives and

coworkers was also evaluated. Relative to men whose wives and coworkers did not smoke, the RRs for fatal and nonfatal CHD combined were 1.0 (95% CI = 0.5-1.9) when coworkers smoked but wives did not, 1.2 (95% CI = 0.4-3.7) when wives smoked and coworkers did not, and 1.7 (95% CI = 0.8-3.6) when both smoked.

This study has several strengths. First, misclassification of active smokers as nonsmokers is minimized since there were baseline and regular measurements of various biomarkers to assess long-term (based on thiocyanate) and short-term (based on carbon monoxide) exposure to tobacco smoke. In this study, nonsmoking men married to smokers had significantly higher levels of expired air carbon monoxide, significantly lower levels of maximum FEV_1, and thiocyanate levels comparable to those of nonsmoking men married to nonsmokers. Although thiocyanate is not specific to ETS exposure and is not considered a sensitive marker for exposure to ETS, serum thiocyanate levels have been used successfully to distinguish between active smokers and nonsmokers (U.S. DHHS, 1986). Second, ETS exposure was based on both wives' and coworkers' smoking habits at baseline, thus covering the main sources of domestic and non-domestic exposure. Third, information on potential confounders for CHD was available. At entry into the study, nonsmoking men married to smokers were similar to those married to nonsmokers in age, diastolic or systolic blood pressure, total, high and low density lipoprotein cholesterol, and income, but differed significantly in weight (heavier), drinking habits (drank more), and education (fewer years). However, the differences in weight and drinking habits between the two groups did not persist by the sixth annual examination. The effect of ETS was observed when potential confounders for heart disease, education, and measures of social class were accounted for in the analysis. Finally, this study examined the effect of ETS on both fatal and non-fatal CHD events. Point estimate of risks were higher for fatal events than for fatal and nonfatal events combined, suggesting that the association between ETS exposure and nonfatal events may be relatively weak (adjusted RRs were not presented separately for nonfatal events).

The main limitation of this study is that this study population may be unrepresentative of the general population. Men selected in the MRFIT study were already at high risk for heart disease, defined by their levels of serum cholesterol and diastolic blood pressure.

Maryland study (Helsing et al., 1988) The role of ETS in the etiology of heart disease mortality in men and women was investigated by Helsing *et al.* (1988), who utilized data from a private census conducted in 1963 covering some 98 percent of the households in Washington County, Maryland. The subcohort for this analysis comprised of 3,454 males and 12,345 females who never smoked and were available for follow-up in 1971. These subjects were followed between 1963 and 1975, and the risk of heart disease mortality was evaluated relative to their household exposure to ETS. CHD listed as an underlying or contributing cause of death was included as a heart disease mortality outcome.

Information on sex, age, race, marital status, years of schooling, and housing characteristics were available and were adjusted for in the analyses. Use of any tobacco products, including cigarettes, cigars, and pipes was recorded for all subjects and their household members. In brief, a score ranging from 0 to 12 was assigned to each adult in the household based on his/her smoking history. A total household smoking score was then calculated by summing the smoking contribution scores of all persons living in that household. Each individual's household ETS exposure was calculated by subtracting his or her own contribution from the total household score. Among nonsmoking men, 29.5 percent reported any household exposure to ETS compared to 65.5 percent among nonsmoking women.

In the never-smokers, there were a total of 370 deaths in men and 988 in women, for whom CHD was listed as the underlying cause of death. The adjusted relative risk for any ETS exposure was 1.31 (95% CI = 1.1-1.6) for men and 1.24 (95% CI = 1.1-1.4) for women (note: in Sandler *et al.* (1989), the RR in women was 1.19 (95% CI = 1.04-1.35); the reason for the discrepancy is not known). There was no clear dose-response trend with increasing ETS exposure in men (*i.e.*, scores of 0, 1-5, 6+), but there was some suggestion of a trend in women (Table 8.1). When data were stratified by gender and by age of study subjects at enrollment in 1963 (25-44, 45-54, 55-64, and 65+), risk for CHD in relation to ETS exposure was increased in seven of eight age-sex groups. The RRs were increased in all age groups of men exposed to ETS and were statistically significant for two subgroups. In women, increased risks were observed in all but the 55-64 age group, and the results were statistically significant for the 65+ age group. Results were similar when the analyses included all deaths with CHD listed as the underlying or contributing cause of death (*i.e.*, a total of 461 and 1,281 deaths in nonsmoking men and women, respectively).

This is one of the larger studies on ETS and heart disease in nonsmoking men and women. The larger sample size allowed analysis stratified by age group and by sex. In addition, exposure to ETS included all household exposures. Unfortunately, the effect due to spouse's smoking alone, typically used as a measure of ETS exposure in other studies, was unavailable for comparison. Data on potential confounding factors for heart disease were not collected so that the RRs were adjusted for demographic factors only.

Scottish study (Hole et al., 1989) This study was conducted to investigate the risk of cardio-respiratory symptoms and CHD mortality among residents, aged 45-64 years, in two western Scottish towns between 1972 and 1976 (preliminary results were presented by Gillis *et al.*, 1984). With about an 80 percent response rate, 15,399 residents completed a standardized self-administered questionnaire on smoking habits, other lifestyle factors, and symptoms of respiratory and cardiovascular disease. By identifying couples living in the same household, the effect of exposure to ETS was investigated in a subsample of 3,960 men and 4,037 women. Eleven percent of the males (n = 428) and 12 percent of the females (n = 489) were lifetime nonsmokers, and their cohabitants were also nonsmokers; they served as controls. Six percent of the males (n = 243) and 32 percent of the females (n = 1,295) were passive

smokers, *i.e.*, the case had never smoked but his or her cohabitant smoked. Thirty-six percent of the males (n = 1,420) and 8 percent of the females (n = 323) were active smokers or ex-smokers and had lived with a cohabitant who never smoked. Forty-seven percent of the males (n = 1,869) and 48 percent of the females (n = 1,922) were active smokers and their cohabitants also smoked. Through a national registry system, incidence of cancer and mortality was followed for 11.5 years (Hole *et al.*, 1989).

The cohort consisted of the 917 (428 men and 489 women) controls and the 1,538 passive smokers (243 men and 1,295 women). Passive smokers compared to controls did not differ in self-reported prevalence of angina (age- and sex-adjusted RR = 1.02) and the relative risk estimate was not significantly changed (RR = 1.11, 95% CI = 0.73-1.70) after adjusting for potential confounders including age, sex, social class, diastolic blood pressure, serum cholesterol, and body mass index. Controls and passive smokers also did not differ in self-reported prevalence of major abnormalities found on electrocardiogram; the age- and sex-adjusted relative risk was 1.10 which increased to 1.27 (95% CI = 0.48-3.35) after adjusting for potential confounders. The effect of passive smoking was more apparent for fatal CHD events. Passive smokers experienced a higher age- and sex-adjusted mortality rate of CHD (47.4 per 10,000) than controls (27.3 per 10,000) (crude RR = 1.74). The relative risk was statistically significant when the analysis was adjusted for the potential confounders mentioned above (RR = 2.01, 95% CI = 1.21-3.35).

Among female subjects, the relationship between ETS exposure and risk of various CHD endpoints was evaluated by intensity of ETS exposure, defined as "low" if their cohabitants smoked <15 cigarettes/day and "high" if they smoked ≥15 cigarettes/day. There was no suggestion of increasing risk of abnormalities on electrocardiogram with increasing intensity of exposure. However, the risk for angina was elevated (RR = 1.61) for those more highly exposed to ETS smoking. A trend of increasing risk with increasing level of ETS exposure was most apparent for fatal CHD events. Compared to women with no exposure, the relative risk was 2.09 for women with low ETS exposure and 4.12 for women with high ETS exposure (no confidence limits were provided).

Although history of angina and abnormalities on the electrocardiogram were based on self-reports, results were believable since the risks associated with ETS and active smoking were stronger for fatal cardiovascular events than for nonfatal events or symptoms of disease. Risk for angina (adjusted for age and sex) increased 2 percent for passive smokers, 67 percent for active smokers living with nonsmokers, and 98 percent for active smokers living with smokers, compared to controls. The corresponding increase in risk for abnormalities on the electrocardiogram was 10 percent, 40 percent and 50 percent, respectively. Compared to controls, risk of death due to CHD increased 75 percent for passive smokers, 123 percent for active smokers living with a nonsmoker, and 122 percent for active smokers living with another smoker (*i.e.*, exposed to ETS). Thus, this study demonstrates that ETS exposure may have considerable effect on risk of both cardiovascular symptoms and CHD death, with a stronger effect for fatal CHD events.

An advantage of this prospective study is that it covered the entire population of men and women aged 45-64 years in two towns. In addition, information on other risk factors for heart disease is available for adjustment in the analysis. Unlike most studies in which smoking habits of spouses were obtained from the nonsmokers under study, the cohabitees (most of whom were spouses) directly provided information regarding their smoking habits, reducing the possibility of misclassification.

Evans County, Georgia (Humble et al., 1990) The association between ETS exposure and CHD mortality was investigated among nonsmoking women living in Evans County, Georgia (Humble *et al.*, 1990). From 1960 to 1961, 92 percent of all residents aged 40-74 years in this rural county participated in a cardiovascular disease study that included complete physical examinations and an interview on demographic and medical history. At enrollment, there was a total of 1,127 women, of whom 943 (554 white, 389 black) reported they had never smoked. The analysis on ETS was restricted to 513 women (328 white, 185 black) who were married to never-smokers or current smokers at baseline. The authors excluded nonsmoking women married to ex-smokers in the analysis on the basis that there may be more misclassification of the smoking habits of index subjects and their husbands if they were ex-smokers. Vital status was determined on May 1, 1980. All mortality due to circulatory diseases (including strokes—codes 390-456, ICD 8th Revision) listed as an underlying cause of death on the death certificates were considered in this analysis.

Results on ETS exposure were presented for all subjects combined, and separately by race and social class. The social class index was based on the occupation, education, and income of the head of household, applicable for rural settings. Nonsmoking women married to current smokers showed higher risks for all CHD mortality than women married to never-smokers. For all subjects combined, the age-adjusted relative risk for all CHD mortality was 1.34. A higher relative risk value was obtained after adjusting for potential confounders including age, diastolic blood pressure, total serum cholesterol, and body mass index (RR = 1.59, 95% CI = 0.99-2.57). The increased risk was observed for all black women (adjusted RR = 1.78, 95% CI = 0.86-3.71) and for white women of high social class (adjusted RR = 1.97, 95% CI = 0.72-5.34), but not for white women of low social class (adjusted RR = 0.79, 95% CI = 0.32-1.96).

There are no obvious explanations for the inconsistent finding between white women of different social classes. However, the numbers of CHD deaths by race and social class were not presented. Subgroup analysis based on small numbers may have produced unstable risk estimates. The authors stated that results were similar for all CHD and for smoking-related CHD, without describing which diseases included under all CHD would be excluded under smoking-related CHD.

This study presented data on subjects' smoking habits both at enrollment and at a later time, providing an assessment of the stability of smoking habits in index subjects as well as in their spouses. Comparison of subjects' smoking status in 1960 and 1967 showed that 98 percent of non-

smoking women again reported that they never smoked in 1967. Similarly, an equal percentage of never smoking husbands maintained their nonsmoking status in 1967, while 25 percent of husbands who smoked in 1960 described themselves as nonsmokers in 1967. This suggests that some husbands who were ex-smokers at baseline might have reported themselves to be lifetime nonsmokers. Although no details were provided regarding how the questions were asked, they are presumed to have been asked in the same way in 1960 and in 1967. These results suggest it is not likely that an index subject or spouse who was a nonsmoker at baseline became a smoker whereas some smokers at baseline would be expected to have stopped smoking over time.

California Seventh Day Adventists (Butler, 1988 [unpublished dissertation]) A large cohort study of Seventh-Day Adventists (SDAs) in California was initiated in 1974 and was designed to investigate the association of lifestyle and nutritional factors with morbidity and mortality. A basic demographic questionnaire containing a question on smoking status was sent to all registered Adventist households with a 58 percent response rate. To examine the role of ETS exposure in this population, two analyses were conducted. One analysis was based on some 11,000 married couples (referred to as the spouse pairs cohort). A second analysis involved 6,467 subjects (referred to as the AHSMOG cohort) who were participants in an air pollution study.

The cohort was followed between 1976 and 1982 for cancer incidence and mortality. Incidence of cancer was based on responses to a questionnaire which was sent annually to all cohort subjects and asked about hospitalizations in the past year. Medical records relating to reported hospitalizations were then reviewed. Mortality rates were determined via linkage with the California Death Files and National Death Index Systems, and reviewing all deaths entered in church records. Death certificates were obtained on all reported fatalities, and information on underlying and contributing causes of death was abstracted.

The definition of ETS exposure differed for the spouse pair cohort and for the AHSMOG cohort. In the spouse pair cohort, ETS exposure was based on the husbands' smoking status at the time of marriage. However, this measure of ETS exposure was crude since subjects were not asked specifically when they started or stopped smoking. A married woman was classified as not exposed if her spouse was a never-smoker or if the spouse's age at marriage equaled or was greater than his age of baptism. This is based on the assumption that the age of baptism was the latest age at which a baptized SDA adult stopped smoking since smoking is a church proscription. On the other hand, a married woman was classified as exposed to ETS if her spouse was a current smoker, or if her spouse was an ex-smoker who was not a baptized SDA, or if the spouse's age of baptism was greater than his age at marriage. In the AHSMOG cohort, specific questions were asked about ETS exposure including the number of years a subject lived or worked with a smoker.

In the spouse pair cohort, there were a total of 9,785 nonsmoking women; of these, 7,246 were married to nonsmokers and 2,309 to smokers

(in 230 subjects, the smoking status of the husband was not known). Based on 87 CHD deaths in nonsmoking women, those married to ex-smokers did not show any elevation in risk (age adjusted RR = 0.96, 95% CI = 0.66-1.66) compared to nonsmoking women married to nonsmokers. However, there was some suggestion of an increased risk for nonsmoking women married to smokers (age adjusted RR = 1.40, 95% CI = 0.51-3.84). The increased risk observed among nonsmokers married to current smokers was based on only four CHD deaths. It is presumed that current exposure in this context means that the spouse was a current smoker and not a past smoker.

In the AHSMOG cohort, there were a total of 70 female deaths and 76 male deaths from CHD occurring among never-smokers during the period of follow-up. Living with a smoking spouse was not associated with an increased risk of CHD in men, but was associated with an increased risk of CHD in women. Compared to women who did not live with a smoker, those who lived with a smoker for 1-10 years or 11+ years showed adjusted RRs of 1.46 (95% CI = 0.7-3.1) and 1.53 (95% CI = 0.9-2.5), respectively (p for trend = 0.21). Years of working with a smoker was also not associated with risk of CHD in men but was associated with an increased risk of CHD in women after adjusting for age. The relative risks for years working with a smoker changed from less than 1.0 in unadjusted analysis to close to 2.0 when the analyses were adjusted for age (Table 8.1).

Thus, the evidence from the spouse pair cohort and the AHSMOG cohort suggest that exposure to ETS at home and at work increased the risk of heart disease mortality in nonsmoking women but not in nonsmoking men. The effect of ETS exposure from work was of borderline statistical significance. There are no apparent reasons for the difference in results by gender. Although ETS exposure in the spouse pair cohort is derived by comparing the surrogate measure for smoking cessation (age at Baptism) to the age at marriage, the extent of misclassification of ETS exposure can be evaluated in a subset of women who responded to specific questions on spouses' smoking in the AHSMOG cohort and were included in the spouse pair cohort. There was an agreement in classification by ETS exposure in 86 percent of subjects included in both cohorts. However, 5.9 percent of the women responded they were not exposed to spouses' smoking in the AHSMOG cohort but were classified as exposed in the spouse pair cohort, and 5.8 percent who responded that their spouse smoked were classified as not exposed.

CPS-I and CPS-II (LeVois and Layard, 1995) The analysis by LeVois and Layard (1995) utilized data from the American Cancer Society CPS-I and CPS-II studies. In brief, the CPS-I study included more than one million men and women who were enrolled in 1959-1960. This analysis was based on 13 years of follow-up (1960-1972). Follow-up was 92.7 percent complete. The CPS-II study included approximately 1.2 million subjects who were enrolled in 1982. For this analysis, the cohort was followed for 6 years (1983-1988). Vital status was ascertained for 98.2 percent of the cohort, and death certificates were obtained for 94 percent of decedents. Both CPS-I and CPS-II collected data on smoking habits, including the number of cigarettes smoked per day. Only self-reported never-smokers who had spouses with known

smoking habits were included in these analyses. Each spouse was categorized as a nonsmoker, former smoker or smoker of 1-19, 20-39, and 40 or more cigarettes per day.

In the CPS-I cohort there was a total of 88,458 male and 267,412 female never-smokers with spouses having known smoking habits. After 13 years of follow-up, there were 7,758 CHD deaths in men and 7,133 CHD deaths in women. As discussed in more detail below, major limitations of the LeVois and Layard analysis of these data include the lack of clarity on selection of subjects for analysis and the inconsistency in their reporting of the results.

In CPS-I, the age- and race-adjusted RR for CHD mortality associated with any ETS exposure from spouses was 0.97 (95% CI = 0.90-1.05) in men and 1.03 (95% CI = 0.98-1.08) in women. Results were unchanged when the amount smoked by spouses was considered. For men whose wives smoked 1-19, 20-39, and 40 or more cigarettes per day, the RRs for CHD mortality were 0.99, 0.98, and 0.74, respectively. For women whose husbands smoked 1-19, 20-39, and 40 or more cigarettes per day, the RRs for CHD mortality were 1.04, 1.06, and 0.96, respectively. Nonsmoking men and women whose spouses were former smokers showed risks for CHD that were close to 1.0 (Table 8.1).

In the CPS-II cohort, among a total of 108,772 male and 226,067 female never-smokers with spouses having known smoking habits, there were 1,966 CHD deaths in men and 1,099 CHD deaths in women. After adjusting for age and race, there was no association between any ETS exposure from spouses and risk of CHD mortality in men (RR = 0.97, 95% CI = 0.87-1.08) or in women (RR = 1.00, 95% CI = 0.88-1.14). However, in both men and women, there was some increase in risk when amount smoked by spouses was considered. The risk of CHD mortality among men who were never-smokers married to women who smoked 1-19, 20-39, and 40 or more cigarettes per day were 1.36, 1.28, and 1.13, respectively, compared to men married to nonsmokers (Table 8.1). The corresponding RRs in never-smoking women were 1.14, 0.98, and 1.27. However, never-smoking men married to women who were former smokers showed a significantly lower risk of CHD mortality (RR = 0.81, 95% CI = 0.70-0.98). The RR for CHD mortality was 0.99 (95% CI = 0.86-1.13) for never-smoking women married to husbands who were former smokers.

LeVois and Layard (1995) combined the CPS-I and CPS-II studies and reported a significant decreased risk of CHD (RR = 0.79, 95% CI = 0.80-0.97) in nonsmoking men married to wives who were former smokers. However, the value of the combined RR presented in the text (RR = 0.88, 95% CI = 0.79-0.97; see p. 188 of LeVois and Layard (1995)) differed from the combined RR presented in Table 4 (RR = 0.79, 95% CI = 0.80-0.97; see p. 189 of LeVois and Layard (1995)). It is unclear which of the combined RRs is correct. The results obtained are inconsistent with those of Steenland *et al.* (1996); these investigators conducted a more complete analysis of the same data set (see below).

Although this study has the advantage that the results were based on the largest number of subjects and CHD events, LeVois and Layard (1995) presented few details about the subjects not included in the analysis. For example, it is unclear what percentage of subjects were excluded in either study because their own smoking habits were missing or because the smoking habits of spouses were unknown. The investigators examined an effect they described as "any" ETS exposure, which encompassed exposure due to any level of cigarette smoking by either current spouses or former spouses, but they did not investigate the effects of ETS exposure due *only* to cigarette smoking (any level combined) by current spouses. The significant finding these investigators emphasized was the reduction in risk among men married to ex-smokers when results from the two CPS studies were combined; we question whether the combined RR is correct (see above).

As pointed out by Steenland *et al.* (1996) and Glantz and Parmley (1995), ETS exposure may have both acute and chronic effects on the heart. The emphasis of LeVois and Layard on "any" (*i.e.*, current or former) ETS exposure from spouses and on exposure from spouses who were former smokers strongly biased the results toward the null. First, results for "any" exposure to spousal ETS diluted the effects associated with exposure to current smokers by including ex-smokers. This is evident when one compares the RRs associated with any ETS exposure versus the RRs associated with amounts currently smoked by spouses (Table 4 of LeVois and Layard, 1995) (RRs associated with any current smoke exposure were not presented and could not be computed on the basis of the data presented). The RRs associated with any ETS exposure was less than 1.0 for men (RR = 0.97) and close to 1.0 for women (RR = 1.0 and 1.03) in the CPS-I and CPS-II analyses. However, almost all the RRs associated with each exposure category (based on amount currently smoked by spouses: 1-19, 20-39, 40+ cigarettes per day) were above 1.0 for women in both CPS-I and CPS-II and for men in CPS-II. In fact, in the CPS-II analysis, five of the six RRs associated with varying amounts smoked by spouses were above 1.13. These RRs by amounts currently smoked by spouses suggest that the RR for any exposure to current smokers is above 1.0. Second, the effect of exposure from former smokers may be negligible, similar to the rapid reduction in heart disease risk seen among active smokers upon cessation of smoking.

CPS-II Cohort (Steenland et al., 1996) The analysis by Steenland *et al.* (1996) utilized data from the CPS-II cohort based on 7 years of follow-up. The original CPS-II cohort consisted of 1,185,102 men and women who were enrolled in 1982. By December 1989, 91.2 percent (1,080,689) were alive, 8.6 percent (101,519) had died, and the remainder had unknown vital status. Including only participants who had never smoked, for whom information on marital status was available and whose spouses had classifiable smoking habits, there remained 353,180 women and 126,500 men. Death due to CHD was reported in 4,911 women and 3,251 men.

Results from four analyses were presented in this report. The first three analyses dealt specifically with ETS exposure from spouses, whereas the fourth analysis investigated the effects of ETS exposure at home, at work, and in other settings. The first analysis was conducted only among those

married individuals with spouses also enrolled in the CPS-II study, and for whom there were valid dates of marriage and sufficient data on smoking cessation to indicate whether the spouses had smoked during marriage. CHD deaths included in this analysis were those which had occured in 101,277 men (2,494 CHD deaths) and 208,372 women (1,325 CHD deaths) after 7 years of follow-up. The second, third, and fourth analyses utilized subsets of eligible subjects derived from the first analysis. The second analysis was conducted only among those with single marriages for whom information on amounts and duration of exposure to smoking during marriage were available. These restrictions led to 58,530 men and 99,821 women and a corresponding number of 1,299 and 572 CHD deaths. The third analysis measured the risk of CHD among individuals who reported current exposure at home and were married to currently smoking spouses as compared to those who reported no current ETS exposure at home and were married to never-smoking spouses. This analysis included 54,668 men with 1,180 CHD deaths and 80,549 women with 426 CHD deaths. The fourth analysis was conducted on nonsmoking individuals who provided information regarding their exposure to ETS at home, at work, or in other social settings. This analysis was based on 1,751 CHD deaths in some 76,710 men and 2,403 deaths in 186,368 women (the number of subjects and CHD events were lower in the analyses on ETS exposure at work or in other social settings). Each of the four analyses adjusted for variables including age; self-reported history of heart disease and use of heart-disease medication; self-reported history of hypertension, diabetes or arthritis; body-mass index; education; use of aspirin, diuretics or estrogens (women only); alcohol use; employment history; and exercise.

Small increased risks for CHD mortality in men and women in association with current exposure to spouses' smoking were found in each of the analyses (analyses 1 to 3, Table 8.1). In the first analysis, nonsmoking men exposed to currently smoking wives showed a RR of 1.22 (95% CI = 1.07-1.40) for CHD mortality whereas nonsmoking women exposed to currently smoking husbands showed a RR of 1.10 (95% CI = 0.96-1.27). These RRs were strengthened slightly when the analyses were restricted to spouses with single marriages (analysis 2). The RR was 1.48 (95% CI = 1.21-1.80) in men and 1.18 (95% CI = 0.91-1.46) in women. An increased RR associated with exposure to a currently smoking spouse was also observed in the third analysis, in which self-reported exposure to ETS concurred with the spouses' reporting of their tobacco use (analysis 3). In this analysis, the RR for CHD mortality in association with currently smoking spouses was 1.23 (95% CI = 1.03-1.47) in nonsmoking men and 1.19 (95% CI = 0.97-1.45) in nonsmoking women. There was, however, no association between risk of CHD mortality in nonsmoking men and women and their being married to spouses who were former smokers (analyses 1 and 2, Table 8.1).

Dose-response relationships in terms of amounts smoked by spouses, duration of ETS exposure, and pack-years of ETS exposure were evaluated. There was no evidence of a smooth trend of increasing risk with increasing number of cigarettes smoked by spouses (analyses 1 and 3, Table 8.1) or with increasing pack-years of ETS exposure (analysis 3, Table 8.1). There

was some suggestion of a trend of increasing risk of CHD mortality in nonsmoking men and women with increasing number of years exposed to spouses' smoking (analysis 2, Table 8.1).

The fourth analysis examined the association between risk of CHD mortality and exposure to ETS at home, at work, and in other settings. Small elevated risks were associated with all sources of ETS exposure, although only the association between CHD risk in nonsmoking men and ETS exposure at home was statistically significant (Table 8.1).

Analyses were also presented separately for subjects aged <65 at baseline and for individuals with a history of heart disease and those without a history of heart disease. Nonsmoking subjects who were aged <65 at study entry showed a slightly higher increased risk of CHD mortality in relation to exposure to currently smoking spouses. For example, nonsmoking men aged <65 at baseline who were married to currently smoking women showed a RR of 1.33 for CHD mortality (this RR was 1.22 for all nonsmoking men). There is also some suggestion that the risk of CHD mortality associated with exposure to a smoking spouse was more apparent in individuals who had heart disease at baseline. For example, the risk of CHD mortality in nonsmoking men associated with exposure to wives who were current smokers was 1.18 (95% CI = 0.98-1.41) among those who had no history of heart disease at baseline and 1.24 (95% CI = 1.01-1.53) among those who had a history of heart disease at baseline.

The differences in findings in this study and those reported by LeVois and Layard (1995) are noteworthy given that both analyses utilized data from the CPS-II study. The size of the relevant study population and the number of CHD deaths included by Steenland *et al.* (1996) differed from those included by LeVois and Layard (1995). In contrast to the detailed description of the inclusion and exclusion criteria presented by Steenland *et al.* (1996), LeVois and Layard (1995) provided few details regarding their study methods. Differences in the follow-up period, in the definition of spousal smoking, or other criteria for inclusion and exclusion may have contributed to the differences in these two reports. The analytic methods used in the two studies also differed. Steenland *et al.* (1996) investigated separately the effects of current and former exposure to ETS from spouses, whereas LeVois and Layard (1995) examined the effects of any spousal ETS exposure. Given that there is little evidence of an increased risk associated with being married to former smokers, LeVois and Layard's (1995) analysis of any spousal exposure to ETS may have diluted the effects of current exposure to spousal smoking on CHD mortality in nonsmokers.

Nurses' Health Study (Kawachi et al., 1997) Kawachi *et al.* (1997) investigated the association between exposure to ETS and risk of CHD using the Nurses' Health Study, a cohort which was established in 1976 and included 121,700 female nurses in the U.S. A self-administered baseline questionnaire was completed by study participants which included information on active smoking history and a large number of lifestyle and dietary factors. Follow-up questionnaires have been completed by participants every two years to update information on cardiovascular disease risk factors and the occur-

rence of major illnesses. In the 1982 follow-up questionnaire, questions related to exposure to ETS were asked. Specifically, two questions were asked to assess current ETS exposure at home and at the workplace. Extent of exposure was categorized as none, occasional, and regular. In addition, subjects were asked the total number of years they had lived as an adult with someone who has smoked regularly.

This analysis comprised incident cases of nonfatal MI (n = 127) and fatal CHD events (n = 25) which occurred after the 1982 questionnaire but before June 1, 1992 among the 32,046 women who had never smoked and remained nonsmokers during the follow-up period (1982 to 1992). The CHD events were confirmed by review of medical records and death certificates by physicians who were blinded to exposure status. Risk estimates were calculated with adjustment for age and multiple risk factors including alcohol intake, body mass index, history of hypertension, diabetes, hypercholesterolemia, menopausal study, use of hormone replacement and oral contraceptives, physical activity patterns, and relevant dietary factors.

Compared to nonexposed women, those reporting occasional exposure to ETS at home or work had a multivariate adjusted RR for total CHD of 1.56 (95% CI = 0.93-2.68), while those reporting regular exposure had an RR of 1.97 (95% CI = 1.11-3.28). In this study population, exposure to ETS was associated with increased risks of both nonfatal MI and fatal CHD events (Table 8.1). ETS exposure, both at work and at home, was associated with an increased risk of CHD. Among women exposed only at work, the multivariate RRs of total CHD were 1.49 (95% CI = 0.71-3.14) among those occasionally exposed and 1.92 (95% CI = 0.88-4.18) among those regularly exposed to ETS. Among women exposed to ETS only at home, the corresponding RRs were 1.19 (95% CI = 0.63-2.23) and 2.11 (95% CI = 1.03-4.33). Self-reported duration of years lived with a smoker was also associated with an increased risk of incident CHD events although there was not a smooth trend of increasing risk with increasing years of exposure. The multivariate adjusted RRs associated with 1-9, 10-19, 20-29, and 30+ years compared to less than one year of exposure were 1.0, 1.19, 1.54, 1.11 and 1.58, respectively.

This study has several important strengths. This analysis was conducted using a cohort study that is widely accepted as one of the best designed and most well conducted prospective studies and has been an extremely valuable resource in identifying and elucidating causes of various disease endpoints. Because of the availability of a large number of lifestyle factors in this study, these analyses controlled for a large number of lifestyle and dietary factors that have been suggested to potentially confound the CHD-ETS association. Although there is some diminution in the RRs with adjustment of these potential confounders, the risks remained elevated and were statistically significant in many of the analyses. This cohort study also provided information on ETS exposure at home and at work, and showed clearly that risk of CHD is increased in association with ETS at home alone, at work alone, and for both exposures combined. Moreover, these investigators showed that the risks associated with ETS exposure in never-smokers are quite compatible with the active smoking findings in this study popula-

tion. Women who smoked 1 to 4 cigarettes per day had an RR for total CHD of 1.94 compared to all never-smokers; this RR was increased to 2.61 when the reference category was set to never-smokers not exposed to ETS. Thus, the RR of 1.97 among women regularly exposed to ETS at home or at work is not incompatible with the active smoking findings.

8.1.2 Case-control Studies

United Kingdom (Lee et al., 1986)

In a case-control study originally initiated to examine the relationship between types of cigarettes smoked and risk of lung cancer, chronic bronchitis, CHD, and stroke, Lee *et al.* (1986) evaluated the relationship between ETS exposure and these health outcomes (Table 8.2). The original study began in 1977, and the questionnaire was modified in 1979 to assess ETS exposure for married patients in four of the ten hospital regions included in the study. Controls were patients without one of the four diagnoses mentioned above; each control was individually matched to a case on sex, age, hospital region, and when possible, hospital ward and time of interview. A total of 507 (286 male, 221 female) currently married patients with CHD answered questions on ETS exposure. It is unclear whether these 507 subjects were nonsmokers since these numbers do not agree with subsequent numbers on CHD presented in the paper.

In one analysis, 118 subjects with CHD and 451 controls were compared in terms of whether his/her spouse smoked and the number of manufactured cigarettes smoked per day. Male CHD patients whose wives smoked during the entire marriage showed a relative risk of 1.24, but the association was absent for female patients (RR = 0.93). In a second analysis, 66 CHD cases and 254 controls quantified their ETS exposure at each of four settings (home, work, during daily travel, and during leisure time) using a 4-point scale (a score of zero indicated no exposure, a score of 3 indicated heavy exposure). To obtain a combined index of ETS exposure, the scores for each setting were summed. There was no association between this combined index of ETS exposure and risk for CHD in men and women. The relative risks were 1.00, 0.52, and 0.61 for the combined indices of ETS exposure of 0-1, 2-4, and 5-12, respectively.

Results from this study and the conclusion of no association are questionable. Information on passive smoking was obtained on a subset of cases and controls, and the different analyses on ETS exposure included substantially different numbers of cases and controls. Thus, selection bias of cases and controls who answered the questions on passive smoking cannot be excluded. In addition, information on potential confounders for CHD was not available.

China (He et al., 1989)

He *et al.* (1989) conducted a case-control study on ETS exposure and CHD in the Peoples' Republic of China; the study included 34 women with CHD and 68 controls (34 hospital-based, 34 population-based). Subjects were interviewed regarding their smoking habits and those of their husbands. Population controls were matched to cases on age, race, residence, and occupation, but it is unclear whether the matching criteria were applied to hospital controls. A significant, 3-fold increase in relative risk (95% CI = 1.3-7.2) for CHD was observed for nonsmoking women

Table 8.2
Case Control Studies on ETS Exposure and Heart Disease

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
United Kingdom (Lee, 1986)	507 males and females with IHD	Nonsmoking men exposed to spouse			Reason for varying sample sizes in analysis was not provided.
		No	26/93	1.00	
	hospital controls	Yes	15/40	1.24 (0.6-2.8)	
	a subset of cases and controls responded to questions on passive smoking	Nonsmoking women exposed to spouse			Combined index of exposure at home, work, during travel and leisure. A score of 0 to 3 is assigned separately to exposure at home, work, during travel, and leisure, for a maximum score of 12. Scores of 0 = not all; 1 = little 2 = average 3 = a lot
		No	22/89	1.00	
		Yes	55/229	0.93 (0.6-1.7)	
		Nonsmoking men exposed to combined sources:			
		score 0-1	15/27	1.0	
		2-4	12/55	0.43(0.2-0.9)	
		5-12	3/15	0.43(0.1-1.4)	
		Nonsmoking women exposed to combined sources:			The confidence intervals were calculated based on the distribution of cases and controls presented in references.
		score 0-1	23/75	1.0	
		2-4	9/61	0.59 (0.2-1.1)	
		5-12	4/21	0.81 (0.2-2.0)	

Table 8.2 (Continued)

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
New South Wales, Australia (Dobson *et al*., 1991a)	Subjects with myocardial infarction (MI) or coronary death, age 35-69, between July 1988-October 1989	Nonsmoking men			ORs adjusted for age and history of MI.
		Not exposed at home	161/259	1.00	
		Exposed at home	22/34	0.97 (0.50-1.86)	
		Not exposed at work	48/126	1.00	Only subset with information on exposure at work.
		Exposed at work	27/79	0.95 (0.51-1.78)	
	Controls selected from a community based risk-factor survey	Nonsmoking women			Data on passive smoke at work available on only a subset, reasons for missing data not explained.
		Not exposed at home	117/433	1.00	
		Exposed at home	43/99	2.46 (1.47-4.13)	
	Cases interviewed by nurses while in hospital, controls completed self-administered questionnaire	Not exposed at work	5/73	1.00	
		Exposed at work	12/124	0.66 (0.17-2.62)	
People's Republic of China (He *et al*., 1989)	34 women CHD (12 MI, 22 diagnosed by coronary arteriography)	Nonsmoking women			The OR was adjusted for personal and family history of hypertension, family history of CHD, drinking, physical exercise, and history of hyperlipidemia.
		Husband smoked			
		Yes	9/38	1.0	
	68 controls (34 population, 34 hospital control)	No	16/25	3.0 (1.3-7.2)	

Table 8.2 (Continued)

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls		OR (95% CI)	Comments
Italy (La Vecchia *et al.*, 1993)	Acute MI patients 113 cases (44 females, 69 males)	Spousal smoking habits	Males cas/ctrl	Females cas/ctrl		OR obtained from multiple regression; adjusted for sex, age, education, coffee intake, body mass index, serum cholesterol, hypertension, diabetes, and family history of MI.
		never-smoker	55/140	11/17	1.0	
		former smoker	2/4	15/19	0.91 (0.4-2.3)	
	Controls admitted to same hospitals for acute conditions not related to CHD	current smoker	7/17	17/20	1.21 (0.6-2.5)	
		<15 cigarettes/dy	5/11	6/8	1.13 (0.5-2.8)	
		15+ cigarettes/dy	2/6	11/12	1.30 (0.5-3.4)	
People's Republic of China (He *et al.*, 1994)	Non-fatal CHD female cases in lifelong non-smokers; identified from the 3 large teaching hospitals in Xian between 1989 and 1992	Passive smoking from husband / work	cases	controls		Crude ORs are shown.
		no / no	11	50	1.0	
		yes / no	15	33	2.07 (0.8-5.6)	
		no / yes	10	18	2.42 (0.8-7.8)	
		yes / yes	23	25	4.18 (1.6-10.9)	
	Controls were from three sources and were combined in all analyses because they did not display significant differences by various characteristics	Passive smoking at work: Number of smokers	cases	controls		OR is adjusted for age, history of hypertension, personality type, total cholesterol, and passive smoking from husband.
		0	26	83	1.00	
		1-2	16	36	1.16 (0.5-2.8)	
		3	12	6	5.06 (1.4-18.0)	
		4+	5	1	4.11 (0.4-43.7)	
		Test for trend				

Table 8.2 (Continued)

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
United States (Muscat and Wynder, 1995)	Subjects with MI identified in four hospitals in the U.S. between 1980 and 1990; hospital controls were used.	Adult exposure	Males		OR was adjusted for age, education, and hypertension.
		None	38/68	1.0	
		1-20 years	12/15	1.7 (0.7-4.5)	
		21-30	5/8	1.5 (0.4-5.2)	
		>30	13/17	1.1 (0.4-2.8)	
	Cases and controls interviewed while in the hospital.		Females		
		None	13/20	1.0	
		1-20 years	12/8	2.0 (0.5-8.1)	
		21-30	5/9	0.9 (0.2-4.4)	
		>30	16/13	1.7 (0.5-5.9)	
United States (Layard, 1995)	Cases and controls were from National Mortality Followback Survey conducted in 1986. Next-of-kin completed a self-administered questionnaire	Spousal smoking			
		cigarettes/day	Males		Causes of death of controls were not specified.
		none	378/783	1.0	
		1-15	38/107	0.8 (0.5-1.1)	
		15-34	45/92	1.1 (0.7-1.6)	ORs were adjusted for age and race; cases were significantly older than controls.
		35+	6/12	0.9 (0.9-2.6)	
		cigarettes/day	Females		
		none	459/969	1.0	
		1-15	139/336	0.9 (0.7-1.1)	
		15-34	224/405	1.2 (0.9-1.4)	
		35+	52/111	1.1 (0.7-1.5)	

Table 8.2 (Continued)

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
New Zealand (Jackson, unpublished)	Cases included acute MI patients and fatal CHD patients Self-respondent population controls and next-of-kin of controls were compared to directly interviewed cases and next-of-kin of fatal CHD patients	Questions on ETS were added to an ongoing case-control study conducted in New Zealand.	Males: 28 acute MI cases compared to 123 controls; 21 fatal CHD cases compared to 61 controls Females: 11 acute MI cases compared to 112 controls; 9 fatal CHD cases compared to 62 controls	Acute MI: M 1.0 (0.3-4.3) F 2.7 (0.6-13.6) Fatal CHD: M 1.1 (0.2-4.5) F 5.8 (1.3-48.0)	ORs were adjusted for age and social class. The baseline comparison had no ETS exposure at home

Abbreviations: MI = myocardial infarction; CHD = coronary heart disease; IHD = ischemic heart disease

whose husbands were smokers. The risks increased with increasing number of cigarettes smoked and with increasing duration of smoking by the husband. The relative risk associated with ETS exposure diminished substantially (RR = 1.50, $p < 0.01$) when other CHD risk factors (including personal and familial history of hypertension, familiar history of CHD, drinking, physical exercise, previous history of hyperlipidemia) were adjusted for in the analysis. Analysis by specific heart disease outcome showed a relative risk of 4.7 ($p < 0.05$) for angina ($n = 21$), and a relative risk of 2.5 ($p > 0.05$) for MI ($n = 13$) in relation to husbands' smoking.

There are several important limitations of this study. First, the study is small, based on 34 cases and 68 controls. Second, only partial information about the study methods was presented. The 34 CHD patients represented cases who were diagnosed by coronary arteriography or had MI during 1985-1987 in one hospital in Xian, China. The criteria for selecting these cases were not described, and it is unclear what percentage of cases diagnosed during the study period was selected. Furthermore, the types of patients included as hospital controls were not described. Some population controls had presumably taken the exercise electrocardiogram test, questioning whether they are truly representative population controls. Thus, selection bias of cases and controls cannot be ruled out. It is also uncertain whether uniform methods were used to collect information from cases, hospital controls, and neighborhood controls.

The significant findings from the study must be interpreted with caution given these serious limitations in study methods. It is also questionable whether the point estimates for angina and MI separately are meaningful given these results were based on 21 and 13 cases respectively.

New South Wales, Australia (Dobson et al., 1991a) A case-control study of ETS exposure and risk of heart attack and CHD death was conducted by Dobson *et al.* (1991a) in New South Wales, Australia. Cases were residents of the study area, aged 35-69 years who had a fatal or non-fatal definite or possible MI, or a coronary death with insufficient information for more specific classification, during the study period (July 1, 1988 to October 31, 1989). To ensure completeness of case ascertainment, the hospital morbidity data system and the official death records were compared. If more than one CHD event occurred during the study period, only the first event was included in the analysis. In addition to diagnostic information, data on medical history, cigarette smoking, and exposure to passive smoking at home and at work were obtained by an interview conducted by the study nurses while subjects were still in the hospital. For subjects who had died, the next-of-kin was contacted (the number of interviews conducted with the subjects themselves versus next-of-kin was not specified). Information on ETS exposure was missing for about 15 percent of all nonsmoking CHD patients because they had died and a next-of-kin interview could not be conducted. Controls had previously participated in a community-based risk prevalence study. For this study, they completed a self-administered questionnaire which covered demographic characteristics, smoking behavior, and medical history. Controls were also asked to donate a blood sample and complete

physical measurements. The participation rate among controls was 63 percent for all three components of the study, and 80 percent for the questionnaire interview.

The study included 183 male CHD patients who had never smoked and 336 who were ex-smokers; the corresponding female CHD patients were 160 nonsmokers and 80 ex-smokers. Male cases were compared to 293 male nonsmoker and 332 ex-smoker controls, respectively, whereas female cases were compared to 532 female nonsmoker and 151 ex-smoker controls. Controls were selected to match cases on age (between ages 35 to 69), but how closely cases and controls were age-matched was not specified.

The ETS effect was considered separately for nonsmokers and ex-smokers after adjustment for age (in 5-year intervals), sex, and prior history of heart disease. Exposure to ETS at home was not associated with risk of heart attack in nonsmoking men (adjusted RR = 0.97, 95% CI = 0.50-1.86) but was associated with an increased risk in nonsmoking women (adjusted RR = 2.46, 95% CI = 1.47-4.13). Based on a small sample of nonsmokers who worked outside the home (75 male cases versus 205 male controls; 17 female cases versus 197 female controls), ETS exposure at work was not associated with risk of heart attack in men (RR = 0.95, 95% CI = 0.51-1.78) or in women (RR = 0.66, 95% CI = 0.17-2.62).

This case-control study has several methodologic deficiencies which may have biased the estimated effect of ETS on risk of heart disease. The percentage of nonsmoking male and female cases and controls who reported exposure to ETS at home was low in this study: 12.0 percent nonsmoking male cases and 11.6 percent nonsmoking male controls reported ETS exposure; the corresponding figures in females were 26.9 percent and 18.6 percent. The percentages of controls who reported ETS exposure were 40-60 percent among controls in most lung cancer studies (U.S. EPA, 1992). Controls in this study were participants in a previous health survey and may have been "healthier" and thus were less likely to have had exposure to ETS. However, this reasoning does not explain the low prevalence of ETS exposure among cases. The precise questions on ETS exposure that were asked were not described (Dobson *et al.*, 1991a), limiting our ability to fully interpret these findings. In addition, different methods were used to obtain information from cases and controls. Whereas most cases were interviewed by nurses while they were in the hospital, controls completed a self-administered questionnaire. Information bias cannot be ruled out, and the direction of bias cannot be determined. Lastly, potential confounders including other risk factors for heart disease and socioeconomic status were not available.

New Zealand (Jackson et al., 1991; Jackson, 1989 [unpublished dissertation]) Jackson *et al.* (1991) conducted a population-based case-control study of non-fatal MI and fatal heart disease in New Zealand. A population register identified nearly 99 percent of the CHD occurring in the study population, which included all white men and women aged 25-64 living in the Auckland statistical area between March 1986 and February 1988 who were also registered on the general electoral rolls. All patients with non-fatal MI requiring

admission to a hospital were invited to participate. The next of kin of subjects who had died of CHD were also invited to participate. Controls were randomly selected from the study population by using the electoral rolls as the sampling frame. For each male and female case who was interviewed, approximately 1.5 male controls and 3 female controls were interviewed. Cases and controls were matched on respondent type (*i.e.*, self-respondent versus next-of-kin respondent). This matching was achieved by using the controls for the subjects with MI (self-respondents) as controls also for those who had died of CHD by interviewing their next of kin about them (the self-respondent controls). The interviews asked about use of tobacco products, current drug treatment of hypertension, leisure time physical activity, and prevalence of angina. Questions on passive smoking were added during year 2 of the study. Specifically, questions were asked about tobacco smoke exposure from any cohabitant and at work.

The analysis on ETS exposure was limited to never-smokers with no history of MI or angina and included 28 male MI cases and 123 male controls, 21 male fatal CHD and 61 male controls, 11 female MI cases and 112 female controls, and 9 female fatal CHD and 62 female controls. The age- and social-class-adjusted OR for MI in relation to ETS exposure at home (and/or work) was 2.7 (95% CI = 0.57-12.3) in women and 1.03 (95% CI = 0.27-3.9) in men. The adjusted OR for fatal CHD was 5.8 (95% CI = 0.95-35.2) in women and 1.1 (95% CI = 0.23-5.2) in men.

Although this study was part of a large case-control study of alcohol intake and risk of CHD conducted in collaboration with the World Health Organization MONICA project (Jackson *et al.*, 1991), questions on ETS exposure were added during year 2 of the study and were unpublished (Jackson, 1989 [unpublished dissertation]). Only a small number of non-smokers were included in this analysis. Selection bias cannot be excluded since it is unclear what percentage of never-smoker cases and controls answered questions on ETS exposure.

Italy (La Vecchia et al., 1993) This Italian case-control study of acute MI was conducted from 1988-1989 within the framework of the GISSI-2 study (a randomized clinical trial of alteplase versus streptokinase and heparin versus no heparin) which included 12,490 cases of acute MI (GISSI-2, 1990; Roncaglioni *et al.*, 1992). From the original study population, 113 cases of acute MI (44 women and 69 men aged 34-74) occurred in never-smokers. Two hundred and twenty-five controls (60 women and 125 men, aged 29-74) were compared to the cases; controls were admitted to the same network of hospitals for acute diseases not related to any known or potential cardiovascular risk factors and were also never-smokers. Exposure to passive smoking at home was based on spouse's smoking habits which included smoking status (never-smoker, ex-smoker, current smoker), number of cigarettes smoked per day, number of years the couple had lived together (presumably as a measure of duration of ETS exposure), and the number of years since the spouse had stopped smoking if he/she was a former smoker.

Compared to subjects married to never-smokers, the adjusted OR for acute MI associated with being married to ex-smokers was 0.91 (95% CI = 0.36-2.28), and the OR for those married to current smokers was 1.21 (95%

CI = 0.57-2.52). Gender, age, education, coffee consumption, body mass index, serum cholesterol, hypertension, diabetes, and family history of acute MI were adjusted for in the analysis. Among subjects married to current smokers, the risk was higher (RR = 1.30, 95% CI = 0.50-3.40) among those whose spouses smoked 15 or more cigarettes per day than those whose spouses smoked less than 15 cigarettes per day (RR = 1.13, 95% CI = 0.45-2.82).

This study has the advantage of being part of a larger study in which some information on passive smoking, other heart disease risk factors, and dietary factors were available. The dietary data from this study suggest that subjects who lived with a smoking spouse and those who lived with a non-smoking spouse did not differ in the dietary intake of selected indicator foods.

Xian, China (He et al., 1994) He *et al.* (1994) conducted a second case-control study in Xian, China. Cases included 59 Chinese women with CHD and 126 controls; all subjects had full-time jobs and had never smoked. Cases had non-fatal, incident CHD and were identified from one of three large teaching hospitals in the study area between December 1989 and November 1992. Three types of controls were interviewed, including patients admitted because of suspected CHD (these subjects were later found to be free of CHD)(n = 26), other hospital controls (n = 65), and a random sample of healthy subjects identified from a community screening program (n = 35).

In-person interviews were conducted with cases and controls using a structured questionnaire which collected information on demographic characteristics; history of hypertension, hyperlipidaemia and diabetes mellitus; family history; history of smoking and passive smoke exposure from husbands and coworkers; drinking history; and exercise.

There were no significant differences between cases and controls in age, marital status, occupation, or education, although a higher percentage of cases were over age 55, were not married, were factory workers and had fewer than 9 years of education. Risk of CHD was significantly increased in relation to ETS exposure from husbands (defined as living with a smoking husband for over 5 years) (crude OR = 2.12, 95% CI = 1.06-4.25) and coworkers (defined as working with smoking coworkers for over 5 years) (crude OR = 2.45, 95% CI = 1.23-4.88). Crude analysis showed that when ETS exposure from husbands and coworkers were considered jointly, the risks increased approximately 2-fold for ETS exposure from husbands only and at work only, and by 4-fold for exposures both at work and from husbands. Although the ORs in relation to passive smoke exposure from husbands (adjusted OR = 1.24, 95% CI = 0.56-2.72) and at work (adjusted OR = 1.85, 95% CI = 0.86-4.00) were substantially reduced after adjustment for other risk factors for CHD (age, history of hypertension, type A personality, total cholesterol, high density lipoprotein), the adjusted OR for any passive smoke exposure (from husband and/or coworkers) remained statistically significant (adjusted OR = 2.36, 95% CI = 1.01-5.55). There were also significant trends of increasing risks with increasing intensity (amount smoked daily, number of smokers) and duration (in years) of ETS exposure at work (Table 8.2).

The main limitation of this study is the modest sample size of cases and controls and the fact that prevalent CHD cases may have been included. However, this study has the advantage of detailed information on ETS exposure at home and at work and on other heart disease factors, and it adjusted the analyses on ETS exposure for other potential confounding factors. Moreover, the opportunity to examine the role of ETS exposure at work was maximized given that all subjects worked full time. This study also attempted to assess the extent of information bias in several ways. First, there is no evidence of selective recall bias for being a patient with CHD: ETS exposure among controls who were initially suspected of CHD but were later found to be free of CHD by coronary arteriography (n = 26) was similar to the ETS exposure experience of other hospital controls (n = 65). Second, there was high concordance (over 70 percent) in responses regarding passive smoke exposure. Some 30 percent of subjects were interviewed a second time by a different interviewer who was blinded to the case-control status of the subject. Some of the husbands were also interviewed directly to validate the passive smoking information provided by their wives.

National Mortality Followback Survey (Layard, 1995) Layard (1995) conducted a case-control analysis to examine the association between CHD mortality and spousal cigarette smoking using data on never-smoking decedents from the 1986 National Mortality Followback Survey, which was conducted in 1986 by the U.S. National Center for Health Statistics. The survey was based on a national probability sample of about 1 percent of all deaths in 1986 of U.S. residents aged 25 years or older.

This analysis included all deaths due to CHD (ICD 9, codes 410-414) among males aged 25-44 years and females aged 25-54 years who were reported by next of kin to be lifetime never-smokers (*i.e.*, had smoked fewer than 100 cigarettes in their entire lives). Decendents were excluded from the analysis if they had never married, their marital status was unknown, or the smoking history of their spouses was unknown (549 males and 692 females subjects were excluded from the analysis for these reasons). After these exclusions, the case group included 1,389 (475 males and 914 females) CHD deaths. Controls (996 males and 1,930 females) were selected from the same study population from those whose causes of death were considered to be non-smoking related. However, the actual causes of death among controls were not presented. Next of kin of both cases and controls completed a mailed questionnaire which provided information on demographic characteristics, dietary patterns, cigarette smoking habits of index subject and their spouses, alcohol use, education, income, and history of other diseases.

In this study, there was no association between exposure to spouse's smoking and risk of CHD death in men (OR = 0.97, 95% CI = 0.73-1.28) or in women (OR = 0.99, 95% CI = 0.84-1.16). Analysis by amount smoked by spouses (<15, 15-34, 35+ cigarettes/day) also did not reveal any association between amount smoked by the spouses and risk of CHD mortality. These results were unchanged after adjustment for potential confounders which

included dietary factors, relative weight, history of diabetes or hypertension, family history of heart attack, education, and family income.

It is, however, difficult to interpret these results. First, it appears that the controls were not matched to cases on age at death or race, since the mean age at death for cases was significantly higher (72.6 years of age in men and 78.2 in women) than that of controls (64.8 years of age in men and 71.9 in women). The percentage of white cases (74.9 percent in males, 73.9 percent in females) was also significantly higher than that in the control group (68.2 percent in males, 68.4 percent in females). Although the OR was adjusted for age, the specific type of age adjustment used was not described. Broad age groups used in age adjustment may not be adequate. Furthermore, the study was supposed to include all deaths among males aged 25-44 years and females aged 25-54 years but the mean ages of male cases were considerably older. The reason for this discrepancy was not explained. Moreover, since the actual causes of death among controls were not presented, whether their causes of death may be related to tobacco smoke exposure cannot be ascertained.

Muscat and Wynder (1995) Muscat and Wynder (1995) conducted a hospital-based case-control study between 1980 and 1990 in four U.S. cities to evaluate the association between exposure to ETS during childhood and adult life and the risk of MI. Cases were newly diagnosed incident cases with MI who were admitted to teaching hospitals in New York, Philadelphia, Chicago, and Detroit. Controls were patients who did not have heart disease and were hospitalized for conditions unrelated to tobacco use. Controls were frequency matched to cases on the basis of age (±5 years), race, and year of diagnosis. Ninety percent of both eligible cases and controls were interviewed. Only patients who reported never smoking cigarettes were included in this analysis.

A standardized questionnaire was administered to all subjects in the hospital by trained interviewers. Subjects who smoked one or less than one tobacco product per day for 12 or fewer months were considered never-smokers. An extensive series of questions were asked regarding exposure to ETS. These questions included childhood exposure, adult exposure, exposure to other people's smoke at work and on any form of transportation. Each set of questions included identifying all sources of exposure (*e.g.* mother, father, spouse, children, other relatives, and roomers) and the duration of exposure in years.

A total of 114 cases (68 males and 46 females) and 158 controls (108 males and 50 females) were interviewed. Cases were somewhat older than controls (55.7 years for male cases versus 52.4 years for male controls; 58.7 years for female cases versus 57.9 years for female controls). Adult ETS exposure was associated with an elevated risk of MI in men (crude OR = 1.3, 95% CI = 0.7-2.4) and in women (crude OR = 1.7, 95% CI = 0.7-3.7). The OR was 1.5 (95% CI = 0.9-2.6) for men and women combined after adjustment for gender, age, education, and hypertension. There was, however, no smooth trend of increasing risk with increasing duration (1-20, 21-30, 31+ years) or pack-years (1-10, 11+ pack-years) of ETS exposure in adult life,

although all the ORs were greater than 1.0 (see Table 8.2). Exposure to ETS at work was associated with a small increased risk in men (OR = 1.2, 95% CI = 0.6-2.2) but not in women (OR = 1.0, 95% CI = 0.4-2.5) whereas exposure to ETS in transportation was associated with an increased risk in women (OR = 2.6, 95% CI = 0.9-8.0) but not in men (this OR was not presented). In both men and women, there was no association between exposure to ETS during childhood and risk of MI.

8.2 DISCUSSION OF EPIDEMIOLOGIC STUDIES

To date there are 18 studies (ten cohort studies, eight case-control studies) which have examined the association between ETS exposure and risk of CHD. In 15 studies (nine cohort studies, six case-control studies) there was some suggestion of a small increased risk of CHD associated with ETS exposure. This result was statistically significant in six studies (Hirayama, 1984; Helsing *et al.*, 1988; Hole *et al.*, 1989; He *et al.*, 1989 and 1994; Kawachi *et al.*, 1997) and in one gender group in two studies (Dobson *et al.*, 1991a; Steenland *et al.*, 1996). A statistically nonsignificant increased risk was observed in the other seven studies, most of which had modest sample sizes (Jackson, 1989; Muscat and Wynder, 1995; La Vecchia *et al.*, 1993; Humble *et al.*, 1990; Helsing *et al.*, 1988; Garland *et al.*, 1985; Butler, 1988). Two (Layard, 1995; LeVois and Layard, 1995) of the three studies (Lee *et al.*, 1986; Layard, 1995; LeVois and Layard, 1995) which did not find an association between ETS exposure and risk of CHD were, in fact, very large studies. However, these three studies had other methodologic limitations. First, all three studies investigated the association between CHD risk and exposure to any smoking spouse (*i.e.*, including former smokers) when there is some suggestion that only current exposure to ETS may influence the risk of CHD (see below). The suitability of the control group and the quality of information on ETS exposure are questionable in the large case-control study conducted by Layard (1995). This study relied exclusively on information provided by the next-of-kin of subjects who died of CHD or other causes, and the completeness of the information is debatable. Moreover, causes of death among the controls were not presented. Thus, selection bias of controls and misclassification bias of ETS exposure cannot be ruled out in this study. Third, LeVois and Layard (1995) combined the data from the CPS-I and CPS-II studies and found a significant reduced risk of CHD associated with exposure to spouses who were former smokers. This RR from the combined dataset is due mainly to a reduced risk (RR = 0.81) in nonsmoking men associated with wives who were former smokers in the CPS-II study. In Steenland's analysis (1996) of the CPS-II study, the RR in nonsmoking men associated with wives who were former smokers was 0.99. Reasons for the discrepancy in study results between the two analyses of the CPS-II study are not apparent. However, as noted above, Steenland *et al.* (1996) conducted a more thorough and comprehensive analysis of the same data set. Moreover, the results reported by Steenland *et al.* (1996) were more credible because increased risks were observed in multiple analyses using different criteria to define eligible subjects. Increased risks were also observed in the analysis, which was restricted to subjects who were concordant for self-reported current exposure to smoking and spousal reporting of current smoking.

A strength of these collective data which support an association between risk of CHD and exposure to ETS is that nine of the 15 studies were prospective studies (Hirayama *et al.*, 1984; Garland *et al.*, 1985; Svendson *et al.*, 1987; Butler, 1988; Helsing *et al.*, 1988; Hole *et al.*, 1989; Humble *et al.*, 1990; Steenland *et al.*, 1996; Kawachi *et al.*, 1997). The cohorts were diverse and included high-risk men (Svendson *et al.*, 1987), subjects in an affluent community (Garland *et al.*, 1985), lower-risk subjects in a rural community (Humble *et al.*, 1990), Seventh Day Adventists (Butler, 1988), nurses in the U.S. (Kawachi *et al.*, 1997) and the general population in the U.S. (Helsing *et al.*, 1988; Steenland *et al.*, 1996), the UK (Hole *et al.*, 1990), and Japan (Hirayama, 1981, 1984, 1990). Although the sample sizes of some of the cohort studies were modest (Svendson *et al.*, 1987; Butler, 1988; Hole *et al.*, 1989; Humble *et al.*, 1990; Garland *et al.*, 1985), the analysis based on the CPS-II study (Steenland *et al.*, 1996) included some 3,000 CHD deaths. Almost all of the case-control studies were also relatively small (He *et al.*, 1989; Dobson *et al.*, 1991a; La Vecchia *et al.*, 1993; He *et al.*, 1994; Muscat and Wynder, 1995; Jackson, 1989) but these studies had an advantage in that specific questions on different sources of ETS exposure were asked and that almost all the cases and controls were interviewed directly regarding their ETS exposure. Although the case-control study conducted by Layard (1995) was large, information on ETS exposure may be less complete and was obtained exclusively from next-of-kin.

Misclassification of ETS exposure is a concern in examining these studies. Almost all the studies used spousal smoking as a measure of ETS exposure, while a few studies included questions on ETS exposure from other settings (see below). Because of the small sample sizes in some studies or because of the way information on smoking was originally obtained, some studies described spousal smoking as "yes" or "no" (Svendson *et al.*, 1987; Hole *et al.*, 1989; Humble *et al.*, 1990; Lee *et al.*, 1986; Dobson *et al.*, 1991a; He *et al.*, 1989) without distinguishing whether spouses were ex-smokers or current smokers. In studies of active smoking and heart disease, risk of heart disease decreases rapidly upon cessation of smoking, although there is still some residual risk of CHD attributable to past smoking (U.S. DHHS, 1990). Thus, any increased risk of heart disease in nonsmokers in relation to living with a spouse who is an ex-smoker needs to be interpreted cautiously. A spouse who was an ex-smoker at study enrollment may have resumed smoking during the period of follow-up. As a different possibility, an ex-smoker spouse may have been a very heavy smoker with the nonsmoking spouse heavily exposed, and the subsequent increased risk observed would be a residual effect of intense previous exposure. Alternatively, subjects married to ex-smokers may be at an increased risk for CHD because of other characteristics in their lifestyles that are also associated with an increased risk of heart disease.

A few studies have provided information on the risk of CHD in association with ETS exposure from ex-smoking spouses (Garland *et al.*, 1985; Butler, 1988; La Vecchia *et al.*, 1993; LeVois and Layard, 1995; Steenland *et al.*, 1996). In one study, nonsmokers married to former smokers and those married to current smokers both showed increases in risk of CHD compared to nonsmokers married to nonsmokers (Garland *et al.*, 1985). In three

other studies (Butler, 1988; La Vecchia *et al.*, 1993; Steenland *et al.*, 1996), an increased risk of CHD was found in association with exposure to spouses who were current smokers but not with exposure to spouses who were former smokers. In one study (LeVois and Layard, 1995), a lower risk of CHD was found in association with exposure to spouses who were former smokers. The association between risk of CHD and exposure to spouses who were current smokers was not evaluated in this study.

Information on a dose-response relationship between exposure to spousal smoking and risk of CHD was available in several studies. A trend of increasing risk with increasing amounts smoked by spouses was suggested in four studies (Hirayama, 1984; He *et al.*, 1989; La Vecchia *et al.*, 1993; Kawachi *et al.*, 1997). However, in other studies, there is little evidence of a smooth trend of increasing risk with increasing amounts smoked by spouses (Helsing *et al.*, 1988; Steenland *et al.*, 1996; Muscat and Wynder, 1995) or with increasing duration of ETS exposure (Steenland *et al.*, 1996; Butler, 1988).

An advantage of the cohort studies is that information bias was largely avoided because information on the smoking status of index subjects and their spouses or other sources of ETS exposure was collected at study enrollment, prior to their illness or death. However, cohort studies are susceptible to misclassification resulting from cessation or resumption of smoking by spouses or family members. In one study which compared smoking habits at baseline and at some later time, there was a high concordance in the nonsmoking status of the index subjects (98 percent) and of their spouses (98 percent) over a 20 year period, although some 25 percent of spouses who were smokers in 1960 reported they had stopped smoking by the late 1960's (Humble *et al.*, 1990). This suggests that misclassification of nonsmokers (*i.e.*, nonsmokers who became smokers) is probably minimal, but that exposure to smoking of spouses or other household members at enrollment may be higher than exposures in follow-up years. Thus, in studies with a relatively long follow-up period without reassessment of the smoking status (Hirayama, 1981; Humble *et al.*, 1990) the reported risk estimates may be associated with spouses' smoking for only part of the follow-up period, suggesting that the risk estimates associated with spouses who smoked during the entire follow-up period may be even higher.

The inclusion of smokers who claimed to be nonsmokers at study enrollment produces an upward bias in the observed relative risk for CHD from ETS exposure (Lee, 1989). The basis for this argument is the smoking concordance between husband and wife, *i.e.*, a smoker is more likely than a nonsmoker to have been married to a smoker (Sutton, 1981). Consequently, an active smoker misclassified as a nonsmoker is more likely than a true nonsmoker to have had exposure to ETS, *i.e.*, by being married to a smoker. Smoking causes heart disease, and thus a misclassified smoker has a greater chance of having heart disease than a nonsmoker. The net effect is that an observed association between ETS exposure and CHD among people who claim to be never-smokers may be partially explained

by current or former active smoking by some of them. However, the extent of misclassification of smokers as nonsmokers in these studies is not known, but is likely to be small.

Two studies provided information on the effect of ETS exposure among ex-smokers. These results differed, probably because ex-smokers are a heterogeneous group of individuals who stopped smoking for different reasons. Ex-smokers who have given up smoking because of heart disease and other health problems may be more likely to avoid other smokers. In the study by Svendsen *et al.* (1987), the risks for CHD death, and for fatal and nonfatal CHD combined in relation to ETS exposure, were substantially weaker in the analysis including ex-smokers than that conducted among never-smokers only, suggesting a relatively weak ETS effect in ex-smokers. On the other hand, in the case-control study conducted by Dobson *et al.* (1991a), the ETS effect was stronger in men who were ex-smokers than nonsmokers, but this was not true in women. Results from these studies suggest that there is not a consistent direction of upward bias if some ex-smokers had misclassified themselves as nonsmokers at baseline.

Information on risk of CHD in relation to ETS exposure from workplace or other settings is available in a few studies (Butler, 1988; Steenland *et al.*, 1996; Muscat and Wynder, 1995; He *et al.*, 1994; Dobson *et al.*, 1991a; Kawachi *et al.*, 1997). In the CPS-II study, any effect of workplace ETS exposure was small and was not statistically significant (Steenland *et al.*, 1996). However, in the Nurses' Health Study (Kawachi *et al.*, 1997), there was a strong effect of ETS at work and risk of CHD. A strong effect of ETS at work was also reported in a case-control study conducted in China (He *et al.*, 1994). This study in China differed from other case-control studies in that all cases and controls had full-time jobs and thus had the opportunity to be exposed at work. Most of the other studies (Muscat and Wynder, 1995; Butler, 1988; Dobson *et al.*, 1991a) had limited ability to investigate the role of workplace ETS exposure since only small numbers of subjects had jobs outside the home.

A second concern is the lack of or inadequate control for confounding factors. Although information on the established risk factors for CHD were not available in all studies, including two large cohort studies (Hirayama, 1984; Helsing *et al.*, 1988), the recent large cohort studies conducted by Steenland *et al.* (1996) using the CPS-II cohort and by Kawachi *et al.* (1997) using the Nurses' Health Study included a large number of dietary and nondietary potential confounders in their analyses. A concern is that nonsmokers with smoking spouses may differ from nonsmokers with nonsmoking spouses in other lifestyle habits that are related to heart disease. There is, however, little evidence that this could have explained the observed findings. In the studies which presented data on other heart disease risk factors (blood pressure, cholesterol, body mass index) and dietary habits among nonsmokers stratified by the smoking status of their spouses (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Humble *et al.* 1990; La Vecchia *et al.*, 1993), nonsmoking women married to nonsmokers and those married to smokers were generally similar in other risk factors for heart disease.

More importantly, in the studies which presented relative risks adjusting for demographic factors only (*i.e.*, age and sex), and relative risks adjusting for demographic factors and other CHD risk factors, the latter relative risks were not invariably lower after such adjustment (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Butler, 1988; Humble *et al.*, 1990). In the Nurses' Health Study (Kawachi *et al.*, 1997), although there was some reduction in the relative risk with adjustment of various potential confounders, the risks remained elevated and were statistically significant.

A more fundamental question is whether the ETS association observed is biologically plausible (see Section 8.3) and whether the magnitude of the effect is consistent with the active smoking relationship with CHD. Although the majority of studies have found a significant positive association between active smoking and CHD in men and in women (U.S. DHHS, 1983), there have been some inconsistent findings (Kannel, 1976). The evidence most often cited as demonstrating no association between CHD and active smoking is the negative finding for uncomplicated angina pectoris in women reported in the Framingham study (Seltzer 1991a and 1991b; Skrabanek, 1992). This negative finding has been attributed to the low percentage of women who smoked in this population, and to the fact that even among women who smoked, most were light smokers, and thus the study did not have the power to detect a significant association (Kuller and Meilahn, 1991). A significant positive association between active smoking and CHD in women has been observed repeatedly in more recent cohort studies and in numerous case-control studies (Table 8.3). The strongest evidence is from a large U.S. cohort study of nurses in which significant increased risks for nonfatal MI, angina, and fatal CHD were observed for smokers compared to nonsmokers, demonstrating an increasing trend in risk with increasing amounts of cigarettes smoked (Willett *et al.*, 1987) (Table 8.3). The relative risks for CHD in relation to light smoking reported in recent studies are considerably higher than the risk estimates reported in studies conducted in the 1950's and 1960's. Specifically, in earlier cohort studies, relative risks of 1.2 to 1.6 were generally reported for men smoking 1-9 cigarettes/day compared to nonsmokers, as noted in a previous review (Wu-Williams and Samet, 1990). In more recent studies, relative risks of 2 to 3 were reported for women (Willett *et al.*, 1987; Palmer *et al.*, 1989) (Table 8.3) and men (Rosengren *et al.*, 1992) who were light smokers (1-4 or 5-14 cigarettes/day) compared to nonsmokers. The higher relative risks for CHD in more recent cohorts may be due to the earlier age of smoking initiation or deeper inhalation during smoking. The 2- to 3-fold risk between active smoking and CHD in contemporaneous studies suggests that the increased risk of about 30 percent for ETS exposure and CHD is believable. As described above, the Nurses' Health Study (Kawachi *et al.*, 1997) allowed direct comparison of the risk of active smoking versus passive smoking relative to the same baseline group (that is, never-smoking women not exposed to ETS) and showed that the effect of ETS exposure at home and at work combined was approximately 75 percent of that of active smoking of 1-4 cigarettes per day.

Because there is some variation in the strength of the association between active smoking and various CHD endpoints, it is also important to

distinguish between the different CHD outcomes in studies of ETS. In studies on active smoking and heart disease, the relative risks observed for MI and CHD deaths are usually stronger than the relative risks for angina (Willett *et al.*, 1987; Beard *et al.*, 1989) (Table 8.3). In studies of ETS and heart disease, some studies included fatal and nonfatal endpoints (Svendsen *et al.*, 1987; Hole *et al.*, 1989; Dobson *et al.,* 1991a; Kawachi *et al.*, 1997) while other studies included only fatal endpoints (Hirayama, 1984; Garland *et al.*, 1985; Helsing *et al.*, 1988; Humble *et al.*, 1990; Layard, 1995; LeVois and Layard, 1995; Steenland *et al.*, 1996) or only nonfatal endpoints (Lee *et al.*, 1986; He *et al.,* 1989 and 1994; LaVecchia *et al.*, 1993; Muscat and Wynder, 1995). It is difficult to directly compare these results since most cohort studies provided information on fatal CHD whereas most of the case-control studies provided information on nonfatal CHD endpoints. Two studies allow direct comparison of the association between ETS exposure and risk of fatal and nonfatal endpoints. In one study (Hole *et al.,* 1989), results were presented separately for angina pectoris and for CHD deaths, and the effect of ETS was stronger for CHD deaths than for angina or other cardiovascular disease symptoms. In another study, the relative risks presented for fatal CHD events were higher than the relative risks for fatal and nonfatal endpoints combined, suggesting that the effect for nonfatal events was weaker and had diluted the overall association (Svendsen *et al.,* 1987).

There is some suggestion that the association between active smoking and CHD may be stronger in younger subjects than in older subjects (Bush and Comstock, 1983; Rosenberg *et al.*, 1985), although in some studies, the difference in relative risks by age was only apparent among the very heavy smokers (Willett *et al.*, 1987; Gramenzi *et al.*, 1989) (Table 8.4). Two studies presented findings on ETS and CHD by age group. In one study, there was an apparent effect in both the younger age group (25-44 years) and the older age group (65+) (Helsing *et al.,* 1988). In another study (Steenland *et al.*, 1996), the association between risk of CHD mortality and exposure to spouses' ETS seemed to be more apparent for subjects aged <65 years old. This finding suggests that age-specific and cohort effects of ETS exposure on risk of heart disease should be monitored in future studies.

8.3 OTHER SUPPORTIVE EVIDENCE

It is important to identify the mechanisms whereby exposure to ETS increases the risk of CHD in nonsmokers, and to understand reasons for the relatively large effects of ETS on heart disease in nonsmokers compared to the magnitude of the effect of active smoking on heart disease. At least five interrelated processes have been proposed to contribute to the clinical manifestations of MI, including atherosclerosis, thrombosis, coronary artery spasm, cardiac arrhythmia, and reduced capacity of the blood to deliver oxygen (U.S. DHHS, 1990). The evidence that active smoking influences these mechanisms is convincing (U.S. DHHS, 1990). Supportive evidence is accumulating that exposure to ETS may also increase the risk of some of these same interrelated processes. The effects of ETS on intermediate processes including internal and common carotid wall thickness, endothelial function, exercise tolerance, lipid profile, platelet function, and fibrinogen levels have been investigated and are reviewed below.

Table 8.3
Risks of Heart Disease and Active Smoking in Women

Cohort Study	Smoking Status	Person-Years	Fatal CHD # Event	Fatal CHD RR	Nonfatal MI #Event	Nonfatal MI RR	Fatal CHD & Nonfatal MI #Event	Fatal CHD & Nonfatal MI RR	Angina # Event	Angina RR	Comments
Willett, 1987	Nonsmoker	302,375	15	1.0	48	1.0	63	1.0	31	1.0	U.S. cohort study
	Ex-smoker	174,237	11	1.2	44	1.5	55	1.5	30	1.6	of 119,404 nurses,
	Current (cig/day)										aged 30-55, followed between
	1-14	61,400	5	1.9	21	2.5	26	2.3	11	1.8	1976 and 1982.
	1-4	15,765	NA	NA	NA	NA	7	2.4	NA	NA	
	5-14	45,635	NA	NA	NA	NA	19	2.1	NA	NA	NA = Not Available
	15-24	95,430	17	4.3	65	4.7	82	4.7	19	1.5	
	25+	63,359	17	5.4	64	6.3	81	6.1	17	2.3	

Case-control Studies	Smoking Status	CA/CO	RR	CA/CO	RR	Comments
Beard, 1989	Smoker		For CHD		For Angina	CHD includes MI and sudden unexpected deaths.
	Yes	17/70	1.0	44/117	1.0	
	No	69/80	5.11*	84/115	2.77*	Subjects aged 40-59.
Palmer, 1989	Active Smoking		For MI			
	Nonsmoker	191/940	1.0			Multi-centered hospital-based cases and controls.
	Ex-smoker	149/550	1.4 (1.0-1.8)			
	Current Smoker (cig/day)					Cases between ages 25-64.
	1-4	11/36	2.4 (1.1-5.1)			
	5-14	54/140	2.5 (1.7-3.6)			
	15-24	213/412	3.0 (2.3-3.8)			
	25-34	110/136	5.1 (3.6-7.1)			
	35-44	120/129	4.9 (3.5-6.8)			* 95% CI excluded 1.0
	≥45	58/21	22 (12-39)			
	any tobacco	570/885	3.7 (3.0-4.7)			

Table 8.3 (Continued)

Case-control Studies	Smoking Status	CA/CO	RR for CHD	Comments
Gramenzi, 1989	Active Smoking		For MI	Hospital-based study in Northern Italy, subjects aged 22-69.
	Nonsmoker	90/346	1.0	
	Ex-smoker	10/16	1.5 (0.6-3.6)	
	Current (cig/day)			
	1-14	57/91	2.3 (1.4-3.7)	
	15-24	65/48	5.9 (3.2-9.3)	
	25+	40/18	11.0 (5.1-23.7)	
Rosenberg, 1985	Active Smoking		For MI	
	Nonsmoker	73/571	1.0	Multi-centered U.S. hospital-based study. Subjects aged 25-49.
	Ex-smoker	35/267	1.0 (0.7-1.6)	
	Current (cig/day)			
	1-14	40/211	1.4 (0.9-2.1)	
	15-24	139/449	2.4 (1.8-3.3)	
	25-34	96/152	5.0 (3.6-6.9)	
	35+	171/190	7.0 (5.2-9.4)	

Table 8.4
Risks of Heart Disease and Active Smoking in Women by Age

Case-control Studies	Smoke	# Event	RR	# Event	RR	# Event	RR	Comments
Willett, 1987	Active Smoking	Age 30-39		Age 40-49		Age 50-59		Outcome: Fatal CHD and Nonfatal MI.
	Nonsmoker	5	1.0	20	1.0	38	1.0	
	Current (cig/day)							
	1-14	0	-	7	1.6 (1.1-2.4)	19	2.4 (1.5-3.9)	
	15-24	6	4.3 (1.3-13.7)	24	3.6 (2.4-5.5)	52	4.1 (2.9-5.9)	
	25+	3	3.5 (0.8-14.5)	33	7.0 (4.8-10.5)	45	5.3 (3.7-7.6)	
Bush and Comstock, 1983	Active Smoking	Age 25-44		Age 45-64		Age 65-74		Outcome: Total arteriosclerotic heart disease deaths.
	Nonsmoker	12	1.0	219	1.0	355	1.0	
	Ex-smoker	4	1.8	18	0.7	13	0.8	
	Current (cig/day)							RRs adjusted for marital status, education, housing index, and frequency of church attendance.
	1-9	4	1.5	38	1.1	20	1.0	
	10-20	10	3.7	73	1.4	17	0.8	
	21+	8	2.4	36	2.2	1	0.1	
	Active Smoking	Age 25-44		Age 45-64		Age 65-74		
	Nonsmoker	5	1.0	116	1.0	171	1.0	No information on other risk factors for heart disease.
	Ex-smoker	4	4.6	11	0.9	10	1.2	
	Current (cig/day)							
	1-9	1	1.1	24	1.3	11	1.1	Outcome: Arteriosclerotic heart disease, sudden.
	10-20	8	4.1	51	1.9	10	0.3	
	21+	6	7.5	24	2.8	1	0.4	

Table 8.4 (Continued)

Case-control Studies	Smoke	CA/CO	RR	CA/CO	RR	CA/CO	RR	Comments
Gramenzi, 1989	Active Smoking		Age <50		Age >50			Outcome included acute myocardial infarction.
	Nonsmoker	NA	1.0	NA	1.0			
	Ex-smoker	NA	2.2	NA	1.0			
	Current (cig/day)							RRs adjusted for age, education, alcohol and coffee intake, diabetes, hypertension, hyperlipidaemia, body mass index, and use of oral contraceptives.
	<15	NA	2.1	NA	2.7			
	15-24	NA	4.6	NA	7.3			
	≥25	NA	7.7	NA	NA			
Rosenberg *et al.*, 1985	Active smoking		Age 25-39		Age 40-44		Age 45-49	Outcome included myocardial infarction.
	Nonsmoker	10/117	1.0	18/156	1.0	45/298	1.0	
	Ex-smoker	5/48	1.2	4/86	0.4	26/133	1.3	
	Current (cig/day)							Unadjusted RRs.
	1-14	4/47	1.0	8/56	1.2	28/108	1.7	
	15-24	25/101	2.9	40/154	2.3	74/194	2.5	
	25-34	23/27	10	28/56	4.3	45/69	4.3	
	≥35	41/37	13	58/61	8.2	72/92	5.2	

8.3.1 Internal and Common Carotid Wall Thickness

Hospital-based and population-based studies (Howard *et al.*, 1994; Tell *et al.*, 1994) have demonstrated that active smoking is associated with significantly greater internal and common carotid wall thickening. The relationship between ETS exposure and carotid wall thickening has been investigated in a large cross-sectional (Howard *et al.*, 1994) and a longitudinal study (Diez-Roux *et al.*, 1995). The cross-sectional study was conducted among participants in the Atherosclerosis Risk in Communities (ARIC) Study. At the baseline examination conducted in 1987 through 1989, carotid artery intimal-medial thickness (IMT) was measured using B-mode real-time ultrasound, and exposure to active and passive smoking was assessed by questionnaires administered to about 15,800 adults aged 45 to 65 years. Sixty percent of the study subjects were either current or past smokers and the remainder were never-smokers. Never-smokers were considered exposed to ETS (n = 3,339) if they reported current exposure for one or more hours per week to ETS and as not exposed (n = 1,774) if they had no regular weekly exposure to ETS. Mean IMT (mm) was higher in nonsmokers exposed to ETS (0.711) than in nonsmokers not exposed to ETS (0.700), but the mean IMT values in both groups of nonsmokers were considerably lower than those in past smokers (0.772) or current smokers (0.775). These differences in IMT between ETS-exposed and non-exposed nonsmokers were observed in each age, race, and gender group. After adjustment for age, race, and gender, a significant difference in IMT of 0.017 mm was estimated between ETS-exposed and non-exposed nonsmokers. Further adjustments for other risk factors reduced the difference to 0.013 mm, which remained statistically significant (Table 8.5). The number of hours of ETS exposure was significantly associated with IMT in men but not in women in this study. Among nonsmoking men with ETS exposure (n = 885), after adjustment for age and race, there was an increase of IMT of 0.00792 mm per 10 hours of weekly ETS exposure ($p < 0.001$). In women with ETS exposure (n = 2,340), the increase of IMT was 0.0011 mm per 10 hours of weekly ETS exposure (p = 0.43).

Results from a longitudinal study further support the association between ETS exposure and carotid artery IMT. In 1975, a population census which also asked about active smoking and household smoking was conducted in Washington County, MD, one of the study populations of the ARIC study (Howard *et al.*, 1994). Diez-Roux *et al.* (1995) linked the household smoke exposure data obtained in 1975 to carotid IMT measurements obtained 12-14 years later in the ARIC baseline visit to establish the temporality of the association of ETS exposure with carotid wall thickening. Information on ETS exposure in 1975 and 1987-1989, and carotid artery IMT was available on 2,073 subjects who had never smoked. In males and females combined, the adjusted mean IM wall thickness was 0.706, 0.731, 0.738, and 0.734 mm, respectively, for subjects who had no ETS exposure, were exposed to ETS in 1975 only, were exposed to ETS in 1987-1989 only, and were exposed to ETS in both study periods. This represented a 3.5 to 4.5 percent increase in intimal thickness in relation to ETS exposure. Mean wall thickness was found to be lowest among never-smokers who had never been exposed to ETS, and ETS exposure in one or both time periods was

Table 8.5
Carotid Artery Intimal-Medial Thickness (IMT) as Measured by B-Mode Ultrasound in Current Smokers, Ever-Smokers, and Never-Smokers

Study	Number of subjects	Exposure	Mean IMT wall thickness (in mm)	Comments
Howard *et al.* (1994)	3,525	Active smokers	0.775	Crude means are shown. The difference between passive smokers and never-smokers was 0.011 mm. This difference changed to 0.017mm after adjustment for age, race, and gender ($p \leq 0.0001$) and to 0.014 mm after additional adjustment for lifestyle factors including education, physical activity, alcohol intake, body mass index, and Key's score ($p = 0.0009$).
	4,315	Ever-smokers	0.772	
	3,339	Passive smokers	0.711	
	1,774	Never-smokers not exposed to ETS	0.700	
Diez-Roux *et al.* (1995)	Males and females		Adjusted means ± standard error	Mean wall thickness was adjusted for gender, age, systolic blood pressure, LDL cholesterol, presence of Key's score, physical activity scores, alcohol intake, and education using multiple linear regression.
	456	Current smokers in 1987-1989	0.807 ± 0.009	
	448	Former smokers in 1987-1989 and in 1975	0.757 ± 0.009	
	259	ETS in 1975, 1987-1989	0.734 ± 0.012	
	282	ETS in 1987-1989 only	0.738 ± 0.011	
	77	ETS in 1975 only	0.731 ± 0.022	
	211	No ETS	0.706 ± 0.013	

associated with an increase in wall thickness ranging from 0.023 to 0.035 mm, after adjustment for other risk factors. All three groups exposed to ETS had consistently greater wall thickness than the no-exposure group.

The significance of small increases in wall thickness in relation to ETS exposure is unclear. Analysis based on the entire ARIC cohort found that an IMT increase of 0.16 mm was associated with a 24 percent increase in risk of coronary heart disease events in men and a 44 percent increase among women, over a 2.2 year follow-up period (Howard *et al.*, 1994). Among Finnish men, for each 0.1 mm increase in IM wall thickness the risk of MI increased by 11 percent (Salonen and Salonen, 1991 and 1993). The magnitude of the differences in carotid wall thickness associated with passive smoking is about one-fourth to one-fifth of that observed with active smoking and may contribute to the risk of future cardiovascular events. The magnitude of difference between active and passive smoking in terms of changes in carotid-wall thickness is similar to the magnitude of difference in excess risk for these groups in terms of coronary heart disease endpoints.

8.3.2 Endothelium Function Endothelial dysfunction is considered an important marker of early vascular damage. Celermajer *et al.* (1996) conducted a study which compared the endothelial function in the arteries of three groups of healthy teenagers and young adults: active smokers (n = 26), lifelong nonsmokers who were exposed to ETS (passive smokers, n = 26), and lifelong nonsmokers who reported to have never been regularly exposed to ETS at home or at the workplace (n = 25). Regular exposure to ETS was defined as self-reported exposure at home, at work, or both for at least one hour per day for at least three years (see Table 8.6).

Vascular reactivity of the brachial artery was analyzed. The ultrasound method was used to measure brachial artery vascular responses to increased flow (an endothelium-dependent dilator stimulator) and to nitroglycerin (an endothelium-independent dilator). The diameter of the vessel was measured in every case by two independent observers who were blinded to the active and passive smoking status of the study subjects. Flow-mediated dilatation and nitroglycerin-induced dilatation were calculated by each observer, and the average results of the two observations were recorded.

Subjects in the three groups were similar in baseline characteristics including their age, systolic and diastolic blood pressure, total cholesterol, low-density and high-density lipoprotein cholesterol, vessel size at rest, and flow at rest. Not unexpectedly, the salivary cotinine levels (ng/ml) were significantly higher in the active smokers (170 ng/ml) compared to the passive smokers (3.7 ng/ml) and the nonsmokers (1.2 ng/ml).

The degree of reactive hyperemia produced by cuff inflation and release was similar in the three groups studied. In response to this increase in flow, arterial dilatation was 8.2 percent in the nonsmokers, 3.1 percent in the passive smokers, and 4.4 percent in the active smokers. Among the passive smokers, the percentage of flow-mediated dilatation was 4.1 in the subjects with light exposure to ETS, 3.1 in those with moderate exposure to ETS,

Table 8.6
Endothelium-Dependent Arterial Dilation in Active Smokers, Never-Smokers Exposed to ETS, and Never-Smokers not Exposed

Study	Number of Subjects	Exposure	Flow-mediated dilatation (mean values + SD; in %)
Celermajer *et al.* (1996)	26	Active smokers	4.4* ± 3.1
	26	Never-smokers exposed to ETS	3.1* ± 2.7
	26	Never-smokers not exposed to ETS	8.2 ± 3.1
		By gender	
		Never-smokers exposed to ETS	
	13	Males	3.2 ± 2.5
	13	Females	3.0 ± 2.9
		Never-smokers not exposed to ETS	
	13	Males	7.3 ± 1.9
	13	Females	9.1 ± 3.9
		By level of ETS exposure	
		Never-smokers exposed to ETS	
	9	Light[a]	4.1 ± 3.3
	9	Moderate[b]	3.1 ± 2.2
	8	Heavy[c]	1.8 ± 2.0

[a] *"Light" is defined as never-smokers who were exposed to 1 to 3 hours of ETS at home or at work for at least 3 years.*
[b] *"Moderate" is defined as never-smokers who were exposed to 4 to 6 hours of ETS at home or at work for at least 3 years.*
[c] *"Heavy" is defined as never-smokers who were exposed to >6 hours of ETS at home or at work for at least 3 years.*
* *P value < 0. 05 for never-smokers exposed to ETS compared to never-smokers not exposed, and for active smokers compared to never-smokers not exposed to ETS.*

and 1.8 in those with heavy ETS exposure. There was no difference in the nitroglycerin-induced dilation in the three groups.

In this study, passive smokers have significantly impaired arterial endothelial function. Impaired bioavailability of nitric oxide, the endothelium-derived relaxing factor, may be particularly important, since nitric oxide acts to inhibit platelet aggregation (Cooke and Tsao, 1994; Deanfield, 1996). Dilatation mediated by brachial-artery flow is endothelium-dependent and is mediated in part by the release of nitric oxide. The activity or

production of endothelial nitric oxide may be impaired in young passive smokers as well as in active smokers. Although only superficial systemic arteries can be studied with this ultrasound-based method, endothelial dysfunction in the brachial artery appears to be well correlated with both coronary endothelial physiology and coronary atherosclerosis.

8.3.3 Exercise Tolerance Of the many toxic agents in ETS, carbon monoxide is a main candidate to influence cardiovascular function, through several possible mechanisms. Carbon monoxide (CO) interferes with oxygen transport by binding to hemoglobin, forming carboxyhemoglobin (COHb), resulting in the displacement of oxygen and the lowering of the oxygen-carrying capacity of the blood. On a cellular level, carbon monoxide can interfere with intracellular oxidation processes and can increase platelet adhesiveness (Anthony, 1989; U.S. DHHS, 1983; U.S. DHHS, 1990). Thus, exposure to ETS, which is rich in carbon monoxide, may result in increased myocardial oxygen demand, which in turn may outstrip the oxygen supply and produce ischemia. Carbon monoxide has also been reported to lower the ventricular fibrillation threshold and may accelerate atherogenesis by altering lipid metabolism or by altering vessel permeability to cholesterol. The COHb levels in nonsmokers exposed to ETS may be up to 1.5 percent. This level of COHb can be compared to levels of 4 to 6 percent among active smokers and 2 to 3 percent among certain occupational groups (*e.g.*, blast furnace workers, traffic officers) (Schievelbein and Richter, 1984).

In four studies, the exercise performance of healthy subjects and subjects with a history of heart disease were evaluated under two conditions: in the absence of ETS exposure, and in the presence of ETS exposure. The conditions with ETS exposure simulate exposure levels typically encountered in public settings (Aronow, 1978; McMurray *et al.*, 1985; Leone *et al.*, 1991; Pimm *et al.*, 1978) (Table 8.7).

The study conducted by Aronow (1978) evaluated the exercise tolerance of ten men who had classical stable exertional angina. This study tested the hypothesis that exposure to ETS may result in earlier onset of angina. The men were exposed to ETS in a well-ventilated room and in an unventilated room. Exposure to ETS resulted in elevation in resting heart rate, blood pressure, and carboxyhemoglobin levels under both room conditions, although the increase was more apparent when patients were exposed to ETS in an unventilated room. Corresponding with the increases in COHb levels, the duration of exercise until angina developed decreased 22 percent ($p < 0.001$) after ETS exposure in the well-ventilated room and 35 percent ($p < 0.001$) when the exposure occurred in the unventilated room. The carboxyhemoglobin level increased 42 percent ($p < 0.001$) when exposure to ETS occurred in a well-ventilated room and 75 percent ($p < 0.001$) when in an unventilated room.

Extending the findings of Aronow (1978), Leone *et al.* (1991) evaluated the acute effects of passive smoking on cardiac performance in nine healthy subjects and ten subjects with a history of MI. Healthy subjects were younger (mean age 30.5) than subjects with MI (mean age 53.8). Each subject underwent two exercise stress tests on a bicycle ergometer. The first

test took place in an enclosed space not polluted by smoking whereas the second test occurred when the ambient atmosphere was polluted by 30-35 ppm CO.

The peak exercise power of healthy men was not altered by exposure to ETS. However, men with a history of MI experienced a 33 percent ($p < 0.01$) reduction in peak exercise power (Table 8.7). The time to recovery of pre-exercise heart rate (in minutes) was significantly prolonged for both groups of men when they were exposed to ETS ($p < 0.01$). Measured levels of expired carbon monoxide (ppm) pre-exercise and post-exercise were similar when there was no exposure to ETS, but were four times higher in healthy men and nine times higher in men with previous MI when there was ETS exposure. Levels of plasma CO were also higher post-exercise than pre-exercise in the ETS-exposed group, although a significant increase was observed only among men with a history of MI.

McMurray *et al.* (1985) evaluated the effects of ETS on submaximal and maximal exercise performance in eight young healthy women (4 smokers, 4 nonsmokers) who were regular participants in an aerobics class. Subjects ran on a motor driven treadmill at submaximal and maximal exercise speeds when there was no ETS exposure and with ETS exposure by breathing air mixed with cigarette smoke (Table 8.7). At maximal exercise capacity, exposure to ETS reduced maximal oxygen uptake (11 percent, $p < 0.05$) and duration of exercise (9 percent, $p < 0.05$). Increased values in the following parameters occurred: maximal respiratory exchange ratio (8 percent, $p > 0.05$), maximal blood lactate (24 percent, $p < 0.05$), ratings of perceived exertion (9 percent, $p < 0.05$), and the ratio of ventilation to oxygen uptake (Ve/VO_2 ratio, in liter/min) (10 percent, $p < 0.05$). Similar adverse effects of ETS exposure were observed under submaximal exercise although statistically significant differences were observed for only some of the parameters measured (Table 8.7).

In a fourth study (Pimm *et al.*, 1978), the exercise responses of 20 healthy young men and women were compared after 7 minutes of exercise on an electronic bicycle ergometer when they were not exposed to ETS and when they were exposed to an environment contaminated with about 24 ppm of carbon monoxide, equivalent to that produced by the smoking of four cigarettes. Heart rate, number of breaths per minute, ventilation rate (liter/min), and maximum oxygen uptake (VO_2, liters/min) were measured as an assessment of exercise response. For both men and women, carboxyhemoglobin levels increased significantly when exposed to ETS, but there were few consistent changes in measures of lung volumes or in exercise responses. The lack of significant changes in exercise responses in these healthy subjects is in fact consistent with results in more recent studies. Compromised exercise performance was more easily demonstrated in subjects with a history of heart disease than in healthy subjects (Leone *et al.*, 1991). Moreover, the exercise test in this study is similar to the submaximal exercise challenge in the study of McMurray *et al.* (1985) in which fewer significant differences were observed compared to the maximal exercise challenge. Most of the parameters studied by McMurray *et al* (1985) were not measured by Pimm *et al.* (1978).

Table 8.7
Effect of Exposure to ETS on Excersise Tolerance

Study	Study Subjects/Test	Parameter	In Well-Ventilated Room Exposure to ETS		In Unventilated Room Exposure to ETS	
			No	Yes	No	Yes
Aronow (1978)	10 men with stable angina exposed to 3 smokers who each smoked cigarettes over 2 hours	Duration of exercise in seconds (SD)	232.3 ± 68.4	181.1 ± 52.4[a]	233.7 ± 64.8	145.8 ± 36.9[a]
	subjects exercised on bicycle ergometer until onset of angina	Plasma Carboxy-hemoglobin (%)	1.25 ± 0.20	1.77 ± 0.16[a]	1.30 ± 0.18	2.28 ± 0.15[a]
			Healthy Subjects, Exposed to ETS		MI Patients Exposed to ETS	
			No	Yes	No	Yes
Leone (1991)	19 nonsmoking males, 9 healthy and 10 with history of MI exposed in an enclosed space with 30-35 ppm CO (with combustion of 15-20 cigarettes within 30 minutes)	Peak exercise (in seconds ± SD)	220 ± 30	220 ± 30	120 ± 20	80 ± 25[b]
		Time to recovery (# min ± SD)	8.50 ± 4	19 ± 4[b]	12.3 ± 2	21 ± 2.5[b]
	subjects underwent exercise stress test on a bicycle ergometer twice	Expired CO (ppm)				
		pre-exercise	2.3 ± 2	2.3 ± 2.01	1.2 ± 0.8	0.6 ± 0.2[c]
		post-exercise	2.1 ± 1.9	8.5 ± 1.6[d]	1.3 ± 0.6	5.2 ± 1.2[d]
		Plasma CO (%)				
		pre-exercise	1.2 ± 0.4	1.4 ± 0.2	1.2 ± 0.1	1.2 ± 0.16
		post-exercise	1.2 ± 0.4	1.7 ± 0.4	1.2 ± 0.3	2.3 ± 0.4[d]

[a] *$p < 0.001$ = Comparing exposed to ETS to not exposed under different ventilation conditions*
[b] *$p < 0.01$ = Comparing exposed to ETS to not exposed*
[c] *$p < 0.05$ = Comparing exposed to ETS to not exposed*
[d] *$p < 0.01$ = Comparing post-exercise to pre-exercise level among subjects exposed to ETS*

Table 8.7 (Continued)

Study	Study Subjects/Test	Parameter	Submaximal Exercise Exposure to ETS		Maximal Exercise Exposure to ETS	
			No	Yes	No	Yes
McMurray (1985)	8 normal women, 4 smokers and 4 non-smokers exposed to pure air and air contaminated with ETS	Max 0_2 uptake (l/min)	1.82	1.85	2.39	2.13[a]
	subjects completed an exercise trial which included running 20 min at about 70% $VO_{2max.}$	Duration of exercise (minutes)	--	--	25.8	23.6[a]
		Maximal R value	0.86	0.91	0.93	1.01
		Lactate (mM)	--	--	5.5	6.8[a]
	increase treadmill grade by 2-1/2% every 2 min until subject could not continue with exercise	Ratings of perceived exertion (units)	11.8	13.8[a]	16.5	17.4[a]
		$Ve/V0_2$ (l air/l 0_2)	27.5	28.4	30.5	33.5[a]
		Heart rate (beats/min)	173	178[a]	194	194

[a] *$p < 0.05$, comparing exposed to ETS to not exposed under submaximal or maximal exercise.*

Table 8.7 (Continued)

Study	Study Subjects/Test	Parameter	Females (n = 10) Exposure to ETS[a] No	Females (n = 10) Exposure to ETS[a] Yes	Males (n = 10) Exposure to ETS No	Males (n = 10) Exposure to ETS Yes
Pimm (1978)	20 healthy men and women, ages 18-30 exposed for 2 hours on alternate days to room air or air contaminated with tobacco smoke (about 24 ppm of CO)	Ventilation (l/min)	48.1	48.3	75.3	75.9[b]
		Number of breaths per minute	31.5	30.7	28.3	29.3
	subjects performed a 7-minute exercise test on an electronic bicycle ergometer (submaximum bicycle test)	Heart rate (beat/min)	164.1	168.7[b]	158.3	159.8
		VO_2 (l/min)	1.51	1.48	2.47	2.65[c]

[a] *Values measured at 7 minutes of submaximum bicycle test.*
[b] *$p < 0.01$ by paired to test.*
[c] *$p < 0.05$ by paired to test.*

In two other studies (Allred *et al.*, 1989; Sheps *et al.*, 1990), exercise performance of subjects with a history of coronary artery disease was shown to be compromised when carbon monoxide was introduced into the environment, resulting in exacerbated ventricular arrhythmias (Sheps *et al.*, 1990) and myocardial ischemia (Allred *et al.*, 1989). These studies differed from previous studies (see Table 8.7) in that the amount of carbon monoxide introduced into the chambers was higher, ranging from 100 to 250 ppm, exceeding levels generally reported for public places such as restaurants and bars with tobacco-smoke exposure. The carboxyhemoglobin levels in test subjects were 4 to 6 percent in one study (Sheps *et al.*, 1990) and 2 to 4 percent in another study (Allred *et al.*, 1989).

In summary, the collective evidence suggests that exposure to ETS containing levels of carbon monoxide that may be encountered in public settings with tobacco-smoke exposure has deleterious effects on the heart by increasing the demands on the heart during exercise and reducing its capacity to respond. This imbalance increases the ischemic stress of exercise in patients with existing coronary artery disease and may precipitate symptoms. The data also suggest that even among healthy subjects, exposure to ETS may similarly impair exercise tolerance, although to a lesser extent.

8.3.4 Lipid profile An altered serum lipid profile is an established risk factor for CHD. Determinants of the serum concentrations of the various lipids include diet, exercise, smoking, and genetic factors. A mechanism whereby smoking influences the risk of CHD is by changing the serum lipid fractions into a more atherogenic profile, *i.e.*, higher levels of low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C) (U.S. DHHS, 1990). The strongest and most consistent effect of smoking on lipid profile is to lower concentrations of high-density lipoproteins (HDL). In different studies, HDL levels were 3 to 8 percent lower in male smokers compared to male nonsmokers and 11 to 13 percent lower in female smokers compared to female nonsmokers (Anthony, 1989). There is also the suggestion that smokers have higher levels of triglyceride and total cholesterol compared to nonsmokers, but the differences were generally small, and the data are not consistent (Anthony, 1989). The effect of smoking on HDL cholesterol levels may be through the effect of nicotine on catecholamine levels (Anthony, 1989).

Two studies have examined the relationship between ETS exposure and lipid profiles in healthy adolescents (Table 8.8). The results from these studies suggest that ETS exposure may elevate plasma lipid levels and change lipoprotein distribution, resulting in an elevated ratio of total cholesterol (C) to HDL-C (total C/HDL-C ratio). The total C/HDL-C ratio is used as a predictor of the risk of CHD since a high ratio generally means high levels of total C and low levels of HDL.

Moskowitz *et al.* (1990) studied the effects of ETS exposure on the cardiovascular and oxygen transport system of 216 preadolescent twins, 105 of whom had at least one parent who smoked and 111 of whom had both nonsmoking parents. Blood samples were collected on almost all subjects and levels of thiocyanate and cotinine were used as measures of smoke

Table 8.8
Effect of Exposure to ETS on Lipid Profile in Children

Study	Study Subjects	Results								
Moskowitz (1990)	111 adolescents with both nonsmoking parents	Exposure to ETS	Thiocyanate (mg/l)	Cotinine (ng/ml)	Cholesterol (mg %)	LDL (mg %)	HDL (mg %)	HDL_2 (mg %)	HDL_3 (mg %)	2-3 DPG (µm/ml)
	105 adolescents with at least one smoking parent	No	3.1±5.0	ND[a]	172.2	86.1	49.1	13.5	35.6	1.97
		Yes	7.1±4.3	1.5±3.1	164.1*	81.3	46.0*	12.5	33.5*	2.09**
Feldman (1991)	274 boys, 117 girls			Total Cholesterol/HDL-C Ratios (±SD) by Serum Cotinine Level						
	34% no exposure; 15% mother smoked only; 17% father smoked only; 12% both parents smoked; 22% friends/siblings smoked.			<2.5 ng/ml (*n* = 347)[b]		2.5 ng/ml (*n* = 44)[b]				
				3.51[b]		3.92				
		Exposure to ETS								
		None		3.47 (±0.87)		3.77 (±0.76)				
		Friend/sib only		3.55 (±0.90)		3.70 (±1.13)				
		Mother, not father		3.34 (±0.55)		4.06 (±1.00)				
		Father, not mother		3.64 (±0.78)		4.22 (±1.04)				
		Father & mother		3.68 (±0.85)		3.91 (±1.02)				

[a] *ND = non-detectable. Data presented are the mean levels of cholesterol, lipoproteins, and 2-3 DPG, adjusted for age, weight, height, and sex.*
[b] *The Total-C/HDL-C for the group with cotinine level <2.5 ng/ml was 3.51, and 3.92 for the group with cotinine level ≥2.5 mg/ml. These values are calculated based on data presented in table (i.e., Table 2 of reference).*
* *$p < 0.05$*
** *$p < 0.001$*

exposure in the children. Levels of total cholesterol and subfractions were also assessed. Only data from a single twin randomly selected from each family were used for statistical analysis.

Children who were passively exposed to parents' smoking showed significantly higher levels of thiocyanate (7.1 versus 3.1 mg/l, $p < 0.0001$), cotinine (1.5 ng/ml versus non-detectable levels), and 2-3 diphosphoglycerate (DPG) (2.09 versus 1.97 µm/ml, $p < 0.001$) compared to children not exposed to parents' smoking. The level of DPG is used as a marker of the body's response to hypoxia—*i.e.*, the oxygen demands of body tissues. Corresponding to these increases, there were significant reductions in levels of HDL (6.3 percent, $p < 0.05$) and total cholesterol (4.7 percent, $p < 0.05$) among children passively exposed compared to those not exposed when age, weight, height, and gender were adjusted for in the analysis. There is internal consistency in the data such that within smoking families, significant positive correlations were observed between thiocyanate levels and total number of cigarettes parents smoked per day ($r = 0.35$, $p < 0.0001$), between thiocyanate and cotinine levels ($r = 0.44$, $p < 0.0001$), and between thiocyanate and DPG levels ($r = 0.29$, $p < 0.02$).

In another study, Feldman *et al.* (1991) compared the ratio of total C/HDL-C in children stratified by exposure to ETS. Included in this analysis were 391 adolescents (presumed to be nonsmokers), of whom 44 percent reported that one or both parents currently smoked, 22 percent reported exposure to smoking of friends/siblings only, and 34 percent reported no exposure. In the main analysis, total C/HDL-C ratio in adolescents whose plasma cotinine levels were ≥2.5 ng/ml ($n = 57$) (the level considered indicative of exposure) was compared to those with lower cotinine levels. Eighty-two percent of subjects with cotinine levels ≥2.5 ng/mL reported exposure to ETS. Plasma cotinine levels ≥ 2.5 ng/mL were associated with low HDL-C and a higher ratio of total C to HDL-C levels. The total C/HDL-C ratio was 8.9 percent ($p < 0.003$) greater and the mean HDL-C level was 6.8 percent ($p < 0.03$) lower in adolescents with higher plasma cotinine concentrations (≥2.5 ng/ml), compared to those with lower cotinine levels. The calculated total C/HDL-C ratios were 3.92 and 3.51, respectively, for children with cotinine levels ≥2.5 ng/ml and <2.5 ng/ml (based on Table 4.2 of Feldman *et al.*, 1991). The higher total C/HDL-C ratios among adolescents with higher cotinine levels were observed regardless of their source of ETS exposure. Information on dietary habits and socioeconomic status were not available in either the Feldman *et al.* (1991) or the Moskowitz *et al.* (1990) study, precluding adjustment for potential confounding effects on the observed association.

The change in lipid profiles among nonsmoking children exposed to ETS compared to nonsmoking children not exposed is compatible with the change observed when children who smoke are compared to nonsmoking children. In a meta-analysis which examined cigarette smoking associated changes in blood lipid and lipoprotein levels in 8 to 19 year olds, Craig *et al.* (1990) reported that active smokers showed significantly lower serum levels of HDL-C (8.5 percent) compared to nonsmoking children in the

same age range. The HDL-C levels were 9 percent lower in active smokers compared to nonsmokers (Craig *et al.*, 1990) and 6-7 percent lower in nonsmokers exposed to ETS compared to nonsmokers not exposed (Moskowitz *et al.*, 1990; Feldman *et al.*, 1991).

Information on lipid profiles in nonsmoking adults exposed to ETS and those not exposed is available in the case-control study of He *et al.* (1989). Similar to the results in children, nonsmoking adults who were exposed to ETS also showed lower levels of HDL-C. The average levels were 1.29 nmol/l in nonsmoking women not exposed, and 1.41 nmol/l in nonsmoking women exposed to spouses' smoking (8.5 percent reduction, $p < 0.05$).

In summary, the findings by Moskowitz *et al.* (1990) and Feldman *et al.* (1991), which show the effects of exposure to ETS on lipid levels, provide support for another mechanism whereby risk of heart disease in those exposed to ETS may be increased. The reduction in HDL-C levels among passive smokers is about two-thirds of that reported for active smokers, providing a possible explanation for the relatively large effect of ETS on heart disease in nonsmokers compared to the effect of active smoking on heart disease.

8.3.5 Platelet Aggregation and Endothelial Damage

Platelets have an important role in the development and progression of atherosclerosis. Although studies on the effect of smoking on platelet function are not all consistent, most studies point to an effect of smoking on the behavior of platelets (U.S. DHHS, 1990; Anthony, 1989; Ozdemir *et al.*, 1992; Rangemark *et al.*, 1992; Chiang *et al.*, 1992). Specifically, some of the changes in platelets that have been demonstrated in smokers compared to nonsmokers include shorter platelet survival (Mustard, 1981), increased response to aggregation induced by various agents including adenosine diphosphate (ADP) or thrombin (Renaud *et al.*, 1984; Blache *et al.*, 1992; Rival *et al.*, 1987), elevated serum and urinary levels of thromboxane and its metabolites (Dotevall *et al.*, 1992; Rangemark *et al.*, 1992; Nowak *et al.*, 1987), decreased endothelial prostacyclin (PGI_2) synthesis (Madsen and Dyerberg, 1984), and decreased platelet sensitivity to PGI_2 (Burghuber *et al.*, 1982 and 1986). In smokers, an increase in levels of thrombaxone (a platelet aggregating agent and vasoconstrictor) in conjunction with a reduction in the levels of PGI_2 (an inhibitor of platelet aggregation and a vasodilator), suggests an imbalance in hemostatic function in favor of aggregation. The overall effect of smoking tends to increase the ease with which platelets aggregate and the ease with which platelet mediators are released (Anthony, 1989).

Of the various measures of platelet functions that have been investigated in active smokers (see above), platelet sensitivity to PGI_2 in smokers and nonsmokers exposed to ETS has been investigated (Sinzinger and Kefalides, 1982; Burghuber *et al.*, 1986).

In one study, platelet sensitivity to the anti-aggregatory prostaglandins before, during, and after ETS exposure in smokers and nonsmokers was measured (Sinzinger and Kefalides, 1982). The unit of measurement of platelet sensitivity is the ID_{50}—the amount of prostaglandins (PG) in ng/ml

Table 8.9
Platelet Sensitivity to Antiaggregatory Prostaglandins[a] Before and After Exposure to ETS

Study	Before	After
Sinzinger (1982) [b]		
Exposed to passive smoking		
Nonsmokers	1.26 ± 0.11	2.16 ± 0.21 ($p < 0.01$)
Smokers	1.75 ± 0.26	2.08 ± 0.19 (nonsig.)
Burghuber (1986) [c]		
Exposed to active smoking [d]		
Nonsmokers	1.61	2.08 ($p < 0.01$)
Smokers	3.33	3.13 (nonsig.)
Exposed to passive smoking [e]		
Nonsmokers	1.25	1.82 ($p < 0.01$)
Smokers	1.89	2.04 (nonsig.)

[a] *Values represent the concentration of protascyclin necessary to inhibit ADP induced platelet aggregation to 50%. Values are in units of PG in ng/ml platelet-rich plasma, means ± serum.*
[b] *Exposure to passive smoking occurred in an 18m^3 room where 30 cigarettes were smoked to give a smoke concentration resembling that in discos or restaurants. Subjects were exposed for 15 minutes. Blood was collected before and immediately after the smoking period, as well as 20 and 60 minutes later.*
[c] *Values shown are calculated in the following way: Sensitivity index of PGI2 were obtained from extrapolating values in Figures 3 and 4 in reference. From these figures, we estimated that the sensitivity iindices were 0.62, 0.48, 0.30, 0.32, 0.80, 0.55, 0.53, 0.49 (values are presented in the order under 'Before' and 'After' columns, for each of the 4 rows). Since sensitivity index equals 1/ID_{50}, where ID_{50} is the concentration of PGI2 necessary to inhibit ADP-induced platelet aggregation to 50 percent, ID_{50} was calculated is 1/sensitivity index (e.g., 1/0.62 = 1.61).*
[d] *Active smoking experiment: Fourteen healthy males smoked two cigarettes within 10 minutes. Blood specimens were collected immediately before and 15 minutes after smoking.*
[e] *Passive smoking experiment: Twenty-two healthy males were exposed for 20 minutes in an 18 m^3 room in which 30 cigarettes were smoked. Blood specimens were collected immediately before and 15 minutes after the passive smoking period.*

platelet-rich plasma necessary to halve the aggregation induced by 1 µmol/l ADP. Exposure to ETS, simulating the concentrations encountered in nightclubs and restaurants (*i.e.*, exposing nonsmokers to smokers who smoked 30 cigarettes) reduced platelet sensitivity to the anti-aggregatory PG. The reduction was marked and was statistically significant in nonsmokers but not in smokers. It is of note that the baseline values were significantly lower ($p < 0.01$) in smokers compared to nonsmokers, and that platelet sensitivity returned to basal values more quickly in nonsmokers than smokers (Table 8.9).

Table 8.10
Measures of Platelet Function in Relation to Exposure to Active Smoking and Passive Smoking

Study	Number of Subjects	Exposure	Platelet Function: Endothelial Cells/Chamber	Platelet Function: Platelet Aggregate Ratios
Davis et al. (1985)		Smoked tobacco cigarettes		
	20	Before[a]	2.3 ± 0.5	0.80 ± 0.06
	20	After	4.8 ± 1.3	0.65 ± 0.07
		Smoked non-tobacco cigarettes		
	20	Before	2.5 ± 1.1	0.81 ± 0.10
	20	After	3.0 ± 1.1	0.78 ± 0.10
Davis (1989)		Control Period		
	10	Before	2.2 ± 0.8	0.88 ± 0.05
	10	After	2.3 ± 1.0	0.88 ± 0.04
		Exposed to ETS[b]		
	10	Before	2.8 ± 0.9	0.87 ± 0.06
	10	After	3.7 ± 1.1	0.78 ± 0.07

[a] *All the 'before' and 'after' differences were statistically significant at $p < 0.01$.*
[b] *Nonsmokers were exposed to ETS for 20 minutes in open hospital corridors by sitting next to smokers.*

In another study, Burghuber *et al.* (1986) studied the response of platelets to exogenous PGI_2 in terms of the sensitivity index of PGI_2 in chronic smokers and nonsmokers; levels in groups were measured under two sets of conditions: prior to and after actively smoking two cigarettes, and prior to and after exposure to an ETS contaminated atmosphere, respectively. To enable us to compare the results reported by Sinzenger and Kefalides (1982) and by Burghuber *et al.* (1986), we converted the latter results to the same units of measurement as the former study. Specifically, we calculated the ID_{50} by taking the reciprocal of the sensitivity index. In smokers and nonsmokers, the sensitivity index before and after active smoking and before and after ETS exposure is estimated from the data presented in Figures 3 and 4 of Burghuber *et al.* (1986) (Table 8.9). Similar to the findings of Sinzinger and Kefalides (1982), platelet sensitivity to PGI_2 in Burghuber *et al.* (1986) was significantly reduced after active smoking and after exposure to ETS. As shown in the study by Sinzinger and Kefalides (1982), the baseline values were in fact significantly lower in active smokers than in nonsmokers. The levels in nonsmokers, even after active smoking or ETS exposure, only approached the baseline levels of smokers. This study also suggests that platelets of smokers are less sensitive to the anti-

aggregatory action of exogenous PGI_2 compared to platelets of nonsmokers. Acute inhalation of tobacco smoke decreases platelet sensitivity to PGI_2 only in nonsmokers, whereas no further decrease could be demonstrated in smokers. Thus, chronic active smoking or passive smoke exposure can desensitize blood platelets to PGI_2. Such platelets may be more ready to aggregate and participate in plug formation, leading to arterial thrombosis.

In addition to the effects on platelet function, smoking has been shown to have a desquamating effect on human endothelium, manifested by an increase in the concentration of anuclear carcasses of endothelial cells in venous blood (Prerovsky and Hladovec, 1979).

In a series of studies, Davis *et al.* compared the endothelial cell counts and platelet aggregate ratios when different types of tobacco products were smoked (Davis *et al.*, 1985; Davis *et al.*, 1990) and when nonsmokers were exposed to ETS (Davis *et al.*, 1989) (Table 8.10). In brief, these studies showed that the number of endothelial cells (per 0.9 µl chamber) more than doubled after smoking tobacco cigarettes, increased by 20 percent after smoking non-tobacco cigarettes (made from wheat, cocoa, and citrus plants), and increased by 32 percent after ETS exposure compared to less than 5 percent increase under control conditions (*i.e.*, no exposure to ETS). Platelet aggregate ratios decreased 19 percent ($p < 0.0002$), 4 percent ($p = 0.004$), and 10 percent ($p = 0.002$) respectively, after smoking tobacco cigarettes, non-tobacco cigarettes, and after exposure to ETS. There was no change in platelet aggregate ratios under control conditions (Table 8.10).

Nicotine is a potential cause of the observed changes in endothelial cells and platelet aggregate ratios after smoking tobacco cigarettes, although other components of cigarette smoke may be important. The modest changes in endothelial cells and platelet aggregate ratios after exposure to ETS may be related to the increase in nicotine and carboxyhemoglobin levels in the blood after exposure to ETS. The changes observed in relation to smoking non-tobacco cigarettes may be explained by the release of small amounts of catecholamines and modest elevation in nicotine levels even when non-tobacco cigarettes are smoked (Davis *et al.*, 1990). These studies demonstrate that brief exposure to ETS under naturally occurring environmental conditions has consistent acute effects on the endothelium and platelets similar to those of active smoking. The exact roles of carbon monoxide, nicotine, and other components of tobacco smoke as causes of observed effects on platelets and the endothelium remain unclear; however, both of the effects seen following exposure of nonsmokers to ETS, platelet activation and endothelial damage, are prominent among the mechanisms thought to be involved in atherosclerosis and arterial thrombosis. These observations suggest another mechanism whereby exposure to ETS may increase the risk of heart disease in nonsmokers.

8.3.6 Fibrinogen Levels In numerous cross-sectional, case-control, and cohort studies (U.S. DHHS, 1990; Dobson *et al.*, 1991b; Meade *et al.*, 1993), fibrinogen levels have been found to be consistently elevated among smokers compared to nonsmokers. Fibrinogen levels are strong predictors of risk of CHD (Wilhelmsen *et al.*, 1984; Meade *et al.*, 1986; Kannel *et al.*, 1987) and

are thought to act by promoting thrombogenesis (Meade *et al.*, 1987; Kannel *et al.*, 1987). Studies of ex-smokers show that fibrinogen levels decreased with smoking cessation; the reduction is observed within 1 to 2 months of smoking cessation. There is some suggestion that fibrinogen levels in ex-smokers approach those of never-smokers 2 to 5 years after smoking cessation (Meade *et al.*, 1987; Dobson *et al.*, 1991b).

In one case-control study (Dobson *et al.*, 1991a), levels of serum fibrinogen were determined among controls to test the hypothesis that fibrinogen concentrations would be higher in smokers than nonsmokers, and higher in nonsmokers exposed to ETS than in non-exposed nonsmokers. Fibrinogen concentrations were highest in current smokers, intermediate in ex-smokers and lowest in nonsmokers, both in men and in women. Nonsmoking men exposed to ETS at home showed higher fibrinogen levels than nonsmoking men not exposed, but this was not observed in women. There was also no difference in levels of fibrinogen for nonsmokers exposed to ETS at work and those not exposed (the mean fibrinogen concentrations and corresponding confidence intervals were presented in two figures in Dobson *et al.* (1991a), but the actual values could not be accurately determined from the figures).

8.3.7 Animal Studies Some animal studies have demonstrated that short-term exposure to ETS promotes the atherosclerotic process. Exposure to high levels of ETS significantly accelerated the development of atherosclerosis in the aorta and pulmonary artery in male New Zealand White rabbits maintained on a high cholesterol diet (Zhu *et al.,* 1993). In a follow-up study in test animals of the same sex and strain, exposure to ETS significantly accelerated the development of arteriosclerosis; while these investigators found that ß-blocker metoprolol decreased the development of arteriosclerosis, it did not protect against the effects of ETS on atherosclerosis (Sun *et al.,* 1994), suggesting that the ß-adrenergic receptor system is not involved in the mechanism of ETS-induced atherosclerosis. In another study, the growth of existing atherosclerotic plaques was accelerated in young cockerels exposed to ETS compared to those not exposed (Penn and Snyder, 1993). Specifically, inhalation of ETS did not influence the number of plaques in this study, but caused a marked increase in plaque size as determined by plaque index measurements. The investigators hypothesized that ETS exposure did not induce formation of plaques but that it stimulated the proliferation of normally quiescent cells. In a subsequent study, ETS exposure levels were decreased by a factor of five and the effect was still seen (Penn *et al.*, 1994). The investigators noted that ETS exposure at levels equal to or below those routinely encountered by people in smoke-filled environments were sufficient to promote arteriosclerotic plaque development. In Sprague-Dawley rats, ETS acutely increased LDL accumulation in perfused carotid arteries after a single exposure (Roberts *et al.*, 1996).

Exposure to ETS increased myocardial infarct size in a (Sprague-Dawley) rat model of ischemia and reperfusion, and longer ETS exposure produced a larger effect on infarct size (Zhu *et al.*, 1994). In an investigation of the mechanism by which ETS exposure causes this effect, L-arginine blocked the increase in myocardial infarct size produced by ETS in the same animal

model, but had no effect on increased platelet aggregation resulting from ETS exposure (Zhu *et al.*, 1996). Since L-arginine is a precursor to nitric oxide, the authors postulated that the protective effect on infarct size might be related to an inhibitory effect of nitric oxide on leukocyte- or free-radical-induced injury.

8.4 CHAPTER SUMMARY AND CONCLUSIONS

In summary, the epidemiologic data, from prospective and case-control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers. Prospective studies have the advantage that information on smoking status and exposure to ETS was obtained prior to diagnosis of heart disease, minimizing selective recall bias and misclassification bias associated with disease status. On the other hand, in some case-control studies, information on ETS exposure was more detailed and included exposure from spouses as well as from other sources. To the extent possible, estimates of risks were determined with adjustment for demographic factors, and often for other factors related to heart disease (*e.g.*, blood pressure, serum cholesterol level, obesity index, dietary factors) which may potentially confound the ETS and heart disease association. Estimates of risks associated with ETS exposure were almost always strengthened when there was adjustment for other cofactors. An overall risk of about 30 percent is supported by the collective evidence and is within the range of risk estimates observed for active smoking and CHD in contemporaneous studies published since the 1970's and 1980's (*e.g.*, RR = 2.4 for fatal CHD and nonfatal MI in women who smoked 1-4 cigarettes/day) (Willett *et al.*, 1987). The association between ETS and CHD is also consistent with the active smoking and CHD association in that the relationship is stronger for fatal CHD outcomes than for nonfatal outcomes and angina.

Supporting the epidemiologic evidence, there are data accumulating from clinical studies which suggest various mechanisms for a causal association between ETS and heart disease. In a number of studies in which nonsmokers were exposed to ETS, carotid wall thickening and compromise of endothelial function were similar but less extensive than that experienced by active smokers. In nonsmokers, including well subjects and those with a history of heart disease, exercise performance is compromised when exercise tests occur under conditions with ETS exposure. There are also data which show that nonsmokers exposed to ETS compared to those with no exposure show a lipid profile that is more atherogenic. In studies of adolescents as well as adults, the reduction of HDL-C levels in nonsmokers exposed to ETS was about two-thirds of that observed when active smokers were compared to nonsmokers. Of the different parameters of platelet function that may be affected by active smoking, platelet sensitivity to the anti-aggregatory effect of PGI_2 has been investigated in nonsmokers. In nonsmokers exposed to ETS, the concentration of PGI_2 required to inhibit platelet aggregation increased 40-70 percent. There was also an increase in the number of desquamating endothelial cells in nonsmokers exposed to ETS. These data collectively show that deleterious effects seen following ETS exposure may account for both short-term and long-term effects of ETS exposure on the heart.

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