State of California
AIR RESOURCES BOARD

APPENDIX III

PROPOSED IDENTIFICATION OF ENVIRONMENTAL TOBACCO SMOKE AS A TOXIC AIR CONTAMINANT

PART B – HEALTH EFFECTS

As Approved by the Scientific Review Panel
On June 24, 2005

The SRP approved Part B is a supporting technical document which is incorporated by reference in the Initial Statement of Reasons (Staff Report)

State of California

Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant

Part B: Health Effects

As Approved
by the Scientific Review Panel
on June 24, 2005

California Environmental Protection Agency
Office of Environmental Health Hazard Assessment

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Secretary for Environmental Protection
California Environmental Protection Agency
Alan C. Lloyd, Ph.D.

Director
Office of Environmental Health Hazard Assessment
Joan E. Denton, Ph.D.

Proposed Identification of Environmental Tobacco Smoke as a Toxic air Contaminant

Part B:

HEALTH EFFECTS ASSESSMENT FOR ENVIRONMENTAL TOBACO SMOKE

As Approved by the Scientific Review Panel June 24, 2005

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH

Prepared By:

Staff

Mark D. Miller, M.D., M.P.H.
Rachel Broadwin, M.P.H.
Shelley Green, Ph.D.
Melanie A. Marty, Ph.D.
Judy Polakoff, M.S.
Andrew G. Salmon, M.A., D.Phil.
Bruce Winder, Ph.D.

Consultants

Sharan Campleman, Ph.D., Public Health Institute (Literature review and draft, Chapter 7)
Delia Dempsey, M.D., UCSF (Literature review and draft, Chapter 3)
Mark Eisner, M.D., M.P.H., UCSF (Literature review and draft of parts of Chapter 6)
Kenneth C. Johnson, Ph.D., Health Canada (Breast cancer meta-analysis)
Dennis Shusterman, M.D., M.P.H., UCSF (Literature review and draft of parts of Chapter 6)

Reviewers

George V. Alexeeff, Ph.D.
Jay Beaumont, Ph.D.
Mari Golub, Ph.D.
Farla Kaufman, Ph.D.
Janice Kim, M.D., M.P.H
Kathleen Vork, Ph.D.

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Executive Summary

The California Air Resources Board entered environmental tobacco smoke (ETS) into the process of identifying substances as Toxic Air Contaminants. As a result, the Office of Environmental Health Hazard Assessment (OEHHA) has, in this document, updated the report on health effects of environmental tobacco smoke first released in 1997 (Cal/EPA, 1997) and later published by the U.S. National Cancer Institute (NCI, 1999). This document, in conjunction with the 1997 OEHHA report (Cal/EPA, 1997; NCI, 1999) serves as the health effects assessment pursuant to Health and Safety Code Section 39660 *et seq*. We summarize the findings of the original report on each endpoint, and add to those findings based on our review of the more recent literature.

The Children's Environmental Health Protection Act of 1999 amended the Toxic Air Contaminants statute by explicitly requiring considerations of any evidence on: 1) differences in exposure patterns between infants and children and adults; 2) special susceptibilities of infants and children to the effects of candidate TACs; 3) interactions between TACs and criteria air pollutants, and 4) interactions of chemicals acting by similar mechanisms. This document examines the evidence for the effects of ETS on infants and children including both prenatal and postnatal exposure. Infants and children may be uniquely susceptible to certain health outcomes related to chemical exposures, including ETS, relative to adults. Children are still developing through adolescence; developing organs can present unique targets for toxicity that are not present in the mature organ or organ system. Thus, developmental toxicity of ETS is an important focus of this report. We have provided summaries of major studies on the effects of ETS exposure on children in each chapter for endpoints that were studied in children. We summarize below the evidence of adverse health effects in children resulting from exposure to ETS. Note that other terms for ETS are described in Chapter 1; we primarily use ETS and "passive smoking" for exposure to ETS throughout the document.

Children are intrinsically exposed to air contaminants at a level exceeding that of adults in the same setting due to higher breathing rates per body weight and lung surface area relative to adults (Snodgrass, 2002; Miller *et al*., 2002). These elevated breathing rates are related to a higher oxygen demand due to growth and development as well as generally higher physical activity levels. This elevated exposure rate would also apply to ETS. In addition, younger children do not generally have a choice of environment. As such, they cannot remove themselves from exposure as an older child or adult could. As described in Part A, this is reflected in the latest serum cotinine measurements in the Third National Health and Nutrition Examination Survey, where levels in people exposed to passive smoke were highest in young children (Mannino *et al*., 2001).

Exposure to environmental tobacco smoke (ETS) has been linked to a variety of adverse health outcomes. Although great strides have been made in the reduction of ETS exposure in the workplace, many Californians are still 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, 1992i) and the National Research Council (NRC, 1986g), and the earlier OEHHA review (Cal/EPA, 1997), 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 these reviews. The State of California has therefore undertaken a broad update of the previous ETS document, 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 (described in Chapter 1) has been used to describe the body of evidence to conclude whether or not 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 and are supported by toxicological evidence in animals. It should be noted that the review of the literature for this update and subsequent weight-of-evidence evaluation did not result in downgrading any of the conclusions regarding health outcomes found to be either causally associated with ETS or for which there was suggestive evidence of an association in the 1997 Cal/EPA report. 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 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 active smoking during pregnancy is not considered to be ETS exposure.

1. General Findings

ETS is an important source of exposure to toxic air contaminants indoors. There is also 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 has a number of serious impacts on infant's and children's health including sudden infant death syndrome (SIDS), exacerbation of asthma, increased respiratory tract infections, increased middle ear infections, and causes developmental toxicity resulting in low birth weight, and impaired lung function growth, predisposition to SIDS (to the extent that this is a developmental effect), and other developmental impacts. If the Air Resources Board lists ETS as a Toxic Air Contaminant, it should be added to the list of TACs that may disproportionately impact children pursuant to Health and Safety Code Section 39669.5(c).

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 SIDS, heart disease mortality and lung cancer death, as well as serious chronic diseases, such as childhood asthma. There are a number of effects for which evidence is suggestive of a causal association, but further research is needed for confirmation, including spontaneous abortion, decreased lung function growth, cervical cancer, and chronic respiratory symptoms 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, adverse male reproductive effects, and rare childhood cancers.

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 lung cancer, where certain California-specific data are unavailable, estimates are derived from figures published for the U.S. population, assuming that the number affected in California would be 12% of the total. The estimates for cardiovascular disease,

middle ear infection, asthma episodes, SIDS, pre-term delivery, and low birthweight were derived using information on prevalence of ETS exposure in California and the U.S.

Relative risk estimates associated with some of these endpoints are small, but because the diseases are common and ETS exposure is frequent and widespread, the overall impact can be quite large. A relative risk estimate of 1.2-1.7 for heart disease mortality in nonsmokers is supported by the evidence; this corresponds to approximately 1,700-5,500 deaths annually in California. The relative risk estimate of 1.38 associated with low birthweight implies that ETS may impact fetal growth of 1,600 newborns in California. It is estimated that at least 31,000 children in California experience one or more ETS-related asthma episodes (new onset or exacerbation) each year. Large impacts are also associated with relative risks for respiratory effects in children such as middle ear infection (RR $\approx$ 1.62) (about 50,000 children annually), and lower respiratory infection in young children (RR $\approx$ 1.5 to 2) (18,000 to 36,000 children annually). ETS exposure is implicated in 21 SIDS deaths per year in California (RR $\approx$ 3.5). About 400 to 1100 lung cancer deaths in California are ETS-related. For nasal sinus cancers, observed relative risks have ranged from 1.7 to 3.0. This is as high as or higher than the relative risks observed for lung cancer. Finally, for breast cancer, when evaluating younger, primarily premenopausal women at diagnosis, a pooled risk estimate of 1.68 is derived in the meta-analysis, and when restricted to the studies with better exposure assessment, an estimate of 2.20 is obtained (see Table ES1). These estimates of association could represent a significant number of cases as this is a relatively common cancer in women. Adding the mid-point of the ranges for lung cancer deaths and heart disease deaths, and including the SIDS point estimate, one can attribute about 50,000 deaths per year in the United States and 4000 deaths per year in California from ETS-associated disease. This does not include the estimates for other ETS-associated cancer deaths.

TABLE ES.1
HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

Effects Causally Associated with ETS Exposure

Developmental Effects
Fetal growth: Low birthweight and decrease in birthweight
Sudden Infant Death Syndrome (SIDS)
Pre-term delivery

Respiratory Effects
Acute lower respiratory tract infections in children
(*e.g.*, bronchitis and pneumonia)
Asthma induction and exacerbation in children and adults
Chronic respiratory symptoms in children
Eye and nasal irritation in adults
Middle ear infections in children

Carcinogenic Effects
Lung cancer
Nasal sinus cancer
Breast cancer in younger, primarily pre-menopausal women

Cardiovascular Effects
Heart disease mortality
Acute and chronic coronary heart disease morbidity
Altered vascular properties

Effects with Suggestive Evidence of a Causal Association with ETS Exposure

Reproductive and Developmental Effects
Spontaneous abortion, Intrauterine Growth Retardation
Adverse impact on cognition and behavior
Allergic sensitization
Decreased pulmonary function growth
Adverse effects on fertility or fecundability

Cardiovascular and Hematological Effects
Elevated risk of stroke in adults

Respiratory Effects
Exacerbation of cystic fibrosis
Chronic respiratory symptoms in adults

Carcinogenic Effects
Cervical cancer
Brain cancer and lymphomas in children
Nasopharyngeal cancer
All cancers – adult and child

Table ES-2. Attributable Risks Associated with ETS

Outcome	Conclusion OEHHA 1997 Annual Excess # in CA	Conclusion OEHHA 1997 Annual Excess # in US	Conclusion Update Annual Excess # in CA	Conclusion Update Annual Excess # in US
Pregnancy:				
Low birth weight	1,200-2,200	9,700-18,600	1,600 [1]	24,500 [2]
Pre-term delivery			4,700 [1]	71,900 [2]
Asthma (in children):				
# Episodes [3]			31,000 [4]	202,300 [5]
# New cases	960-3120	8,000-26,000	N/A	N/A
#Exacerbations	48,000-120,000	400,000-1,000,000		
Lower respiratory illness	18,000-36,000	150,000-300,000	N/A	N/A
Otitis media visits	78,600-188,700	700,000-1,600,000	50,200	790,000 [6]
SIDS	120	1,900-2,700	21 [7]	430 [8]
Cardiac death (Ischemic heart disease death)	4,200-7,440	35,000-62,000	3,600 (range: 1,700-5,500) [9]	46,000 (range: 22,700-69,600) [10]
Lung cancer death	360	3000	400 [11]	3400
Breast cancer – diagnosis in younger, primarily premenopausal women			All studies: OR 1.68 (95% CI 1.31-2.15) [12] Best studies: OR 2.20 (95% CI 1.69-2.87) Approximate 68-120% increased risk	

1 Based on California Dept Health Services (CDHS, 2000a), Table 2-6, Number and percent of live births with selected medical characteristics by race/ethnic group of mother, California 2000, and Gilpin *et al*. (2001).

2 Based on CDC (2002b) National Vital Statistics Report. Vol 51(2) 2002. Births: Final data for 2001, and on adult females reporting exposure to ETS in NHANES III for 1995 (Pirkle *et al*., 1996).

3 The data to distinguish number of new cases from number of exacerbations were not available for the updated calculations; thus, OEHHA considered that these estimates were best described as number of episodes.

4 Based on number of asthma attacks or episodes in previous 12 months for 0-17 year olds. Calculated from California Health Interview Survey for 2001.

5 Based on number of asthma attacks or episodes in previous 12 months for 0-14 year olds in Mannino *et al*. (2002b) CDC-MMWR 51(SS01)).

6 Based on Freid *et al*. (1998) National Center for Health Statistics Series 13 No. 137. Ambulatory Health Care Visits by Children: Principal Diagnosis and Place of Visit for yrs 1993-1995.

7 Based on California Dept Health Services (CDHS, 2000b), Table 4-10 for yr 2000 Leading causes of infant death by race/ethnic group of child, California 2000.

8 Based on CDC (2002a) National Center for Health Statistics (2002). . www.cdc.gov/nchs/fastats/infort.htm for yr 2000

9 Based on California Dept Health Services (CDHS, 2000c), Table 5-7, Deaths, death rates, and age-adjusted death rates for leading causes by sex, California, 1999- 2000.

10 Based on Anderson and Arias (2003). National Vital Statistics Report. Vol 51(9) Table 2 for yr 2000 Ischemic heart diseases including AMI.

11 Assuming California exposure and death rates are similar to national rates and California population is 12% of national population.

12 OEHHA is unable at this time to calculate an attributable risk as it is not possible to account accurately for the portion attributable to other known risk factors. The OR for all studies is based on our meta-analysis of all studies with risk estimates for younger primarily premenopausal women. The OR for best studies is based on the OR for studies which evaluated younger primarily premenopausal women and which did a better job of ascertaining exposure – see Part B Section 7.4.1.3.2 and Table 7.4.1I.

N/A = data not available.

Citations for documents cited in above table appear in Part B Chapter 1 references.

2. Specific Findings and Conclusions

2.1. Developmental Toxicity - Perinatal Manifestations of Prenatal ETS Exposure

ETS causes 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. ETS is also associated with pre-term delivery. Premature babies are also at higher risk for a number of health problems.

The impact of ETS on perinatal manifestations of development other than fetal growth and pre-term delivery is less clear. The few studies examining the association between ETS and perinatal death are relatively non-informative. Studies on spontaneous abortion are suggestive of a role for ETS, but further work is needed. Although epidemiological studies suggest an 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 studies, with the most consistent association seen for neural tube defects.

2.2. Developmental Toxicity - Postnatal Manifestations of Pre- and/or Post-natal ETS Exposure

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, and many of these studies demonstrated a dose-response gradient.

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 on growth in otherwise healthy children. As discussed in greater detail below, developmental effects of ETS exposure on the respiratory system include childhood asthma induction and possibly adverse effects on lung growth and development.

2.3. Female and Male Reproductive Toxicity

Active smoking by women has been found to be associated with decreased fertility in a number of studies, and active smoking appears to be anti-estrogenic. The epidemiological data on ETS exposure, though not conclusive, are suggestive of adverse effects on fecundability and fertility, and possibly on menstrual cycle disorders, although not many studies are available on this endpoint. 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.

2.4. 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 (in children and adolescents/adults) as well as for increasing the severity of disease among children and adults 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 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.

2.5. Carcinogenic Effects

The role of ETS in the etiology of cancers in nonsmokers was explored, because active smoking has been recognized as an established cause of cancers in a number of organs including: lung, larynx, oral cavity, naso-, oro-,and hypo-pharynx, nasal cavity and sinuses, esophagus, kidney, urinary bladder and ureter, uterine cervix, pancreas, liver, bone marrow (myeloid leukemia), stomach (IARC, 2004). Also, ETS contains a number of constituents that have been identified as carcinogens in animals and humans.

Reviews published in the 1986 *Report of the Surgeon General* (U.S. DHHS, 1986), by the National Research Council (NRC, 1986g), and by the U.S. EPA (1992i), as well as the original OEHHA report (Cal/EPA, 1997) concluded that ETS exposure causes lung cancer. Since the previous OEHHA review (Cal/EPA, 1997), numerous epidemiological studies and several meta-analyses have examined the association between passive smoking and lung cancer. 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. The studies examining the effect of ETS exposure on nasal sinus cancers consistently (though not uniformly) show statistically significant associations, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. Finally, studies suggest an association between ETS exposure and elevated risks of nasopharyngeal cancers.

Many population-based case-control studies (as well as three cohort studies), controlling for several important reproductive, dietary and other potential confounding factors, have identified elevated breast cancer risks for residential and occupational exposure overall or in individual strata. Higher risks were noted in several studies for breast cancer diagnosed in women under age fifty (primarily premenopausal), or with long duration or high intensity exposure. The toxicological data on carcinogenicity of tobacco smoke constituents strongly support that the risk associated with ETS exposure is highly plausible. Overall, the weight of evidence (including toxicology of ETS constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women. In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause, risk estimates cluster around a null association (see Figure 7.4.4). There are, however, elevated risk estimates in some studies for postmenopausal women either overall or in specific strata. The evidence to date for older/postmenopausal women is, therefore, considered inconclusive. Further research indicating a positive association would be necessary prior to altering this finding.

The epidemiological and biochemical evidence suggest that exposure to ETS may increase the risk of cervical cancer. Positive associations were observed in three of four case-control studies and a statistically nonsignificant positive association was observed in the only cohort study conducted. A new population-based cross-sectional study found statistically significant elevated risks for cervical cancer. Findings of DNA adducts in the cervical epithelium as well as nicotine and cotinine in the cervical mucus of ETS-exposed nonsmokers supports biological plausibility.

In adults, the epidemiological evidence for an association between ETS exposure and risk of brain tumor remains weak and inadequately researched. More recent studies have focused on the potential association between ETS and childhood brain tumors. In children, recent studies or others not previously reviewed by OEHHA, provide no substantial evidence for an association between maternal smoking and childhood brain tumors, with risk estimates generally near the null. Several studies indicated a slightly stronger association with paternal smoking and brain cancer, although the association is still somewhat weak. Overall, the generally positive, but inconsistent, associations reported between paternal smoking and childhood brain tumors, in combination with biological plausibility, provide suggestive evidence of an association between ETS and brain cancer in children. Similarly, suggestive evidence of an association between exposure to ETS and childhood cancer is noted for lymphomas and acute lymphocytic leukemia (children of paternal smokers). These observed associations may reflect an effect of pre-conceptional paternal smoking on sperm, rather than an effect of ETS exposure.

For other cancer sites in adults, there has been limited ETS-related epidemiological research in general. The evidence to date regarding the relationship between ETS exposure and the risk of occurrence of cancer in sites other than lung, nasal cavity, breast, and possibly brain and lymphoma and leukemia, is inconclusive. 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 well designed population based study has been performed for this site. 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 case-control studies and one cohort study conducted to date, although both studies were limited in their ability to detect an effect.

The epidemiological data are insufficient to assess potential associations between ETS exposure and rare childhood cancers. Some studies found small increased risks in children 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.

2.6. 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, support a conclusion that there is 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, such as blood pressure, serum cholesterol level and obesity index. Risks associated with ETS exposure were almost always strengthened by adjustment for other confounders. The association between CHD and risk is stronger for mortality than for non-fatal outcomes, including angina. It is also evident that these effects exacerbate or are exacerbated by underlying conditions, and individuals with other chronic conditions such as diabetes, vascular disease or hypertension comprise a susceptible population at even greater risk from ETS exposure.

Data from clinical and animal studies suggest various mechanisms by which ETS causes heart disease. In a number of studies in which nonsmokers were exposed to ETS, carotid wall thickening, lesion formation, aortic distensibility and reactivity, 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. The data reviewed also suggests that the effects of ETS may also contribute to stroke, the etiology of which includes atherosclerosis of the carotid and large arteries of the brain, and degeneration of intracerebral arteries.

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Chapter 1. Introduction

1.0. Impact of ETS on the Health of Californians – Update to the OEHHA 1997 Report

Exposure to environmental tobacco smoke elevates the risk of a number of diseases in humans. In this document, the Office of Environmental Health Hazard Assessment (OEHHA) updates the report on health effects of environmental tobacco smoke first released in 1997 (Cal/EPA, 1997) and later published by the U.S. National Cancer Institute (NCI, 1999). This health effects assessment has been prepared by OEHHA under the Toxic Air Contaminant program, for use in the deliberations by the state's Scientific Review Panel on Toxic Air Contaminants (SRP) and the Air Resources Board on the identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. The Children's Environmental Health Protection Act (SB 25, statutes of 1999; Health and Safety Code Section 29669.5) requires OEHHA to evaluate exposure patterns and special susceptibility of infants and children when conducting a health effects assessment under the Toxic Air Contaminants program. Consistent with this statutory requirement, we review a number of health endpoints relevant to infants and children in this document, including SIDS, asthma, low birth weight, pre-term delivery, and childhood cancers.

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 or work, or in public places. Authoritative reviews over the past two 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, 1986a), as well as reviews by the National Research Council (NRC, 1986g) and the U.S. Environmental Protection Agency (U.S. EPA, 1992a), concluded that ETS exposure causes lung cancer. The NRC (1986g) and U.S. EPA (1992b) 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 estimates of the numbers of people potentially affected in California and nationally. 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) public education campaign through the Tobacco Control Program, have significantly reduced ETS exposures of nonsmokers in California. The predictions in Table 1.2, which are developed in later chapters of this document, estimate the number of Californians adversely impacted by ETS utilizing the most recent data from the California Adult Tobacco Surveys (CDHS, 2001), where appropriate. Adding the mid-point of the ranges for lung cancer deaths and heart disease deaths, and including the SIDS point estimate, one can attribute about 4,000 deaths per year in California and 50,000 deaths per year from ETS-associated disease in the

United States. This does not include the estimates for other ETS-associated cancer deaths. Exposure to ETS remains a significant public health concern in California.

Evidence of ETS-related effects has expanded considerably since the major comprehensive reviews contained in the *Reports of the Surgeon General* and published by U.S. EPA and NRC and the 1997 Cal/EPA report. We summarize the findings of the original 1997 Cal/EPA report on each endpoint, and add to those findings based on our review of the more recent literature.

1.1. Preparation of the Report

Initial drafts of the chapters in Part B were written by OEHHA staff and external consultants selected by OEHHA because of their expertise and familiarity with the topics covered in this report. These individuals and their specific contributions are listed in the acknowledgements section of this report. OEHHA staff then used these drafts, modifying them as appropriate, to prepare the initial public review draft of the document. The public review draft was released for a public comment period in December 2003. OEHHA revised the draft based on the submitted public comments. A peer review was conducted by the independent Scientific Review Panel on Toxic Air Contaminants (SRP); meetings were held November 30, 2004, January 6, 2005, March 14, 2005, and June 24, 2005. OEHHA revised the report based on the comments from the peer review. While some outside consultants were involved in this process, OEHHA takes full scientific responsibility for the contents of the report.

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1.2. Organization of the Report

This report is organized in parallel with the 1997 Cal/EPA report. The update begins with introductory material on the methodology of the update. Part A, prepared by the Air Resources Board (originally Chapter 2 in Cal/EPA 1997) is organized as a free-standing section separate from this volume. It comprises an updated overview of 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. Thus in this update, we leave chapter 2 blank in order to preserve the original sequence of the 1997 document. 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. Chapter 7 describes the evidence for carcinogenic effects of ETS exposure beginning with a discussion of all sites combined for children and adults. Chapter 7 then describes the evidence for specific sites: lung, nasal sinus, cervical, stomach, bone marrow (leukemia), and bladder cancer (sites for which active smoking has been causally linked to cancer induction), and breast, brain, lymphomas, non-Hodgkin's lymphomas and other rare childhood cancers (sites for which previous reviews have determined there was equivocal or suggestive evidence for an etiologic role for active smoking). Chapter 8 updates the review of the evidence for the impact of ETS exposure on coronary heart disease and stroke. Each chapter starts with a table presenting the conclusions of the 1997 report and this update for each health outcome discussed in the chapter. Previous findings are summarized, followed by a review of the studies for each health endpoint published since the earlier report, discussion of these newer studies and conclusions.

1.3. Definition of Environmental Tobacco Smoke (ETS) and Terminology

Environmental tobacco smoke (ETS) is also called "second-hand smoke", and ETS exposure is called "involuntary smoking" or "passive smoking." In this document we use ETS exposure and "passive smoking" interchangeably. ETS is formed from the smoldering of a cigarette or other tobacco product, and from smoke exhaled by the smoker (NRC, 1986g). 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 or passive smoking. 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". Although exposure of the fetus due to maternal smoking during pregnancy is not considered ETS exposure in this report, recent studies examining effects related to fetal exposure from maternal smoking are reviewed in some instances. These studies are helpful in understanding potential additive effects of prenatal and postnatal exposures (i.e., for SIDS, and for effects on cognition and behavior). In a similar vein, active smoking is reviewed briefly for some of the other endpoints including reproductive toxicity, and cancer.

Except where otherwise specified, the effects of ETS exposure included in this report are for non-smokers. The definition of non-smoker varies somewhat from study to study, but generally ranges from never smoked at all to never smoked more than 100 cigarettes in the subject's lifetime. In general, the studies upon which health outcomes described in this report are based examined risk for lifetime non-smokers, although many studies also report information on ex-smokers.

1.4. Methodology

1.4.1. Study Identification

This update and the original review are based on exhaustive searches of the literature, including electronic searches (*e.g.*, Medline, Toxline), and formal requests for information ("data call-in") by ARB through mailed notices and a *California Regulatory Notice Register* announcement. Key terms for ETS used in the literature search included: side stream smoke, environmental tobacco smoke, ETS, passive smoking, passive smoke, involuntary smoke, tobacco smoke pollution, secondhand smoke, and involuntary smoking. As a result of the data call-in, OEHHA received numerous papers (both published and unpublished) from industry, academia, non-governmental organizations, and interested individuals. Thus, while the published, peer-reviewed literature serves as the primary source of data, additional sources such as abstracts, doctoral dissertations, and unpublished reports are included. Additional material was obtained through the public comment process, and by evaluation of papers cited in the studies reviewed. Since this was an update of the 1997 report, we present in detail only those studies published since the 1997 report, and a few that were covered only briefly in the earlier report. Our literature search covered primarily the period from 1996 to 2003, although studies published in 2004 and early 2005 were added for health outcomes where the literature is rapidly evolving (for

example, breast cancer, heart disease and asthma). We include descriptions of all relevant health outcomes identified in the literature. The considerations of causality include results of studies discussed in the 1997 report as well as results of the newer studies described in this update.

1.4.2. Measures of Association

The association of ETS exposure and a specific outcome in an epidemiologic study is usually reported as an odds ratio or a rate ratio or relative risk with a confidence interval. Odds ratios and relative risks adjusted for potential confounders in the original studies are included when available. One consideration in examining causality is whether a dose-response gradient was found, so when available measures of association reported for groups stratified by exposure are included (see discussion of weight of evidence below).

In general, in evaluating the findings of a study, the statistical significance of single comparisons, as indicated by the p-value or 95% confidence intervals, 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). Unfortunately, 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 relative risk of the effect is expected to be not much greater than 1.0, as is anticipated for several of the potential ETS endpoints (due to either a small absolute magnitude of the effect or a substantial background rate). Finally, comparisons simply on the basis of statistical significance do not take into account possible sources of bias in the studies.

1.4.3. Weight-of-Evidence Evaluations and Criteria for Causality

A "weight-of-evidence" approach has been used to describe the body of evidence on 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 particularly in toxicology studies of ETS and ETS constituents, are considered in making a scientific judgment. Methodological issues that were considered in the review of the epidemiologic literature in the original report and this update 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 (most rigorous). Additional important study characteristics with respect to exposure assessment are discussed for specific health outcomes (see for example Section 7.4.1.4).

In evaluating associations between ETS exposure and health effects, criteria recommended by IARC (2004), the Institute of Medicine (2004), and standard epidemiologic texts (*e.g.* Lilienfeld and Lilienfeld, 1980a; Rothman and Greenland, 1998) were considered. Much discussion has ensued over the last two centuries on causal inference. Most epidemiologists utilize similar sets of causal guidelines, proposed by Hill (1971), which OEHHA has employed. Commonly used

causal criteria are described briefly below and in more detail in Rothman and Greenland (1998) and the Surgeon General's Reports on Smoking (U.S. DHHS, 2004a).

1. Strength of Association. A strong association between a factor and a disease (historically considered to be a relative risk or odds ratio ≥ 2; and statistically significant) makes alternative explanations for the disease less likely. Small magnitude associations (i.e. risk estimate > 1 but ≤ 2) make alternative explanations (undetected biases or confounders) more likely. However, such small magnitude associations do not necessarily indicate lack of causality and are relatively common in environmental epidemiology. For example, the widely-accepted associations between air pollution and cardiovascular/pulmonary mortality, and passive smoking and lung cancer (see Chapter 7, Section 7.2.1), are considered small magnitude associations (risk estimate >1 and < 2). It is important to avoid confusing small magnitude of association with statistical insignificance. From a public health perspective, such small magnitude associations for a common disease can mean large numbers of people affected by the health outcome when exposure is frequent and widespread.

2. Consistency of Association. If several investigations find an association between a factor and a disease across a range of populations, geographic locations, times, and under different circumstances, then the factor is more likely to be causal. Consistency argues against hypotheses that the association is caused by some other factor(s) that varies across studies. Unmeasured confounding is an unlikely explanation when the effect is observed consistently across a number of studies in different populations.

   Associations that are replicated in several studies of the same design or using different epidemiological approaches or considering different sources of exposure and in a number of geographical regions are more likely to represent a causal relationship than isolated observations from single studies (IARC, 2004). If there are inconsistent results among investigations, possible reasons are sought (such as adequacy of sample size or control group, methods used to assess exposure, range in levels of exposure), and results of studies judged to be rigorous are emphasized over those of studies judged to be methodologically less rigorous. For example, studies with the best exposure assessment are more informative for assessing the association between ETS and breast cancer than studies with limited exposure assessment, all else being equal (see Section 7.4.1).

3. Temporality. Temporality means that the factor associated with causing the disease occurs in time prior to development of the disease.

4. Coherence and Biological Plausibility. A causal interpretation cannot conflict with what is known about the biology of the disease. The availability of experimental data or mechanistic theories consistent with epidemiological observations strengthens conclusions of causation. For example, the presence of known carcinogens in tobacco smoke supports the concept that exposure to tobacco smoke could cause increased cancer risk. Similarly, if the mechanism of action for a toxicant is consistent with development of a specific disease, then coherence and biological plausibility can be invoked. For example, cigarette smoke causes atherosclerosis, and atherosclerosis is involved in heart

disease; thus, there is coherence with the epidemiologic finding that smoking elevates risk of heart disease.

5. Dose-Response. A basic tenet of toxicology is that increasing exposure or dose generally increases the response to the toxicant. While dose-response curves vary in shape and are not necessarily always monotonic, an increased gradient of response with increased exposure makes it difficult to argue that the factor is not associated with the disease. To argue otherwise necessitates that an unknown factor varies consistently with the dose of the substance and the response under question. While increased risk with increasing levels of exposure is considered to be a strong indication of causality, absence of a graded response does not exclude a causal relationship (IARC, 2004).

   The dose-response curves for specific toxic effects may be non-monotonic. Under appropriate circumstances, where the dose response shows saturation, the effect of exposures could be nearly maximal, with any additional exposure having little or no effect. For example, in the range of exposures characteristic of ETS, the magnitude of some cardiovascular endpoints show little difference between active smoking and passive smoking.

   It has been argued that the causality of a presumed health effect of ETS depends on it being observed (generally, to a greater extent) as a result of active smoking. This is based on the assumption that ETS is just diluted mainstream smoke. This assumption is problematic when a particular biomarker of exposure such as carboxyhemoglobin (for carbon monoxide) is used as the index of exposure to tobacco smoke for both active and passive smokers. The composition of mainstream smoke and ETS differs, so there is not a constant ratio between a biomarker of exposure like carboxyhemoglobin and the actual exposure to a different toxicologically active component like 4-aminobiphenyl for both types of tobacco smoke exposure (see Part A and Tables 7.4.1E). Evidence of dose-response is more important within than between active smoking studies and passive smoking studies.

6. Specificity. Specificity is generally interpreted to mean that a single cause is associated with a single effect. It may be useful for determining which microorganism is responsible for a particular disease, or associating a single carcinogenic chemical with a rare and characteristic tumor (e.g., liver angiosarcoma and vinyl chloride, or mesothelioma and asbestos). But it is not helpful when studying diseases that are multifactorial, or toxic substances that contain a number of individual constituents, each of which may have several effects and/or target sites. Thus, specificity is not particularly relevant to the evaluation of health effects of tobacco smoke.

7. Experimental evidence. While experiments are often conducted over a short period of time or under artificial conditions (compared to real-life exposures), experiments offer the opportunity to collect data under highly controlled conditions that allow strong causal conclusions to be drawn. Experimental data that are consistent with epidemiological results strongly support conclusions of causality. There are also “natural experiments” that can be studied with epidemiological methods, such as when exposure of a human population to a substance declines or ceases; if the effect attributed to that exposure

decreases, then there is evidence of causality. One example of this is the drop in heart disease death and lung cancer risk after smoking cessation.

It should be noted that the causal criteria are guidelines for judging whether a causal association exists between a factor and a disease, rather than hard-and-fast rules. Lilienfeld and Lilienfeld (1980a) note that "*In medicine and public health, it would appear reasonable to adopt a pragmatic concept of causality. A causal relationship would be recognized to exist whenever evidence indicates that the factors form part of the complex of circumstances that increases the probability of the occurrence of disease and that a diminution of one or more of these factors decreases the frequency of that disease. After all, the reason for determining the etiological factors of a disease is to apply this knowledge to prevent the disease.*"

OEHHA evaluated the body of evidence to evaluate whether ETS exposure was associated with a number of health outcomes in this report. We divided our findings into three categories: causal, suggestive, and inconclusive. In this report:

- 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. The evidence must satisfy several of the guidelines used to assess causality noted above, such as: strength of association, biological plausibility and coherence, evidence of dose-response, consistency of association, and temporal association.

- 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, or there are results from other well-conducted studies that are inconsistent. For example, suggestive evidence for an effect might be provided by at least one rigorously-conducted study reporting a positive association that is sufficiently free of bias, and which included adequate control for confounding. Alternatively, several less rigorous studies which show consistent positive associations and the results of which are probably not due to bias and confounding can provide a basis for a finding that an association is suggestive. When we found additional evidence through the literature review for a health outcome that was labeled suggestive in the 1997 report, but that evidence is not sufficient to describe the association as causal, we describe that finding as "suggestive (strengthened)" in the summary tables at the beginning of each chapter.

- For several health outcomes in this report, the evidence was judged to be inconclusive, since it was not possible to determine 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.

Many ETS-related health impacts are directly observable through studies of people in widely experienced exposure situations. 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 that the data are inconclusive based on inadequate evidence should be seen as preliminary.

ETS differs from many of the other compounds that OEHHA has considered for listing as toxic air contaminants in that there is a relatively large amount of human epidemiological data with real world exposures available. This situation contrasts with a number of other health effects assessments of TACs for which OEHHA had only animal toxicology data, or human data from occupational studies (which typically involve higher exposure levels than the general population experiences). Because the epidemiologic data on ETS are extensive, they serve as the primary basis on which findings of ETS effects are made. Experimental animal data are reviewed to determine the extent to which they support or conflict with the human data. In some cases, studies of ETS constituents in experimental animals are used to support the weight-of-evidence judgment. As noted above, this is standard practice in risk assessment. In many instances in the Toxic Air Contaminants program, chemicals have been identified as TACs and emissions have been regulated based on animal toxicological data alone. This is important in the public health setting because often adequate epidemiological data do not exist to base conclusions upon.

The wealth of epidemiological studies that are available on ETS allows OEHHA to be very confident in statements made about effects on humans (rather than relying on animal data or extrapolation from higher occupational exposures). At the same time, the large number of studies raises the issue of how to combine the results of all these studies to draw integrated conclusions. OEHHA has approached this problem as follows:

First, we consider the results of the individual studies. A particularly rigorous study with a statistically significant positive result that cannot be readily explained by confounding provides strong evidence for the conclusion that ETS increases the risk of a given health outcome. Conversely, studies with a null result may be uninformative, if such results arise through bias or lack of power to discern an effect. True negative results of rigorous studies with adequate statistical power are considered important in this review.

Second, we consider whether the values of the point estimates of risk are above or below 1.0 for all the studies. If ETS has no effect on the risk of a particular disease, then one would expect about half the point estimates of the risk associated with the disease to be below 1.0 and about half of the risk estimates to be above 1.0. If the majority of the point estimates are above 1.0, this supports the conclusion that ETS increases the risk of the disease. This semi-quantitative overview approach was taken in evaluating diesel engine exhaust as a TAC (OEHHA, 1998). There are a number of figures throughout the document plotting the risk estimates of studies for various outcomes. These figures provide a picture of where the point estimates lie relative to 1, and how many are statistically significant. For example, in figure 7.2.1 for lung cancer it is clear that most point estimates fall above 1. We discuss formal quantitative meta-analysis in Section 1.4.4.2 below.

1.4.4. Analyses of Risk from ETS Exposure

In addition to considering results of individual studies, OEHHA examined estimates of risk using meta-analyses, either published in the literature or conducted by us. We considered overall results presented in published studies as well as results of strata of the study populations in evaluating effect estimates under certain circumstances. We also estimated attributable fraction to estimate public health impacts of ETS exposure.

1.4.4.1. Stratification in Epidemiological Studies

Epidemiologists often divide the analysis of their data into subgroups, a process known as *stratification,* as a way to take into account the effects of real or potential confounding variables by doing separate analyses for different groups of people based on these variables. Stratification can be based on age, gender, exposure intensity or duration, or other factors that the investigators thought might be important. Stratifying the exposed groups can help to identify sensitive subpopulations, dose-response relationships, and possibly provide insight into mechanisms of action. Presentations of stratified analyses can highlight susceptible subpopulations by reducing the diluting effects of considering sensitive and relatively insensitive people together as in an unstratified analysis. Such subgroupings are often based on hypotheses such as inherent susceptibility due to genetic polymorphisms or age-at-exposure effects.

While stratification and subgroup analysis are well-established epidemiological procedures, the fact that many of the studies of ETS present stratified analyses does present some problems for OEHHA in the assessment of the resulting data. Different studies often stratify their results using different variables or different cut points (for example on age), which complicates comparison of the results of different studies. Investigators also stratify their studies based on variables that they believe to be important, so the stratification patterns depend on the hypotheses that individual researchers seek to investigate. While there may be good reasons to present a stratified analysis, stratification can also increase the risk of a false positive error by increasing the number of subgroup analyses. The presence of multiple risk estimates for the different strata in a given study also raises the question of which risk estimate to use from a given study when conducting a pooled analysis of several studies.

OEHHA has approached the analysis of study results as follows:

- We consider the results of all strata within the studies that are discussed and present key results (generally in tabular form) to the reader.

- We present the results of stratified analyses published in the literature to provide additional insights into the health effects of ETS exposures. For example, where investigators stratified subjects into different exposure categories, the results are presented to evaluate dose-response relationships.

- When appropriate, OEHHA uses the results of stratified analyses to estimate risks for sensitive subgroups in order to provide the best available evidence on the magnitude of the risk for these subgroups. For example, in estimating risk of breast cancer from ETS exposure, OEHHA evaluated younger primarily premenopausal women separately from

all women where studies allowed because of a number of studies indicating elevated risks in premenopausal women.

- When available, OEHHA presents the results of stratified analysis to identify specific risks to children to meet the requirements of SB 25.

1.4.4.2. Pooled Risk Estimates

While examination of the primary literature was the main objective of the review, discussion of published meta-analyses was included. Meta-analysis is performed to help clarify the level of consistency in the data, evaluate heterogeneity of study results, derive a more precise estimate of the magnitude of the association, and thus help understand complex data. This report includes two original meta-analyses performed by OEHHA (on childhood asthma, Chapter 6, and breast cancer, Chapter 7), as well as other published meta-analyses of numerous endpoints. It would in principle be desirable to provide updated meta-analyses for all end points that are causally related to ETS exposure. However, resource limitations made it necessary for OEHHA to limit these additional analyses to endpoints determined to be causally related to ETS exposure, for which meta-analyses were already in progress either by OEHHA staff (update of the previous childhood asthma meta-analysis) or by our consultants (breast cancer). We note that OEHHA did not base any conclusion of causality solely on the results of a meta-analysis.

In a meta-analysis, the results of several studies are pooled to provide a more accurate estimate of the magnitude of the risk (point estimate), and of the uncertainty associated with this risk estimate (confidence interval). OEHHA uses standard procedures for meta-analysis, including using random effects models when there is evidence of study heterogeneity (Rothman and Greenland, 1998; Greenland and Longnecker, 1996). When computing a pooled estimate, studies with more precise estimates of the risk (generally the larger studies) are weighted more heavily than studies that yield less precise estimates (generally the smaller studies). In the meta-analyses conducted by OEHHA (childhood asthma induction and breast cancer), studies are essentially weighted according to the inverse of the variance using the standard STATA statistical package (STATA 8). To evaluate influence of any single study on the pooled estimate of association, the program is run dropping out one study each time. In our analyses, no single study made a substantive difference in the final pooled estimates.

In selecting data for inclusion in a meta-analysis, all available studies meeting minimum inclusion criteria are included. When conducting a pooled analysis to estimate the overall likelihood that ETS causes a given effect, OEHHA uses the risk estimate based on the least level of stratification (e.g., all ever-exposed vs. referent group). In some instances, this means combining strata reported in a study. This approach biases the pooled estimated effect towards the null, and so reduces the risk of a false positive conclusion. The risk estimates used in the pooled analyses for breast cancer are provided in tables in Section 7.4. The analysis performed for childhood asthma is presented only in summary since it is submitted for publication (the general rules of publishing would disallow publication if the analysis were presented in its entirety here).

In some cases, OEHHA also conducts additional analyses, for instance with more stringent inclusion criteria (i.e. higher quality studies only) or, based on consideration of possible

mechanisms of effect, sensitive subgroups (e.g., younger primarily premenopausal women for breast cancer, or children for asthma) to provide the best available estimates of the actual risk associated with ETS.

1.4.5. Attributable Fraction

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. In this document, the attributable fraction (a) is generally calculated using the formula: $a = p(R-1)/(p(R-1) + 1)$ (Lilienfeld & Lilienfeld, 1980b), where p is the exposure prevalence and R is an estimate of the relative risk. The odds ratio can be substituted for the relative risk when its value is close to 1. A different approach was used to calculate the attributable risk for lung cancer modeled on that used by U.S. EPA (1992c) and described in Appendix B to chapter 7.

U.S. EPA (1992c) 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 (1992c) were used as part or all of the basis for deriving California-specific values for childhood asthma induction and exacerbation, bronchitis or pneumonia in young children, and lung cancer in the 1997 OEHHA document: the U.S. estimate was multiplied by 12%, the fraction of the U.S. population then residing in the State. U.S. statistics reported in the published literature for ETS-related heart disease mortality (Cal/EPA, 1997) were similarly used to estimate California-specific impacts. In this report, we calculate California-specific values for specific endpoints, using California prevalence data for ETS exposure and appropriate relative risk values to first estimate the attributable fraction. In some cases, these values are lower in the new report as the prevalence of exposure has substantially decreased.

To the extent that smoking prevalence and ETS exposure have been declining in recent years, attributable risk estimates may be slightly inflated, 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 in smoking prevalence should not significantly impact the accuracy of the California estimate. For heart disease mortality, this issue is more difficult to judge since the current exposures are more important than past exposures, although both contribute to risk. In addition, the population of both California and the U.S. has increased. Thus, more people are exposed even as smoking rates decline. 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.

1.5. Important Considerations in Evaluating the ETS Literature

1.5.1. Measures of ETS 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 individuals' exposures. 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 exposure levels or biomarkers. Some studies also ascertained childhood exposure from parental smoking. 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 Part A (update of Chapter 2 in the 1997 report) provides more detail on exposure measurement. A study's measurement precision and potential for misclassification are important considerations when reviewing epidemiologic studies, particularly environmental epidemiology studies (Hertz-Picciotto, 1998). These are discussed in the following two subsections.

1.5.1.1. Precision of ETS Exposure Measures

Precision in epidemiological measurements is related to the reduction of random error, and may be increased by increasing the size of the study and/or improving the efficiency with which information is obtained from study participants. For example, many studies assess ETS exposure in the home with a single question regarding spousal smoking, which in most cases is an imprecise measure of exposure to ETS, since there are substantial exposures to ETS at work or in other social situations. The measurement precision of these studies could be improved with additional questions regarding other smokers in the home, frequency and duration of smoke exposure, and exposures at work or in other settings. 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. Measurement imprecision and resulting 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 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. Studies that have more detailed exposure assessments generally have higher precision and are considered of higher quality. Imprecision in measurement blurs the distinctions among exposure groupings and biases the effect estimate towards the null.

1.5.1.2. Exposure Misclassification

Misclassification of exposure status occurs when individuals are categorized as being more or less exposed than they actually were. If the likelihood of exposure misclassification does not depend on whether the study subjects are diseased or not (that is, misclassification is "nondifferential"), then an association between exposure and the disease will be more difficult to detect (i.e., the results will be biased towards the null). Misclassification is a concern in studies that rely on the ascertainment of spousal smoking status, because ETS exposures also occur

outside the home, e.g. at work. Friedman *et al*. (1983) found that using spousal smoking to classify persons as ETS-exposed resulted in considerable misclassification in both directions. Forty to fifty percent of persons with non-smoking spouses reported passive smoke exposure and as many as thirty five percent of those married to smokers reported no exposure.

Misclassification can also occur when exposures observed at one point in time are assumed to apply to other time periods. This is a particular problem when there are windows of susceptibility at a particular lifestage, but exposure information is missing for that important window. For example, when adults are not asked about childhood exposures from parental smoking, important susceptibility windows are likely missed for some health endpoints. Studies utilizing a limited evaluation of exposure, such as a single question about spousal smoking at baseline, have been shown to underestimate risk of lung cancer (Johnson *et al*., 2001) and cardiovascular disease (Whincup *et al*., 2004). In addition, Whincup *et al*., (2004) evaluated cotinine levels at baseline in their prospective studies and demonstrated that the magnitude of the risk of heart disease was larger at given cotinine levels in the earlier years than the later-years of follow-up , as the exposure measure was further removed in time. This is an important exposure assessment problem in cohort studies that evaluate exposure only at baseline.

Misclassification of exposure to passive smoking by limited exposure ascertainment results in referent groups that contain people who have been or are exposed to ETS. This is an important problem in studies of health effects of ETS exposure and biases the results towards the null. Virtually all nonsmokers have been exposed at some point to ETS, particularly in the past when smoking was more prevalent and there were no restrictions on smoking in the workplace, at schools, or in public places. Thus, practically speaking, while a referent group may have a stray light smoker, almost 100% of the people in the referent group of all studies with poor ascertainment of exposure have had at least some exposure to ETS, and in many cases significant long-term exposures. Fontham *et al*. (1994) found that 64% of never-smoking women in the U.S. reported passive exposure in childhood, 14% non-spousal adult household exposure, 24% social exposure and 60% reported exposure at work. The majority of these exposures occurred over many years. The implication is that the referent categories of non-exposed people can in fact be highly contaminated with exposed individuals if the study only assesses spousal smoking status. Even studies that do a more thorough assessment of all sources of ETS exposure are likely to have some individuals in the referent category with at least some ETS exposure. The result of such misclassification is to bias the results towards the null, which could lead to loss of significance of results, particularly for relative risks between 1 and 2 as in the case for ETS and lung cancer. Examples of exposure misclassification reducing risk estimates for ETS-associated cancers are found in Chapter 7, Sections 7.2. and 7.4.

To increase precision and 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.

Assessment of current ETS exposure of children is somewhat less problematic. Although concerns similar to those discussed above regarding measurement imprecision and exposure misclassification remain, children, especially infants and young children, are likely to be exposed to tobacco smoke in fewer circumstances than adults, and are much less likely to smoke themselves (though this is considered important to exclude). Cotinine concentrations in children are well correlated with smoking by the mother (Greenberg *et al.*, 1989); 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.

1.5.1.3. Smoker Misclassification

In studies of the health effects of ETS exposure, misclassification of smokers as nonsmokers (smoker misclassification) is a potential problem, and smoker misclassification has been a criticism of ETS studies, particularly studies of lung cancer because the relative risk for lung cancer in smokers is so large. Misclassification of smokers as nonsmokers can inflate a risk estimate if such individuals, who have a higher risk of lung cancer, are in the passive-smoke-exposed nonsmokers group in a study. However, the misclassification of ever-smokers as never-smokers affects a very small percent of the nonsmoking referent group in the majority of studies (Nyberg *et al*., 1997, 1998b; U.S.EPA, 1992d). For example, smoking misclassification was evaluated extensively in a validation study conducted at three of the 12 centers from the IARC study of ETS and lung cancer (Nyberg *et al*., 1998b). Comparing the results of questionnaire data from index subjects and next of kin (spouses or children), they found that 1.7% of the subjects who said they had never smoked regularly were actually former regular smokers. Furthermore, the misclassification was non-differential with respect to disease status, which tends to bias results towards the null. Nyberg *et al*. (1997) found less than 5% of ever-smokers were classified as never-smokers. These investigators also note that the misclassified ever-smokers have much lower risks of lung cancer than either current active smokers or former regular smokers because they tend to be either long-time ex-smokers or light smokers, who have only moderately elevated risks for lung cancer. This makes it even less likely that misclassified smokers significantly impact the lung cancer risk estimates from ETS exposure. Finally, in diseases where the relative risk for smokers is small, the impact of smoking misclassification is even less important.

1.5.2. 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 reports insufficient 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 than studies of only mainstream smoke. Of course a

mixture of mainstream and sidestream smoke would be most relevant since ETS comprises both fractions.

There is a wealth of information on many constituents of ETS from toxicity testing in animals. Consideration of such animal toxicity data is routine practice in regulatory risk assessment, and provides important information on potential health effects in humans. Therefore, in evaluating causality for a particular endpoint, the overall body of evidence including information from toxicological testing of ETS constituents is carefully considered.

1.5.3. Case-Control vs. Cohort Study Design

A cohort study follows a group of people, defined by some characteristic (e.g., nurses) over time to learn about incidence of disease in the group and associations between exposure to putative causal factors and the disease. In general, they are prospective in nature although retrospective cohort studies are also conducted. A case-control study evaluates individuals within a cohort of people who have a disease (cases) and compares them with individuals who do not have the disease. The cases and controls are matched for common characteristics such as age, gender, SES, and so forth. The exposure to putative factors is evaluated in both the cases and controls to examine any potential associations. When the exposure history is evaluated, one is looking back in time on exposures in the cases and controls, and thus these studies are retrospective in nature. Sometimes a study looks only at a current exposure to a purported etiological agent or characteristic or a current disease; in these cases, the studies are cross-sectional in design.

The studies included in this review are predominantly of prospective cohort and case-control designs, which differ in their strengths and weaknesses, including susceptibilities to bias. Case-control studies can suffer from selection bias of either cases or controls. In hospital-based studies, for instance, controls selected from those hospitalized for another disease may not be representative of the general population. If the disease for which the "controls" are hospitalized is affected by the etiological factor of interest for the case disease, then you may bias the result towards the null. Exposure reporting bias can also be a problem in case-control studies if interviewers probe more deeply with cases (not a problem with self-administered questionnaires) or when cases remember past exposure differently than healthy controls (recall bias). These biases are more apt to occur if interviewers or subjects are not blinded to the main hypothesis(es) of the study. Exposure assessment in both case-control and cohort studies may suffer from poor recall, since the subjects of the prospective cohort studies are typically adults at entry and are asked to report about ETS during earlier periods of life where exposure may be critical. While assessment of exposure at baseline in a prospective cohort study may be potentially free of recall bias, studies that fail to re-assess exposure during follow-up risk misclassification when subjects' exposure status changes over time. This failure is of particular concern with studies of ETS exposure. If only one question about household exposure is asked at baseline, and the household structure changes, then that individual may be misclassified as to ETS exposure. Similarly in a prospective cohort study, if ETS exposure is assessed only from the household, then someone exposed at work may be misclassified into the non-exposed referent group. Thus, a study's ability to accurately measure exposure is critical in the evaluation of its overall quality.

Prospective cohort studies tend to be larger than case-control studies and therefore have potentially more power to detect an effect. Case-control studies with a large enough number of

cases and ratio of controls to cases can also be statistically powerful. The potential increased power of a prospective study and the lesser potential for recall bias are the prime reasons that cohort studies are considered by some to be preferable to case-control studies for attempting to assess causality. As noted above, however, if the exposure assessment is poor or loss to follow-up is great, then the advantage of a large sample size and lack of recall bias in a prospective cohort study is diminished. Case-control studies can be used as the basis for causal conclusions. For example for passive smoking and lung cancer, for which a causal association is widely accepted, the majority of the information comes from case-control studies, not cohort studies (see Table 2.2, page 1234, IARC, 2004).

1.5.4. Publication Bias

Publication bias is the tendency of researchers and journals to publish studies with statistically significant "positive" results in preference to studies that fail to reject the null hypothesis. While such bias is always a possibility, OEHHA does not believe that publication bias is a practical problem in studies of ETS. Many of the individual studies which are not large enough to reach statistical significance, but report elevated point estimates of the risk, are published nonetheless. Second, given the high level of interest and the incentives to publish research on subjects of high interest such as ETS, it is unlikely that individual investigators would not attempt to publish all studies. Third, OEHHA was exhaustive in searching for results, including abstracts, and dissertations, as well as inviting interested parties to submit data through the data call-in. Finally, Bero *et al* (1994) specifically examined the evidence of whether there was bias against publication of statistically non-significant studies on the relationship between ETS and lung cancer and concluded that there was no such bias.

For these reasons, OEHHA does not believe that there is a publication bias against negative studies that would significantly affect the conclusions in this report. In fact there are a large number of null studies published on ETS.

1.5.5. Other Confounding

Confounding is the influence other risk factors may have on an association attributed to the purported etiological agent. There are standard procedures used in epidemiological studies to account for the effects of known confounders on the estimate of the magnitude of the association. Studies that adjusted for known confounders for specific health outcomes are thus considered better studies, all else equal, and are emphasized in our assessment of causality. Specific confounding factors are discussed in the summaries of individual studies for each health outcome. Residual confounding can occur when a factor, which is related to both the health outcome of interest and ETS exposure, has not been measured adequately or at all, or has not been included in the analysis. Residual or poorly controlled confounding is particularly important for effects whose relative risks or odds ratios are between 1 and 2. Such relatively weak associations may be more easily explainable by confounding. Thus, confounder control is particularly important in studies of ETS exposures.

Characterization of the association between ETS exposure and some specific outcomes can be particularly challenging due to confounding. For example, for developmental effects which manifest perinatally or in the first year of life, effects of maternal direct smoking can be

significant. 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. Though all studies were considered, studies that exhibited the better control for potential confounders were given more emphasis in this review.

1.6. Summary

In summary, in order to update the 1997 OEHHA (Cal/EPA, 1997) report on health effects of ETS exposure, OEHHA conducted an exhaustive review of the more recent literature and evaluated the evidence using a weight-of-evidence approach. We evaluated results of individual studies considering limitations of the study design, control for confounding, and study results overall and in stratified subgroups. We also looked at an overview of all the studies in a semi-quantitative fashion, plotting study results (point estimate and 95% CI) to visualize the number of studies with risk estimates above 1, below 1, and which ones were statistically significant. We evaluated results of published quantitative meta-analyses and conducted two of our own. Results of the weight-of-evidence evaluations are presented for specific health outcomes in tabular form at the beginning of each chapter, and discussed within the chapters. The individual studies are described in text and tables. The executive summary of this report describes the results in brief.

Table 1.1 Attributable Risks Associated with ETS

Outcome	Conclusion OEHHA 1997 Annual Excess # in CA	Conclusion OEHHA 1997 Annual Excess # in US	Conclusion Update Annual Excess # in CA	Conclusion Update Annual Excess # in US
Pregnancy:				
Low Birth Weight	1,200-2,200	9,700-18,600	1,600 [1]	24,500 [2]
Pre-Term Delivery			4,700 [1]	71,900 [2]
Asthma (in children):				
# Episodes [3]			31,000 [4]	202,300 [5]
# New cases	960-3120	8,000-26,000	N/A	N/A
#Exacerbations	48,000-120,000	400,000-1,000,000		
Lower respiratory illness	18,000-36,000	150,000-300,000	N/A	N/A
Otitis media visits	78,600-188,700	700,000-1,600,000	50,200	790,000 [6]
SIDS	120	1,900-2,700	21 [7]	430 [8]
Cardiac death (Ischemic heart disease death)	4,200-7,440	35,000-62,000	3,600 (range: 1,700-5,500)[9]	46,000 (range: 22,700-69,600) [10]
Lung Cancer Death	360	3000	400 [11]	3400
Breast cancer – diagnosis in younger women (primarily pre-menopausal)			All studies: OR 1.68 (95% CI 1.31-2.15) [12] Best studies: OR 2.20 (95% CI 1.69-2.87) Approximate 68-120% increased risk	

1 Based on California Dept Health Services (CDHS, 2000a), Table 2-6, Number and percent of live births with selected medical characteristics by race/ethnic group of mother, California 2000, and Gilpin *et al*. (2001).

2 Based on CDC (2002b) National Vital Statistics Report. Vol 51(2) 2002. Births: Final data for 2001, and on adult females reporting exposure to ETS in NHANES III for 1995 (Pirkle *et al*., 1996)

3 The data to distinguish number of new cases from number of exacerbations were not available for the updated calculations; thus, OEHHA considered that these estimates were best described as number of episodes.

4 Based on number asthma attacks or episodes in previous 12 months for 0-17 year olds. Calculated from California Health Interview Survey for 2001

5 Based on number asthma attacks or episodes in previous 12 months for 0-14 year olds. Mannino *et al*. 2002b CDC-MMWR 51(SS01).

6 Based on Freid *et al*. (1998) National Center for Health Statistics Series 13 No. 137. Ambulatory Health Care Visits by Children: Principal Diagnosis and Place of Visit for yrs 1993-1995.

7 Based on California Dept Health Services. (CDHS, 2000b), Table 4-10 for yr 2000 Leading causes of infant death by race/ethnic group of child, California 2000.

8 Based on CDC (2002a) National Center for Health Statistics (2002). www.cdc.gov/nchs/fastats/infort.htm for yr 2000

9 Based on California Dept Health Services. (CDHS, 2000c), Table 5-7, Deaths, death rates, and age-adjusted death rates for leading causes by sex, California, 1999- 2000.

10 Based on Anderson and Arias (2003). National Vital Statistics Report. Vol 51(9) Table 2 for yr 2000 Ischemic heart diseases including AMI.

11 Assuming California exposure and death rates are similar to national rates and California population is 12% of national population.

12 OEHHA is unable at this time to calculate an attributable risk as it is not possible to account accurately for the portion attributable to other known risk factors. The OR for all studies is based on our meta-analysis of all studies with risk estimates for younger primarily premenopausal women. The OR for best studies is based on the OR for studies which evaluated younger primarily premenopausal women and which did a better job of ascertaining exposure – see Section 7.4.1.3.2 and Table 7.4.1I.

N/A = data not available.

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Chapter 2. Exposure Measurement and Prevalence

Chapter 2 is now Part A prepared by the California Air Resources Board

Chapter 3. Developmental Toxicity
1: Perinatal Manifestations of Prenatal ETS Exposure

A summary of the conclusions regarding the evidence of a causal association between prenatal ETS exposure and perinatal manifestations from the 1997 OEHHA report and this update are provided below in Table 3.0. These findings are based on a weight of evidence approach.

Table 3.0 Prenatal ETS Exposure and Pregnancy Outcomes: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	# Additional Studies in Update	Findings: OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
Birth Weight	24	18	Conclusive	Conclusive (strengthened)
Low Birth Weight	13	9 (2 meta) [a]	Conclusive	Conclusive (strengthened)
Pre-Term Delivery	6	7	Suggestive	Conclusive
Intrauterine Growth Retardation[b]	5	8	Suggestive	Suggestive (strengthened)
Spontaneous Abortion	5	4	Suggestive [c]	Suggestive [c]
Malformations	5	6	Inconclusive	Inconclusive

Low birth weight is defined as less than 2500 grams at birth. [a]meta = # meta-analyses – not included in counts of studies. [b]Includes SGA. [c]interpretation is complicated by role of paternal smoking.

In summary, there is evidence that ETS causes developmental toxicity: prenatal exposure to ETS has been shown to cause a decrease in birth weight (BW), an increased risk of low BW, and preterm delivery. There is also suggestive evidence of an association between ETS exposure and intrauterine growth retardation. Impacts on the respiratory system are discussed in Chapter 6.

3.0. Introduction

The detrimental effects of active smoking upon pregnancy are well documented and unequivocal, providing a framework for investigating the effects of environmental tobacco smoke (ETS) exposure upon reproduction and development. Maternal active smoking adversely affects fetal growth and is associated with decreased BW, small for gestational age babies, preterm deliveries (especially prior to 33 weeks gestation), placenta previa, placental abruption, spontaneous abortions, and fetal demise (Andres and Day 2000; U.S.DHHS, 2001).

Since the previous monograph, there have been important developments in our understanding of active smoking and pregnancy that materially affect the evaluation of the effects of ETS on non-smoking pregnant women.

3.1. Exposures and Mechanisms of Injury to Reproduction from Tobacco Smoke

It has been assumed that the main deleterious effect of active smoking has been due to nicotine and carbon monoxide in tobacco smoke. Nicotine's adverse effects have been thought to be due to its vasoconstrictive properties resulting in reduced maternal and fetal placental blood flow (Quigley *et al.,* 1979). Human and animal studies indicate that this is probably not the only mechanism of nicotine toxicity upon pregnancy (Lambers and Clark, 1996), although it continues to be widely stated (Horta *et al.,* 1997). Nicotine functions as a neurotransmitter (acetylcholine) and nicotine's detrimental effects upon the fetus are probably due to the consequences of inappropriate stimulation of nicotinic cholinergic receptors (Dempsey and Benowitz, 2001; Slotkin, 1998).

Carbon monoxide is a potent fetotoxicant (Koren *et al.,* 1991; Norman and Halton, 1990) which avidly binds to maternal and fetal hemoglobin and displaces oxygen. Fetal carboxyhemoglobin levels are higher than maternal levels (Bureau *et al.,* 1982) and carboxyhemoglobin has a half-life of 5 to 6 hours. Binding of carbon monoxide to hemoglobin adversely affects the release of hemoglobin-bound oxygen. This detrimentally affects the transfer of oxygen across the placenta from the mother to the fetus, and the transfer of oxygen from the fetal blood to fetal tissue, resulting in chronic fetal tissue hypoxia (Longo, 1977). Whether the low levels of nicotine and carbon monoxide exposure associated with ETS exposure could alone account for the adverse outcomes attributed to ETS is not clear.

Tobacco smoke contains thousands of toxic chemicals including oxidative gases, heavy metals, cyanide, and carcinogens (Hoffmann *et al.,* 1997). Numerous studies have revealed a wide variety of molecular biologic differences between non-smoking pregnant women, their fetuses and newborns compared to active smokers and their progeny (Dempsey and Benowitz, 2001). Many of these differences are not due to nicotine or carbon monoxide exposure. Presently, the clinical significance of many of these differences is unknown, but the additive or synergistic effects of exposure to nicotine, CO, and thousands of other chemicals may be responsible for the adverse reproductive outcomes associated with maternal smoking. The following are a few examples from a recent detailed review of this topic (Dempsey and Benowitz, 2001).

Active maternal smoking is associated with premature rupture of the chorio-amniotic membranes, especially prior to 33 weeks gestation, resulting in premature delivery (Meyer and Tonascia, 1977). The copper enzyme lysyl oxidase is important in the biosynthesis and maintenance of collagen, an important component of the chorio-amniotic membrane that surrounds amniotic fluid. Exposure to nicotine and/or tobacco smoke appears to reduce lysyl oxidase activity in hamster lungs (Osman *et al.,* 1985) and neonatal rat lung (Maritz *et al.,* 2000), and may well have a similar effect in the placenta. Impairment of placental lysyl oxidase may lead to premature rupture of membranes precipitating preterm delivery. Cadmium may impair lysyl oxidase by decreasing available copper due to induction of metallothionein (King *et al.,* 1997). It is known that copper levels are altered in mothers and fetuses of active smokers compared to non-smokers (Kuhnert *et al.,* 1993; Chambers *et al.,* 1994). Whereas in non-smokers, cadmium exposure is primarily through diet, in smokers the main source of cadmium is cigarette smoke, even in people who reside in proximity to a cadmium smelter (Lagerkvist *et al.,* 1993). Vitamin C, an antioxidant, is very important for the maintenance of the chorio-amniotic

membranes. Low vitamin C levels are associated with preterm rupture of membranes and premature delivery (Casanueva *et al.,* 1993). Pregnant smokers have lower vitamin C levels than non-smokers, and this has been attributed to consumption of vitamin C by the oxidative gases in cigarette smoke as well as to reduced dietary intake (Schectman *et al.,* 1989; Klesges *et al.,* 1998). In addition, among children consuming equivalent amounts of vitamin C in their diets, ETS exposure has been associated with significantly ($p = 0.002$) lower plasma vitamin C levels (Preston *et al.,* 2003). Fibronectin, formed in the placenta and amnion, is thought to be important in intracellular adhesion and may play a role in pre-term delivery (PTD) (Shimizu *et al.,* 1992). Two volatile compounds in cigarette smoke, acrolein and acetaldehyde, individually inhibit fibronectin (Carnevali *et al.,* 1998). A rise in amniotic fluid levels of platelet activating factor (PAF) may be important in the initiation of labor. Cigarette smoking may contribute to preterm labor by its effect on PAF. Platelet activating factor is inactivated by PAF-acetylhydrolase (Narahara and Johnston, 1993). Components of cigarette smoke (other than nicotine and CO) inactivate PAF-acetylhydrolase (Bielicki *et al.,* 2001). Reduced deactivation of PAF due to smoking would allow PAF to rise in amniotic fluid and precipitate labor. (Further information on the effects of ETS on platelet function is reviewed in the cardiovascular chapter.) These are examples of ways in which toxicants in tobacco smoke may contribute to premature rupture of membranes and/or premature delivery, and the same may be true for ETS exposure. Other differences between pregnant active smokers and pregnant non-smokers include alterations in estrogen levels, beta 1-glycoprotein, norepinephrine, vanillylmandelic acid, dopamine, human macrophage metalloelastase, epidermal growth factor, human placental lactogen, prolactin, human chorionic gonadotropin, prostacyclin, prostaglandin E2, prostaglandin F2a, phospholipase A2, and erythropoietin (Dempsey and Benowitz, 2001).

The picture that emerges from these data is that the deleterious effects of active smoking upon pregnancy may be due to a myriad of pathophysiological processes acting additively or synergistically. Adverse reproductive outcomes are probably not due solely to the effects of one or two toxicants in cigarette smoke. For example, in newborn infants, there is a statistically significant difference in the plasma levels of polychlorinated biphenyls and hexachlorobenzene between those born to non-smoking mothers exposed to ETS and those unexposed to ETS (Lackmann *et al.,* 2000). When the toxicity of cigarette smoke is viewed from the perspective of fetal exposure to hundreds or thousands of chemicals, it is much more biologically plausible that the sum of the toxicants in ETS could materially affect pregnancy through a host of pathologic processes.

In contrast to the observed toxicity of tobacco smoke components is a paradoxical observation regarding the effects of active maternal smoking on survival of the fetus and neonate. It has often been observed that at birth weights (BW) below 3000 g, the mortality rates among offspring of smoking women are lower than among neonates of nonsmoking women, while at higher BWs, this trend is reversed. This could lead to the conclusion that maternal active prenatal smoking provides some survival advantage to low BW infants, which in turn might suggest health benefits of ETS exposure for infants. However, as demonstrated in a recent study, this is apparently an artifact of the methods used for calculating infant mortality rates. Using a "fetuses-at-risk" approach, Joseph *et al.* (2004) found that the fetuses and infants of smoking women in fact have higher rates of fetal growth restriction and perinatal mortality at all gestational ages than do the offspring of non-exposed women. While this approach has yet to be

applied to studies of maternal ETS exposure and perinatal mortality, the results of this study are a reminder that the interactions between fetal growth, preterm delivery and BW are complex.

3.1.1. Gene-Environment Interactions

The ability to metabolize and eliminate drugs and toxicants has significant variability in the population, part of which is due to genetic polymorphism of metabolizing enzymes. For example, occupational exposure to low levels of benzene is associated with a small decrease in the gestational age at birth when compared to an unexposed control group (Wang *et al.,* 2000). When the exposed and control groups were stratified by genotype for two drug metabolizing enzymes, CYP1A1 and GSTT1, mothers occupationally exposed to benzene who had the genotype CYP1A1 (AA) and GSTT1 (absent) had the greater decrease in gestational age compared to controls or benzene-exposed mothers with the genotype of CYP1A1 (Aa or aa) and GSTT1 (present). Among women who were unexposed to benzene, there was no effect of genotype on gestational age (GA) (Wang *et al.*, 2000).

Several gene interactions with active maternal smoking have now been reported (Hong *et al.,* 2001; van Rooij *et al.,* 2001). Important cigarette smoke carcinogens include polycyclic aromatic hydrocarbons (PAH), arylamines, and N-nitrosamines. The phase one enzyme arylhydrocarbon hydroxylase (CYP1A1) metabolizes PAH to highly reactive electrophilic intermediates, which in turn are converted to polar metabolites by conjugation with glutathione via glutathione-S-transferase (GSTT1) and excreted from the body. The effects of differences in the genotypes of these enzymes on two birth outcomes were examined in a case control study enrolling 207 PTD and/or low birth weight (LBW) infants, and 534 full-term non-LBW infants (Wang *et al.,* 2002). All infants were singletons without malformations. Among babies born to mothers who were non-smokers, the genotypes of the CYP1A1 enzyme and/or GSTT1 were not associated with decreased BW. Maternal smoking was associated with a mean decrease in BW of 377 g (SE 89 g; $p<0.001$). When babies born to smokers were stratified by genotype, the CYP1A1 (AA) genotype was associated with a mean decrease of 252 g (SE 111 g; $p=0.02$) while the Aa or aa genotype was associated with a 520 g (SE 124 g; $p<0.001$) decrease. The presence of the GSTT1 genotype was associated with a 285 g (SE 99 g; $p=0.004$) decrease while absence of the genotype was associated with a 642 g (SE 154 g; $p<0.001$) decrease. There were 11 babies born to mothers with the CYP1A1 (Aa or aa) genotype and GSTT1 absent genotype, and their average BW reduction was 1,285 g (SE 234 g, $p<0.001$). These data suggest that there was an interaction between genotype and smoking with deleterious effects upon both BW and GA. These data demonstrated a very large effect of smoke exposure on BW associated with the ability to metabolize carcinogens in cigarette smoke. Similarly, these data indicate that it is biologically plausible that maternal ETS exposure may adversely affect pregnancy outcomes in selected groups based on genetic ability to metabolize chemicals in cigarette smoke.

3.1.2. Effects of Pregnancy upon the Biomarker Cotinine

In non-pregnant adult smokers, cotinine, the major proximate metabolite of nicotine, is a validated biomarker of smoking and correlates with the daily intake of nicotine from cigarette smoke much better than the count of cigarettes smoked per day (Benowitz, 1999). Studies of the effect of active smoking upon reproduction have found cotinine levels to correlate with adverse outcome measures in a dose-dependent manner. The levels of cotinine in saliva and blood are

very similar, while the levels of cotinine in urine are approximately six times that of blood (Benowitz, 1999). There is good correlation between blood, saliva, and urine levels of cotinine. The mean blood or saliva level of cotinine in ETS-exposed non-smoking adults in the U.S. is well below 10 ng/ml, usually in the neighborhood of 1 ng cotinine per ml (Pirkle *et al*., 1996). Blood cotinine levels for self-reported ETS-exposed and unexposed non-smokers greatly overlap and there is also some overlap with active smokers. The mean blood cotinine level for an ETS-exposed non-smoker has been reported as 0.8 ng/ml (Pirkle *et al*., 1996). In non-pregnant adults, the mean half-life of cotinine is between 17 and 20 hours and tends to remain at steady state from day to day. In non-pregnant adults, the blood cotinine level generally used to separate smokers from non-smokers is 10 ng/ml (Pirkle *et al.,* 1996; Rebagliato *et al.*, 1998).

Since publication of the previous monograph, we have expanded our knowledge of the effect of pregnancy upon the biomarker cotinine and the utility of cotinine as a biomarker during pregnancy. A recent study found the mean half-life of cotinine in pregnant women was 8.8 hours (95% CI 5.5-12) compared to 16.6 hr for the same women 3 months postpartum (16.6 hr; 95% CI 14.8-19) (Dempsey *et al.,* 2002). Gestational age was not found to affect the clearance of cotinine. The more rapid clearance of cotinine in pregnant women means that the cotinine levels in occasional and light smokers (<5 CPD) may fall into the range of non-smokers during periods of abstinence such as nighttime sleeping (Benowitz and Jacob, 1994). These data also explain the findings of Rebagliato, who found that the saliva cotinine was 3.5 ng/ml saliva per cigarette per day (CPD) during pregnancy and 9.9 ng/ml saliva per CPD postpartum (Rebagliato *et al.,* 1998). Based on these data, blood cotinine levels of 10 ng/ml in a non-pregnant woman and 3.6 ng/ml in a pregnant woman represent approximately equivalent smoke exposures. As a result, the cotinine blood or saliva levels of 10 ng/ml or higher that investigators have used to separate non-smoking pregnant women from active smokers are probably too high for pregnancy and would include light active smokers among their non-smokers. As a biomarker of exposure during pregnancy, a blood cotinine level below 3 ng/ml is probably a more suitable cut off to discriminate between maternal smokers and non-smokers.

A biomarker of exposure is needed because quantitating ETS exposure by history is very difficult. Urine levels of cotinine are approximately six times that of saliva or blood (Benowitz, 1999). This greater concentration relative to blood or saliva may allow for separation of non-smokers with no ETS, non-smokers with ETS and maternal smokers (Wang *et al.,* 1997). In addition, cotinine may still be detectable in the urine even if it is below the level of detection in blood or saliva. Presently, urine cotinine levels are probably the best available biomarker of ETS exposure during pregnancy. In a study of newborns of smoking mothers the mean concentration of cotinine in their urine was 151 ng/ml while the sum of the concentrations of nicotine and four other nicotine metabolites was 745 ng/ml (Dempsey *et al.,* 2000). In a study of pregnant smokers, urine cotinine accounted for only 18.3% of the sum total of nicotine and its metabolites in the urine (Dempsey *et al.,* 2002). Methodologies are being developed for LC-MS-MS assays of nicotine and five metabolites (nicotine glucuronide, cotinine glucuronide, 3'-hydroxycotinine, and 3'-hydroxycotinine glucuronide) (Jacob *et al.,* 2002). It may be that the sum of nicotine metabolites in urine may serve as a superior dose-dependent biomarker for ETS exposure during pregnancy compared to blood cotinine.

Maternal and newborn hair levels of nicotine have also been used as a biomarker of ETS exposure during pregnancy, but there has been poor correlation between maternal and neonatal hair nicotine levels (Nafstad *et al.,* 1998). There are practical and methodological limitations to hair analysis. Some newborns are bald or nearly bald and so obtaining a sample may be difficult. Adult hair is highly variable as to thickness, color, and curl, which may affect nicotine deposition. Additionally, dyeing, bleaching, and perming hair may also affect the nicotine content. There appears to be, however, good correlation between maternal smoking histories and maternal nicotine hair levels (Eliopoulos *et al.,* 1996).

3.1.3. ETS Exposure in Pregnancy: the Association Between Self-Report and Cotinine

Studies of the effects of ETS exposure tend to rely heavily on maternal self-report. With the establishment of cotinine as a biomarker of ETS exposure along with the determination of levels that discriminate exposed and truly non-exposed pregnant women, it is possible to examine the association between self-reported ETS exposure and that indicated by serum cotinine levels.

A population-based sample of 680 pregnant women in California was used by DeLorenze *et al.* (2002) in a comparison of serum cotinine levels in blood taken during the mid-second trimester of pregnancy with the women's responses to an ETS exposure question asked around the time of delivery. The question on ETS specifically asked how many hours per day, during the fourth and fifth months of the pregnancy, the mother spent indoors with other people who were smoking at home, work and other places. The assay used for cotinine was highly sensitive with a limit of detection of 0.05 ng/ml. Multivariate analysis was used to estimate the mean change in log serum cotinine as a function of hours per day of ETS exposure at all sites, combined and separately.

After controlling for marital status, payment source for prenatal care, language spoken at home, and tea consumption, the analyses showed that self-reported total hours per day of ETS exposure was a significant predictor of (log) serum cotinine when modeled as a function of a cubic polynomial ($R^2 = 0.27$). The data were also predictive when coded categorically as any hours per day of ETS exposure at any site ($R^2 = 0.17$).

Based on responses to the ETS question, 72% (n = 490) of the participants reported no ETS exposure. However, the corresponding cotinine values for this group indicated a wide range of ETS exposures (0.001-3.67 ng/ml). Regression analysis incorporating demographic variables indicated that the reportedly unexposed women with higher cotinine levels were more likely to be unmarried and of lower socioeconomic status. These data suggest that studies of ETS exposure in pregnant women that rely on an hours-per-day ETS exposure question likely misclassify some portion of ETS-exposed women as non-exposed. As a result, the association of ETS exposure with pregnancy outcomes would be under-estimated in such studies.

In a related article conducted in the same population of pregnant women, Kaufman *et al.* (2002) examined the agreement between a question about the number of smokers in the household and serum cotinine levels. The results showed that even when no ETS exposure was reported at home, at work or in other places, serum cotinine levels were twice as high in women reporting living with one or more smokers (0.08 ng/ml, 95% CI 0.05-0.13) as compared to women reporting no smokers in the home (0.04 ng/ml, 95% CI 0.04-0.05). Although the authors

acknowledged the result may be due to ETS exposure in other places that was not adequately measured in this study, it was proposed that the higher cotinine levels may have resulted from exposure to nicotine emitted from a smoker's clothes or hair. Nicotine from ETS is deposited on surfaces such as walls, carpets, and clothes, and can be emitted back into the air from these surfaces. Low levels of nicotine have been measured in the air in rooms where smoking had occurred in the past, and urinary cotinine concentrations have been measured in subjects exposed to a room where smoking occurred in the past (Nelson *et al.,* 1991). This component of ETS exposure may help to explain some of the variability between serum cotinine concentrations and questionnaire data of exposure, especially where levels of exposure are low.

3.2. Fetal Growth and Preterm Delivery

3.2.1. Epidemiological Studies

This section includes studies published since the previous monograph that investigate the following topics: birth weight (BW), low birth weight (LBW), small for gestational age (SGA), small for dates (SFD), intrauterine growth retardation (IUGR), preterm delivery (PTD), spontaneous abortion (SAB), and pregnancy wastage. Studies presenting data on the effects of ETS on fetal growth retardation, measured as IUGR and SGA, are summarized in Figure 3.3. The cited studies generally defined the birth outcomes as follows. LBW was a term birth of less than 2,500 g. SGA was defined as BW more than two standard deviations below the population mean, or below a reference median weight for the infant's gestational age based on gender, race and an age-specific fetal growth reference. SFD and SGA are synonymous. IUGR was defined as a BW below the 10^{th} percentile of BW distribution for the gestational week and gender. PTD was any birth before gestational week 37; very PTD (vPTD) was birth at less than 35 weeks gestation.

Several issues regarding covariates and confounders need to be considered. The most important determinant of BW is gestational age (GA). Thus GA is an extremely important covariate of studies of ETS exposure and BW. Between 36 and 40 weeks of gestation, fetal weight increases by approximately 100 g per week, so a one-week difference or even a three to four day difference in mean GA may result in a mean difference in BW of 50-100 g. This magnitude of difference in BW to GA is greater than or similar to the BW decrements reported by some authors to be associated with ETS exposure. Studies that include GA in their models will be given greater weight in the discussions and conclusions.

A confounder of studies of ETS exposure is maternal active smoking. Inadvertent inclusion of active smokers in the cohorts of non-smoking pregnant women may occur if active smokers self-identified themselves as non-smokers, or it may occur if inclusion is based on biomarkers. Due to the increased clearance of cotinine during pregnancy, it is possible for the cotinine level of a light smoker (2-3 CPD) to fall to very low levels between the last cigarette smoked and the time of sampling.

In addition, non-smokers and smokers have been shown to have statistically significant differences in their lifestyles (Koo *et al.,* 1988; 1997), especially when both parents smoke. These differences include time of entry into prenatal care, illicit drug use, alcohol consumption, socioeconomic status, maternal age, marital status, and parental education; and these lifestyle

factors have also been associated with adverse reproductive outcomes. The risk factors with greatest magnitude of effect upon BW are a prior history of low BW or pre-term delivery. Other important risk factors include: ethnicity, maternal pre-pregnancy weight or body mass index, maternal weight gain during pregnancy, maternal height, and parity. These factors are adjusted for in many of the newer epidemiological studies.

Table 3.1 ETS and Fetal Growth, Preterm Delivery and Birth Weight.

Reference Country	Study description	Smoke exposure measure	Findings and OR (95% CI)	Comments
Kharrazi *et al*., 2004 US	Prospective study of maternal serum cotinine and birth outcomes. n=2,777	Maternal cotinine 0.5-1.0 ng/ml >1.0 ng/ml Per unit increase in log cotinine	Change in birth weight -31 g -101 g Pre-term Delivery 1.78 (1.01-3.13) OR adverse outcome 1.36 (1.07-1.72)	Significant increases in adverse birth outcomes associated with maternal serum cotinine. ORs adjusted for maternal age, ethnicity, parity, infant gender, gestational age, insurance.
Goel *et al*., 2004 India	Retrospective (cross-sectional) study of the effect of passive smoking on birth outcomes. n=576	Maternal passive only	Pre-term Delivery 1.15 (0.69-1.92) Small for gestational age 2.10 (1.27-3.48)	ETS exposure by questionnaire: primarily spousal smoking. ORs adjusted for age, education, occupation, birth order, number of live births and anemia. Traditional Indian smoking materials.
Hanke *et al.* 2004 Poland	Prospective study of smoke exposure on fetal biometry n=183	Maternal serum cotinine < 10 ng ng/ml	Regression coefficient BPD -0.172 p = 0.06 BW –100.486 p = 0.09	Marginally significant decrements in BW and bi-parietal diameter with ETS exposure during pregnancy.
Dejmek *et al*. 2002 Czechoslovakia	Retrospective study of effects of active and passive smoking on birth outcomes n=6,866	Maternal passive only	OR low birth weight 1.51 (1.02-2.26) OR IUGR 1.08 (0.82-1.43)	ETS, defined as passive exposure to 5 or more cigarettes/day, significantly raised risk of low birth weight but not IUGR.
Jaakkola *et al.* 2001 Norway	Cohort study of ETS and hair nicotine on birth weight n=389	Maternal exposure per µg nicotine/g hair ETS home ETS work hair nicotine <4.0 µg/g ≥4.0 µg/g	Birth weight -0.91 g (-20-+18) -99 g (-273-+75) -101 g (-258-+56) Pre-term Delivery 1.30 (0.31-5.58) 6.12 (1.31-28.7)	No significant association of nicotine or ETS with birth weight but no control for gestational age. Significant association for pre-term delivery with high maternal hair nicotine.

BPD biparietal diameter; BW birth weight; CPD cigarettes per day; HC head circumference; IUGR intrauterine growth restriction; L body length; LBW low birth weight; SES socioeconomic status.

Table 3.1 ETS and Fetal Growth, Preterm Delivery and Birth Weight.

Reference Country	Study description	Smoke exposure measure	Findings and OR (95% CI)	Comments
Kukla *et al.* 2001 Czechoslovakia	Prospective study of smoke exposure and birth outcomes. n=4,530 1,178 ETS exposed 2,987 no exposure 365 active smokers	Maternal exposure passive <15 CPD passive >15 CPD active <10 CPD	Neonate parameters -4 g BW; +0.01 cm L +0.11 cm HC -49 g BW; -0.34 cm L +0.01 cm HC -79 g BW; -0.48 cm L -0.28 cm HC	High ETS similar to active smoking on birth weight, body length and head circumference but data not adjusted for, parity, SES, maternal height or weight, or other predictors of pregnancy outcome. Authors note gestational age not different among groups.
Haug *et al.* 2000 Norway	Retrospective study on birth weight and parental smoking n=22,883	Parental smoking Active maternal only Active paternal only Both	Birth weight decrease 153 g (128-178) 1 g n.s. 201 g (185-218)	Statistically non-significant decrease in BW with maternal exposure to ETS unless she is also an active smoker.
Matsubara *et al*, 2000 Japan	Prospective population-based cohort study of smoke exposure and birth outcomes. n=7,411; 6,335 nonsmokers	Maternal passive Active paternal only Any passive	OR IUGR 0.95 (0.72-1.26) Birth weight decrease 19 g p<0.05	Significant decrease in BW but statistically non-significant decrease in IUGR with maternal exposure to ETS.
Hruba & Kachlik, 2000 Czecholslovakia	Retrospective study of ETS and birth weight. n= 1,047 non-smokers	Maternal passive only Never smokers +ETS Former smokers +ETS Former smokers -ETS	Change in birth weight -65 g +2 g +32 g	ETS apparently decreased BW for never smokers and modified weight gain in former smokers but no statistical analysis provided.
Windham *et al.* 2000 US	Prospective study of ETS and birth weight in non-smokers. n=3646	Maternal passive only Moderate ETS High ETS 12 hr ETS/day > 30 yr old	Change in birth weight +0.68 g +8.2 g -88 g OR Pre-term Delivery 2.8 (1.2-6.6)	Study group comprised women in pre-paid plan seeking prenatal care; not representative of general population. All birth weight CIs included 0
Hanke *et al.* 1999 Poland	Retrospective study of birth weight and ETS in non-smokers. n=1751	Maternal passive only ETS > 7 hr/d	Change in birth weight -100 g (no CI given) OR Pre-term Delivery 1.86 (1.05 -3.45)	BW decrease became non-significant after adjustment for gestational age.

BPD biparietal diameter; BW birth weight; CPD cigarettes per day; HC head circumference; IUGR intrauterine growth restriction; L body length; LBW low birth weight; SES socioeconomic status.

Table 3.1 ETS and Fetal Growth, Preterm Delivery and Birth Weight.

Reference Country	Study description	Smoke exposure measure	Findings and OR (95% CI)	Comments
Windham *et al*., 1999a US	Retrospective study of ETS and birth weight. n = 992	Maternal passive only	Low term birth weight 1.8 (0.64-4.8) OR small-for-gestational age 1.4 (0.79-2.5)	Small-for-gestational age ORs adjusted for multiple confounders but BW adjusted only for race, alcohol and caffeine consumption.
Peacock *et al.* 1998 UK	Prospective study of maternal plasma cotinine and birth weight. n=703 non-smokers Also meta-analysis	Maternal passive only Meta-analysis +ETS	Change in birth weight -6.7 g (-84; 97) -31 g (-44- -19)	BW adjusted for gestational age, maternal height, parity and gender. Meta analysis of 11 studies found significant decrease in BW with ETS.
Luciano *et al.*, 1998 Italy	Prospective cohort study. Maternal passive and light active smoking on fetal growth. n=112, 89 non-smokers	Maternal None ETS only Light active	BW Placenta wt 3604 g 603 g 3351 g 553 g 3378 g 541 g p< 0.013 p<0.001	Significantly lower BW, placental weight, cranial circumference, length, etc. with passive and active smoking. Limited confounder control.
Dejin-Karlsson *et al.* 1998 Sweden	Prospective study. ETS and risk of small-for-gestational-age infants. n=826	Maternal exposure Non-smoker + ETS Active smoker + ETS	OR small-for-gestational age 3.9 (1.4-10.7) 6.0 (2.1-17.5)	ETS, as dichotomous variable, raised risk of SGA births. ORs adjusted for maternal age, weight, height, nationality and education.
Nafstad *et al.* 1998 Norway	Case-control study of small-for-gestational-age and hair nicotine. 58 cases; 105 controls	Maternal exposure Maternal hair nicotine < 0.75 µg/g 0.75-4 µg/g > 4 µg/g	OR small-for-gestational age 1 (reference) 3.4 (1.3-8.6) 2.1 (0.4-10.1)	Increased risk for nonsmokers with maternal hair nicotine > 0.75 µg/g. Apparent lower risk at >4 µg/g likely due to small number of individuals in this category. Neonatal hair nicotine not correlated with outcome.

BPD biparietal diameter; BW birth weight; CPD cigarettes per day; HC head circumference; IUGR intrauterine growth restriction; L body length; LBW low birth weight; SES socioeconomic status.

Table 3.1 ETS and Fetal Growth, Preterm Delivery and Birth Weight.

Reference Country	Study description	Smoke exposure measure	Findings and OR (95% CI)	Comments
Ahluwalia *et al.* 1997 US	Retrospective study of the interaction of age and ETS on birth weight and premature births. n=17,412 (13,497 non-smokers)	Maternal passive only <30 yr old >30 yr old <30 yr old >30 yr old <30 yr old >30 yr old	OR low birth weight 0.97 (0.76-1.23) 2.42 (1.51-3.87) OR preterm birth 0.92 (0.76-1.13) 1.88 (1.22-2.88) Change in birth weight 8.8 g (43.7--26.1) -90 g (0.8--180.9)	ETS during pregnancy significantly increased risk of LBW and preterm delivery in non-smoking women over 30 yrs old, but not in younger women.
Wang *et al.* 1997 US	Prospective study of smoke exposure during pregnancy and birth outcomes. n=740	Urine & serum cotinine Per 1,000 ng increase in urine cotinine	Birth outcomes BW -59 ± 9 g Length -0.25 ± 0.05 cm Head circ-0.12 ±0.03cm All p<0.01	Smoke exposure during pregnancy may adversely affects fetal growth. However, reference group with urinary cotinine < 31 ng may have included active smokers.
Horta *et al.* 1997 Brazil	Retrospective study n=5,166 singleton births, 3,368 non-smoking mothers	Maternal passive only Maternal passive only Maternal active Paternal smoking	OR low birth weight 1.18 (0.94-1.48) OR pre-term delivery 1.25 (0.99-1.57) 1.02 (0.80-1.29) OR IUGR 1.33 (1.05-1.68)	Significance of results hard to evaluate as ETS was not quantified, and little data were given on BWs and sizes of exposure groups.
Lodrup Carlson *et al.* 1997 Norway	Prospective cohort study of asthma. Birth weight and ETS data. n=803.	Maternal passive only No ETS ETS exposed	Birth weight (SD) 3.6 kg (49 g) 3.5 kg (46 g) p=0.04	Significantly lower BW with ETS but values unadjusted for gestational age or other confounders.
Jedrychowski & Flak, 1996 Poland	Retrospective study of cotinine, smoke exposure and birth weight. 1007 non-smokers.	 Maternal passive only Maternal passive only	Change in birth weight -57.9 g (p=0.004) OR low birth weight 1.46 (0.83-2.6)	ETS significantly decreased BWs but not OR for LBW.

BPD biparietal diameter; BW birth weight; CPD cigarettes per day; HC head circumference; IUGR intrauterine growth restriction; L body length; LBW low birth weight; SES socioeconomic status.

Kharrazi et al. (2004) examined the effects of maternal ETS exposure during pregnancy on several birth outcomes including gestational age, BW and fetal death. The study population included pregnant women from 11 counties in central California who were enrolled in the state's maternal serum alpha-fetoprotein prenatal screening program in 1992. Statewide, approximately 60% of women delivering live births that year were enrolled in the program. The criteria for inclusion identified 2,777 woman-live birth pairs and 19 woman-fetal death pairs as eligible for analysis. ETS exposure during pregnancy was assessed from serum cotinine levels in blood taken at 15-19 weeks of gestation. The assay for cotinine was highly sensitive with a limit of detection of 0.050 ng/ml. Multiple linear and logistic regression analyses were used and adjusted for five covariate risk factors that had a significant effect on the cotinine regression coefficients, changing the unadjusted value by ≥ 10%. The analyses were thus adjusted for mother's ethnicity, age, parity, source of payment for prenatal care, and infant gender, but not for marital status, adequacy of prenatal care, and maternal education.

For the analysis, log cotinine levels were split into quintiles and women with serum cotinine levels above 10 ng/ml were excluded as likely smokers. Several study outcomes had elevated ORs or lower means in the highest quintile of cotinine (0.236-10 ng/ml) compared to the lowest (<0.026 ng/ml), including PTD, term-LBW, and adverse pregnancy outcome. Inverse linear relationships were seen between log cotinine and BW, and infant length. In the adjusted analysis, the BW decreased by 109 g and the length shortened by 0.84 cm over the range of log cotinine values. The adjusted mean BW using commonly assessed cotinine categories resulted in a –31 g change in BW for maternal cotinine levels of 0.5-1.0 ng/ml, and –101 g for > 1.0 ng/ml (Table 3.2). No association was seen between ETS and head circumference in the adjusted analysis.

Among the 19 fetal deaths included in this study, elevated death rates were seen at the highest cotinine level (0.50-10 ng/ml) with some evidence of a dose response at lower levels. As cotinine levels rose, fetal deaths occurred at earlier gestational ages resulting in higher cumulative death rates (<0.05 ng/ml 0.6%; 0.05-0.10 ng/ml 0.9%; 0.10-0.50 ng/ml 1.1%; 0.50-10.0 ng.ml 1.8%).

Lower gestational age at birth was associated with higher maternal cotinine levels and approximately 10% of the ETS effect on BW was due to increased PTD. Thus the adverse effect of tobacco smoke exposure on BW was primarily through slowing fetal growth. Evidence of gestational shortening was found at cotinine levels as low as 0.1 ng/ml. The authors report that there was no evidence of an ETS threshold below which there was no reduction in BW and infant length. Reduction in BW showed a dose response effect with increasing maternal cotinine levels.

Table 3.2 Adjusted Differences in Mean Birth Weight as a Function of Maternal Cotinine

Cotinine (ng/ml)	N	BW change (g)
>1.0-10	135	-101
>0.5-1.0	142	-31
>0.1-0.5	808	-30
0.05-0.1	652	-15
<0.05	1022	Ref

The odds of an adverse outcome (fetal death, PTD or term-LBW) increased from 5% to 12% in a linear fashion between 0.05 ng/ml and 4 ng/ml. In multivariate attributable risk analyses, ETS levels >0.05 ng/ml (62% of the study population) accounted for 12% of all adverse pregnancy outcomes (fetal death, LBW and PTD).

Table 3.3 Odds Ratios and 95% CIs of Selected Birth Outcomes and for Each Unit Increase in Log Cotinine in Adjusted Logistic Regression Models

	Risk at cotinine ≥ 0.236		Risk per unit increase	
Outcome	N	OR (95% CI)	N	OR (95% CI)
Fetal death	8/562	3.36 (0.81-13.96	19/2777	1.58 (0.78-3.21)
Preterm delivery*	43/554	1.78 (1.01-3.13)	123/2759	1.29 (0.97-1.72)
Term low birth weight*	15/554	1.76 (0.65-4.81)	54/2759	1.41 (0.91-2.17)
Adverse pregnancy outcome	66/562	1.91 (1.19-3.07)	196/2777	1.36 (1.07-1.72)

*Among live births only

Strengths of this study include the large and diverse study population, and the use of a sensitive objective assay of ETS exposure. The authors suggested that the enhanced sensitivity of the cotinine assay contributed to the stronger results compared to other continine-based studies. In prior studies with higher minimum detection levels, some women with low ETS exposure would have been included among the non-exposed controls, thereby diminishing the apparent ETS effect. On the other hand, for the endpoints measured in this study, it is not clear during what portion of gestation the fetus is most sensitive to the effects of smoke exposure. Thus the use of a single ETS measure in mid-pregnancy may not have accurately reflected fetal smoke exposure during critical developmental stages. In addition, if maternal smoking habits changed during pregnancy, some exposure misclassification may have occurred that might alter the reported effect sizes. However, the most likely direction of change would underestimate the ETS effect. This study suggests that even low-level ETS exposure during pregnancy can result in adverse gestational outcomes.

Goel et al. (2004) conducted a retrospective (cross-sectional) study of birth outcomes in a group of 507 non-smoking women who gave birth to singleton live infants at a hospital in India. Exposure to ETS was determined by questionnaire. In the social context of this study this exposure was primarily the result of spousal active smoking, although active smoking by parents was also reported. Unadjusted ORs for the association with ETS exposure with PTD (OR 1.60, 95% CI 1.01-2.54), Caesarian section (OR 1.17, 95% CI 0.78-1.75), LBW (OR 1.43, 95% CI 0.95-2.16), small for gestational age (SGA; OR 2.25, 95% CI 1.43-3.55), and congenital

malformation (OR 1.16, 95% CI 0.20-4.92) were all elevated to some degree, but of these only the OR for SGA was clearly statistically significant. A multivariate analysis was also presented which included consideration of age, education, occupation, birth order, number of live births and anemia. Adjusted ORs for the birth outcome variables were reduced in this analysis, and close to 1.0, except for SGA, which remained statistically significant (OR 2.10, 95% CI 1.27-3.48), and congenital malformation. The congenital malformation result was actually slightly higher in the multivariate analysis (OR 1.27, 95% CI 0.33-5.55), but the extremely wide confidence bounds on this value (presumably due to the small number of actual cases involved) prevent any conclusion being drawn concerning this endpoint.

This study is interesting in providing a clear positive result for SGA (defined as BW less than the 10^{th} percentile of weight for that gestational age), consistent with several other reports. The nature of the exposure may be somewhat different from that seen in North American or European populations, due both to the different living conditions and different type of tobacco (bidis and pipe tobacco in hookas, as well as US/European style cigarettes). There was an apparent correlation of adverse outcomes with lower socioeconomic status. The authors hypothesized that this resulted from high exposures due to more crowded living conditions, inferior domestic ventilation, and lack of education leading to lack of smoke-avoidance behavior. In spite of these differences, this result may be considered supportive of the association between ETS exposure and LBW, small birth size for gestational age and related parameters of fetal growth and development in European and North American populations.

Hanke et al., 2004. Hanke and associates investigated the effect of tobacco smoke exposure in early pregnancy (20-24 weeks) on fetal biometry. A group of 183 pregnant women in Lodz, Poland were interviewed and asked about smoking habits. The women described themselves as either non-smokers, passive smokers (exposed to ETS) or active smokers. The women were tested for cotinine levels, and the investigators used these cotinine measurements to assign the women to specific exposure groups: nonsmokers not exposed to ETS (cotinine < 2 ng/ml); nonsmokers exposed to passive smoke (cotinine 2-10 ng/ml); smokers (>10 ng/ml). All the pregnant women were given ultrasound examinations early in pregnancy (at 20 to 24 weeks gestation) that included measurement of three parameters: bi-parietal diameter (BPD), abdominal circumference (AC), and femur length (FL). BPD is a measurement of the size of the fetal brain. In addition, immediately after birth, data were obtained on BW, length, and abdominal and thoracic circumference of the neonates.

Mean values of the three parameters decreased nonsignificantly with increasing values of maternal serum cotinine. Use of a multiple regression model for BPD revealed a statistically significant negative coefficient for serum cotinine after adjustment for gestation time, gender, and maternal weight. Although similar tendencies were observed for the other two parameters (AC and FL), neither was statistically significant. A significant negative effect of cotinine level on BW was found, as has been observed in numerous earlier studies. Serum cotinine at 20-24 weeks gestation was inversely associated with BW after controlling for pregnancy duration, maternal pre-pregnancy weight and infant gender (p=0.004). When passive smokers were compared to non-smokers (assignment based on cotinine levels) a large but statistically nonsignificant decrement in BW was found, (-100 g; p=0.09).

An effect of tobacco smoke from active or passive smoking on BW has long been known. These investigators were attempting to determine whether a precursor of this effect could be found early in pregnancy using ultrasound biometrics. They did find such a significant effect based on one parameter (BPD) and non-significant indications of effects on the other two parameters (AC and FL) relative to serum cotinine levels at 20-24 weeks gestation. This appears to be a well-conducted study that indicated that exposure to tobacco smoke early in pregnancy affects the growth of the fetus by 20 to 24 weeks of gestation. The study was not able to discriminate between the effects of active or passive smoking at this early stage. One cannot conclude from this study that passive smoking alone would be sufficient to affect fetal development at this stage.

Dejmek et al., 2002. This is a retrospective study of 6,866 mother-infant pairs conducted in the Czech Republic. Data regarding smoking habits and ETS exposure before and during each trimester of pregnancy were obtained by questionnaire during the hospitalization for birth and by medical record review. The analysis controlled for maternal age, geographic location of home, ethnicity, parental education, and parity, sex of infant, maternal height, pre-pregnancy weight, and alcohol consumption and season of the year. There were 4,309 women who were non-smokers prior to conception, 1,500 were moderate smokers (1-10 CPD), and 1,049 were heavy smokers (>10 CPD). ETS exposure was defined as exposure to smoke from five or more CPD, smoked by another person in the presence of the mother. Among non-smokers 25% were ETS exposed (mean ETS 11 CPD), while 67% of moderate smokers were ETS exposed (mean ETS 14 CPD) and 85% of heavy smokers were ETS exposed (mean ETS 23 CPD). Among those smoking prior to pregnancy, 734 quit during the first trimester, 467 quit during the second trimester, and 52 quit during the third trimester.

The adjusted decrease in BW for non-smokers exposed to ETS from 5 or more CPD was 53 g (95% CI 24-82). The adjusted OR for a LBW baby if the mother was a non-smoker exposed to ETS was 1.51 (95% CI 1.02-2.26). The adjusted OR for IUGR among non-smokers exposed to ETS was 1.08 (95% CI 0.82-1.43). A strength of this study was the collection of smoke exposure data at several points during the pregnancy so that the analysis reflected changes in ETS exposure as smoking habits changed.

Jaakkola et al., 2001. The cohorts for this study were drawn from a larger Finnish study that enrolled all 2,751 births born into two geographically defined hospital districts between May 1996 and April 1997. Of the mother-infant pairs in the original study, 1,621 self-identified as non-smokers. In the present study, 189 self-identified as non-smokers with ETS exposure and 283 with no ETS. Of the non-smokers with no ETS, 142 were living with a non-smoker or a spouse who had quit over 12 months ago, and 141 lived with a smoker. Smoking status and exposure assignment were based on self-administered questionnaires, prenatal care records, birth registries, and hair nicotine. Hair nicotine levels are believed to reflect the previous two months of exposure. The final cohort assignments were based on hair nicotine levels: low nicotine exposure, 151 mother-infant pairs (hair nicotine < 0.75 μg/g); medium exposure, 186 pairs (0.75 to < 4.0 μg/g); and high exposure, 52 pairs (≥ 4.0 μg/g). The low nicotine group is the reference group.

The three groups based on nicotine hair levels were similar except for alcohol consumption. Among women who denied exposure to ETS, there was a substantial difference between those who lived with a smoker and those who did not (median 1.32 vs. 0.61 μg/g). Only 29% (n = 55) of ETS exposed mothers gave quantitative data of exposure in CPD, and among these the higher the exposure the higher the hair nicotine levels (1-9 CPD; 2.68 SD ± 1.99 μg/g; 10-19 CPD, 3.4 SD ± 2.4 μg/g; ≥ 20 CPD, 5.17 SD ± 7.24 μg/g). Mean BW for cohorts based on hair nicotine levels were: low exposure, 3,559 g (SD ± 472); medium exposure, 3,554 g (SD ± 534); high exposure, 3,547 g (SD ± 547). Confidence intervals or p values were not given. A model adjusting for confounders (infant gender, maternal age, pre-pregnancy body mass index, marital status, parental education, alcohol consumption, and employment) found a 17 g decrease in BW between the reference group and those with the highest hair nicotine levels, but the confidence interval was wide and included zero (95% CI -178-145), and the model did not appear to control for GA. For most of the confounders used in the model, the percents given for the reference and the high exposure groups were very similar except for increased alcohol consumption (35% vs 28% in reference group) and lower education for the high-exposure groups. When hair nicotine was treated as a continuous variable, there was no significant association between BW and nicotine levels (-0.91 g BW per μg nicotine per g hair, 95% CI -20-18). Birth weight was not significantly related to ETS exposure at home (-99 g 95% CI -273-75) or work (-101 g 95% CI -258-56). On the other hand, PTD (< 37 wks) was significantly related to ETS, particularly at hair nicotine levels above 4 μg/g, which confounds the analysis of BW. As maternal hair nicotine levels increased from < 4.00 to ≥ 4.00 μg/g, the adjusted ORs for PTD increased from 1.30 (95% CI 0.30-5.58) to 6.12 (95% CI 1.31-28.7). There was evidence of a dose-response for both exposures at home and at work. For ETS exposures, the OR for home only was 0.65 (95% CI 0.06-6.81); work only was 2.35 (95% CI 0.50-11.1); while the OR for both was 8.89.

Kukla et al., 2001. The European Longitudinal Study of Pregnancy and Childhood (ELSPAC) is an international longitudinal study that includes approximately 40,000 women in six European countries. This study follows women during labor and delivery and their children's postnatal development. Women repeatedly filled out questionnaires, and standardized data were collected from physicians in charge. Results presented here were for 4,530 mother-infant pairs residing in the Czech Republic, of whom 2,987 were not exposed to ETS. Of the 1,178 non-smokers exposed to ETS, 864 were exposed to <15 CPD and 314 were exposed to >15 CPD. There were 365 smokers of whom 298 smoked less than 10 CPD and 67 smoked more than 10 CPD. Infants born to passively and actively exposed mothers had lower mean BW, length and head circumference when compared to those with no smoke exposure. Birth weight does not appear to be corrected for GA. Compared to no ETS exposure, the babies of mothers passively exposed to <15 CPD had a mean BW that was 4 g lower, a mean length 0.01 cm longer, and a mean head circumference that was higher by 0.11 cm; none of these was statistically significant. The babies of mothers passively exposed to >15 CPD had a mean BW that was 49 g ($p<0.06$) lighter, a mean length 0.34 cm ($p<0.01$) shorter, and a mean head circumference of 0.01 cm larger. By comparison, babies of mothers smoking <10 CPD had a BW 79 g ($p<0.01$) lighter, they were 0.48 cm ($p<0.001$) shorter, and their head circumference was smaller by 0.28 cm ($p<0.001$). The data indicate that high maternal ETS exposure affects fetal growth, specifically BW and length. The data would be more compelling if growth parameters had been adjusted for GA and other predictors of pregnancy outcome instead of a statement that gestational ages were similar among the smokers and nonsmokers. Occupational ETS exposure was not ascertained. As a result

some women included as non-smokers may have been exposed at work thus diminishing a possible ETS effect.

Haug et al., 2000. This is a Norwegian retrospective study that relied upon maternal recall. In the original study, the primary outcome of interest was SIDS. Postal questionnaires were sent in 1992 to mothers of singleton births, whose babies had no congenital anomalies, and were alive at 1 year of age. The survey years were 1970, 1975, 1980, 1985, 1989, 1990, and 1991; 34,799 questionnaires were sent out and 22,883 were returned. Smoking habits were recorded as yes/no to maternal smoking and yes/no to paternal smoking. Birth weight increased with maternal age for non-smokers regardless of paternal smoking status. Birth weight increased for babies born to maternal smokers and smoking fathers until the mother was 24 years old and then it plateaued. For babies born to smoking mothers and non-smoking fathers, the BW plateau occurred at a maternal age of 29 years. Among non-smoking mothers, there was a non-significant difference of -1 g in BW if the father was a smoker. Among smoking mothers, there was a statistically significant decrease in BW of 48 g ($p<0.01$) if the father was also a smoker, although this effect of paternal smoking abated between 1970 and 1985. The mean decrease in BW of babies with two smoking parents, adjusted for maternal age, was 201 g (95% CI 185-218), while it was 153 g (95% CI 128-178) if only the mother smoked. In general, the effect of maternal active smoking upon BW declined between 1970, when the mean decrease in BW was 221 g, and 1985 when the mean decrease was 178 g. From 1980 onward, there was a decrease in the effect of paternal smoking upon the BW of babies born to smoking mothers. Between 1970 and 1991, the prevalence of smoking among Norwegian men decreased from 59% to 36%; among women it declined from 32% to 27%.

Recall bias is a concern with this study as it relied on maternal memory of smoking behaviors after a period of as much as two decades. In addition, since only the presence or absence of smoking by either parent was recorded, there is no information on exposure intensity or duration. For example, it is possible that the decrease in the apparent effect of paternal smoking was a result of the decrease in smoking prevalence among fathers during that period, consistent with an effect of paternal ETS. Thus the resulting mixing of exposure levels and durations in the analysis, and possible misclassification due to recall bias, may have obscured the effects of exposure.

Matsubara et al., 2000. This Japanese study investigated the association between smoking, both active and passive, on BW, GA, PTD, SGA, and IUGR. In Japan, pregnant women must register the pregnancy with the government. The study population included all pregnancies registered in Nagoya, Japan (n = 15,207), between April 1, 1989 and March 31, 1991. At the time of registration, 15,207 women were given a self-administered questionnaire regarding smoking habits and ETS exposure; 8,624 (56.7%) women returned the questionnaire. There was no difference between women who filled out the smoking questionnaire and those who did not regarding maternal age, blood pressure, and hemoglobin. Those who filled out the questionnaire started their pre-natal care earlier than those who did not and more of them were nulliparous. Of the 8,624 women who filled out the smoking questionnaire data, 7,411 were used in the analysis. Of these, 6,335 were non-smokers, 285 (or 3.8%) were smokers, 726 (8.4%) were smokers who quit upon learning that they were pregnant (mean GA at time of quitting 8.8 weeks), and 65 women were missing smoking status. Birth weights in this study were adjusted for maternal age,

maternal height, BMI, education, working status, alcohol intake, parity, infant gender, and GA at birth.

Among non-smokers, 41.5% of husbands did not smoke, 1.5% of husbands quit smoking upon learning of the pregnancy, and 56.4% of husbands smoked. When the data were stratified by paternal smoking status, there was a non-significant difference in BW between babies born to non-smokers whose husbands smoked (mean BW 3,091 g) and non-smokers whose husbands did not smoke (mean BW 3,102 g; no 95% CI or SD given). When BW was analyzed by paternal cigarettes per day (CPD), babies of non-smoking mothers exposed to ETS from 20 or more CPD were 22 g lighter (mean BW 3,104 g) than those not exposed (mean BW 3,082 g), but the difference was not statistically significant.

When stratified according to the presence or absence of ETS at work or from the husband, neonates of non-smoking ETS-exposed women were 19 g lighter than those of ETS non-exposed women (3,108 g and 3089 g, respectively; $p<0.05$). However, the data were contradictory when ETS was categorized by duration of exposure. Babies (n = 1,730) born to women exposed to ETS for less than 2 hr/d were significantly lighter than in the absence of ETS (mean BW 3,082 g vs. 3,108 g; $p<0.05$), while there was no significant difference in BW when the mothers were exposed to ETS for more than 2 hr/d (mean BW 3,101 g vs. 3,108 g).

A strength of this study is the assessment of smoking early in the pregnancy, however, it's not known if there were changes in smoking behavior during the pregnancy. The authors also acknowledge that defining home ETS exposure solely by whether or not the husband smoked may have resulted in some misclassification. Of the non-smoking women whose husbands smoked, 25% reported no ETS exposure at home. This inclusion of non-exposed women in the ETS-exposed group could have led to the apparent lack of a significant ETS effects.

Hruba and Kachlik, 2000. This is a Czech study of singleton births delivered at Brno Obstetric Clinic. Medical students interviewed mothers of newly delivered babies. Little data are provided regarding the description or the selection of the cohort in this study. There were 1,097 mother-infant pairs enrolled. Of 727 never smokers, 127 were exposed to ETS. Of 320 former smokers, 165 were exposed to ETS. There were 50 maternal smokers. The reference population comprised babies born to never smokers unexposed to ETS. A decrease of 64 g in mean BW was found in full-term babies born to mothers who never smoked but were exposed to ETS. While an increase in BW of 2 g was found in babies of former smokers exposed to ETS, former smokers not exposed to ETS had an increase of 31 g in the BW of their babies over the reference BW.

This study also examined the prevalence of LBW and PTD. Among never-smokers not exposed to ETS the prevalence of PTD was 6.5%, and 11.2% for LBW. Among never-smokers with exposure to ETS at home and work, the prevalence of either birth outcome increased to 16.7%.

The statistical significance of these data is hard to determine as there were no confidence intervals or p values reported, and no evidence of adjustment for any covariates. In addition, there was potential reporting bias as interviewers were instructed to provide anti-smoking education.

Windham et al., 2000. This is a prospective California study of 4,099 women in a prepaid health plan who enrolled in prenatal care during the first trimester. Women were recruited in 1990-1991 and phone interviewed regarding smoking, ETS exposure, alcohol and caffeine consumption, demographics, stress, employment, and reproductive history. Outcome measures were obtained from computerized hospital records and medical charts. The model used to investigate the effect of ETS exposure was limited to non-smokers. Non-smokers (n = 3646) were categorized into three groups by ETS exposure: none (ETS <0.5 h/d, n = 2887); moderate (0.5-6.5 h/d, n = 625, ETS); and high (≥ 7 h/d, n = 134, ETS). Multivariate regression models of pregnancy outcomes including BW were adjusted for pre-pregnancy weight (BMI), parity, prior pregnancy losses, race, parental education, marital status, employment status, stress, caffeine and alcohol intake. In this study, there was no significant effect of ETS exposure on mean BW in non-smokers. There were 28 non-smoking pregnant women who reported 12 or more hours per day of ETS exposure, which was associated with a decrease of 88 g (SE 103) in the adjusted BW. When non-smokers were categorized by paternal smoking status, there was a decrease of 32 g in the adjusted BW (95% CI -81-18). Data were also categorized by ethnicity and by age of the mother to investigate if ETS was associated with significant changes in BW in selected populations. Decreases and increases in BW were found in selected populations and all the 95% CIs included zero.

Among non-smokers exposed to ETS, most of the ORs for LBW, SGA, and PTD outcomes were elevated, but their CIs included one. Those ORs and 95% CIs are given in Tables 3.4, 3.5, 3.6. Among selected populations of non-smokers with heavy ETS exposure there were significant elevations in risk. Heavy ETS exposure in non-Caucasian, non-smoking mothers was associated with an adjusted OR for LBW of 3.8 (95% CI 1.5-9.8). Heavy ETS exposure of non-Caucasian, non-smoking mothers was associated with an adjusted OR for PTD of 2.4 (95% CI 1.1-5.5), and for very PTD the OR was 3.8 (95% CI 1.3-10.7).

ETS exposure assessment was based on self-report of hours exposed and did not include exposure outside of the home and work. In addition, exposure was ascertained during the first trimester and thus did not reflect any changes in exposure during pregnancy. The small number of individuals in the high exposure group limited the study's power. On the other hand, the prospective design and extensive follow-up of a population with equal access to medical care should have diminished possible confounding.

Hanke et al., 1999. This is a Polish Study of 1,751 rural and urban non-smoking mother/infant pairs. Mothers were interviewed in 1996-1997 within days of birth by physicians about their exposure to ETS. There were 827 mothers with ETS exposure, 924 without. Compared to no ETS, mothers with ETS exposure were less educated, shorter, had fewer prenatal visits, more were unmarried, and more resided with a smoker. There was an approximately 100 g decrease in BW of the 174 babies born to mothers exposed to 7 or more hours of ETS per day when compared to the 924 babies born to unexposed mothers after adjusting for maternal height and age. But, after adjusting for GA, there was no significant difference in BW between babies of ETS exposed and unexposed women. However, the effects of ETS on BW may be mediated in part by a shortening of the pregnancy. A significant excess risk of PTD among mothers exposed to ETS for 7 hr/d was seen in the authors' multivariate analysis (OR 1.86, 95% CI 1.05-3.45). ETS appeared not to significantly affect the incidence of SGA babies.

Windham et al., 1999a. For this California retrospective study, the study population of 992 non-smokers was the control population from a study of spontaneous abortions conducted between 1986 and 1987 (Windham *et al.*, 1992). Mothers were interviewed by telephone on average six months after delivery regarding maternal ETS exposure for three months prior to pregnancy and during the first half of the pregnancy. Paternal smoking habits were also ascertained for the same time interval. Women were considered to be ETS exposed if they regularly spent one or more hours per day in a room where someone was smoking. SGA was defined as BW less than the tenth percentile for GA at each week of gestation for weeks 24-44. LBW babies were defined as those weighing less than 2500 grams. Multivariate regression models used to examine the effects of ETS on mean BW were adjusted for GA, maternal age, education, parity, marital and employment status, hypertension, race, alcohol consumption, and caffeine consumption. In the logistic regression analysis of LBW and ETS exposure, only the last three variables were included as the other variables were found not to confound the association. On average, babies born to ETS exposed mothers weighed 34 g more (95% CI -43-111) than those of ETS unexposed mothers. After adjustment for covariates, including GA, this estimate decreased to 13.8 g (95% CI -53.8-81.4) with wide confidence intervals that include no effect. The adjusted OR for an LBW baby was 1.0 (95% CI 0.52-2.1). The adjusted OR for a term LBW baby was 1.8 (95% CI 0.64-4.8) and the adjusted OR for a SGA baby was 1.4 (95% CI 0.79-2.5). This report included a meta-analysis of studies examining ETS and BW differences as well as LBW. Among the eight studies considering ETS exposure from all sources and providing adjusted estimates for BW differences, the pooled mean decrement in BW was -24.0 g (-39.3--8.6), a significant decrement in weight. The pooled OR for LBW was also statistically significant (1.38; 95% CI 1.01-1.87)].

Peacock et al., 1998. This prospective study of women booking for prenatal care between 1982 and 1984 was conducted in London to investigate whether maternal plasma cotinine levels, determined three times during pregnancy, were a better predictor of BW deficits from active smoking than a count of the CPD corrected for nicotine yield of the cigarette. A subsidiary goal of the study was to look at the relationship between cotinine levels and BW in maternal non-smokers whose smoking status was validated with a cotinine level. Of 1,860 pregnant women enrolled, 1,254 had all data elements collected including plasma cotinine levels. The plasma cotinine level, separating smokers and non-smokers, was 15 ng/ml. Histories of active smoking were obtained by trained interviewers. Passive smoking data were obtained by the question, "Does anyone else in the house smoke?" Among self-reported smokers, the data reported here support previous work by Bardy *et al.* (1993) that found that maternal cotinine levels were a better predictor than maternal CPD of BW deficits associated with active smoking. Among non-smokers, 283 reported ETS exposure at home, while 420 were reportedly ETS-unexposed. Almost all non-smokers reporting ETS exposure had cotinine levels that fell below 2.5-ng/ml plasma. Non-smokers were divided into quintiles based on cotinine levels (0-0.180, 0.181-0.291, 0.292-0.480, 0.481-0.795, $\geq$ 0.796 ng/ml). Smokers with ETS exposure had higher cotinine levels than non-smokers but there was substantial overlap in levels.

There was a mean 73 g decrease in BW in babies born to ETS-exposed mothers in the highest continine quintile compared to the lowest (95% CI -28-174). But after adjusting for gestational age, maternal height, parity, and sex of newborn, the decrease dropped to 6.7 g (95% CI -84-+97). Although this study lacked sufficient power to be conclusive, there was evidence that a

reduction in cotinine levels, especially early in pregnancy, partially mitigated the effects of ETS on BW.

The authors also conducted a meta-analysis of 11 studies, including the data reported here, and found a pooled estimate of difference in mean BW of -31 g (95% CI -44--19) between ETS-exposed and ETS-unexposed. They suggested that studies showing a large effect of maternal ETS exposure upon BW did not correct for GA.

Luciano et al., 1998. This was an Italian prospective cohort study of the effects of maternal passive and light active smoking on intrauterine growth and body composition in 112 neonates born after normal pregnancies. Questionnaires were used to assess maternal smoke exposure (active and passive; at home and at work) prior to and during pregnancy, paternal smoking during pregnancy, maternal weight gain, alcohol and drug use, placental and BWs, and paternal height and weight. After exclusion of women with gestational diabetes, alcohol consumption, drug addictions, first trimester infections, and exposure to radiation or teratogens, the remaining 112 mother-infant pairs were divided into three smoke exposure groups: nonsmokers with no ETS exposure; nonsmokers with significant ETS exposure (≥ 20 CPD); light active smokers (<10 CPD). Anthropometric measurements were taken within 24 hours of birth.

Compared to newborns of women with no smoke exposure, intrauterine growth was significantly lower in newborns of women with either passive or light active smoke exposure ($p<0.001$), but not significantly different between passive and active smokers. All auxometric measures (including birth and placental weights, fat mass, cranial circumference, height and other measures) were lower in children of women exposed to either passive or light active smoking compared to children of non-exposed women. The differences in individual measures were statistically significant for most measures ($p\leq 0.04$).

This is a relatively small study with no apparent control for potential confounders such as diet. The authors note there was no difference in gestational age among the three exposure groups. No biochemical assessment of ETS exposure was made and the ETS-exposed group included only those with exposure to ≥ 20 CPD (and a decrement in BW of 53 g). While a dose-response effect cannot be demonstrated in this study, the data indicate that heavy passive smoke exposure and light active smoking have comparable deleterious effects on intrauterine growth.

Dejin-Karlsson et al., 1998. This is a Swedish study of 826 nulliparous women delivering singleton births in one city during a one-year period. Data were collected at the first prenatal care visit where a single yes/no question assessed ETS exposure at home or work. Routine ultrasound examinations, performed in 97.6% of the women at 16-18 weeks and at 32 weeks of gestation, were used to date pregnancies and assess fetal growth. Babies with BW two standard deviations below the population-specific GA-related mean were classified as SGA. Of the 826 mothers analyzed for the effects of ETS on SGA, 243 were smokers and 530 were ETS-exposed. Fifty five babies were small for gestational age (SGA), 11 babies were born prematurely, and 26 babies had BW below 2,500 g. Among non-smokers there were 240 without and 323 with exposure to ETS. There were 243 maternal smokers, 32 of whom were unexposed to ETS. Active smokers were included in the analysis of the effect of ETS exposure on fetal growth. The adjusted OR (maternal age, height and weight, nationality, and maternal education) for SGA babies delivered by a non-smoker exposed to ETS was 3.9 (95% CI 1.4-10.7). The authors also

found an increase in the risk of a smoker delivering a SGA baby if she was ETS-exposed (OR 6.0, 95% CI 2.1-17.5).

One of the strengths of this study is the use of ultrasound measurements and population-specific growth curves in estimating SGA. This study did not evaluate the intensity or duration of ETS exposure but did include ETS exposure at work as well as at home. Participants were seen at both public and private clinics suggesting a potentially broad range of socioeconomic status for which there was no adjustment in the analysis, although there was adjustment for maternal education, which is correlated with SES.

Nafstad et al., 1998. This is a Norwegian case control study of 58 SGA babies (BW ≤ 90% of GA-corrected BW), and 105 controls, all born after 28 weeks gestation and excluding malformed babies or babies that required intensive intervention after birth. Data collection and maternal interview occurred within 30 hours after delivery. Maternal smoking status and ETS exposure was determined for each trimester. Nicotine was determined in maternal and neonatal hair samples. The limit of detection was 0.01-μg/g hair, with a 15 mg hair sample. The smoking status of the mothers of SGA babies was: 22 non-smokers with no ETS; 17 non-smokers with ETS; 10 smokers of <10 CPD; and 9 smokers of >10 CPD. The smoking status of the mothers of controls was: 48 non-smokers with no ETS exposure; 37 non-smokers with ETS; 16 smokers of <10 CPD; and 6 smokers of ≥10 CPD. Nicotine was detected in all maternal hair samples and the levels in smokers were 7-9-fold higher than in non-smokers. Four of 68 non-smokers without ETS and 5 of 54 non-smokers with ETS had nicotine hair levels above the 25th percentile for smokers. Otherwise, over half of the maternal nicotine levels in non-smokers with and without ETS had levels below the lowest level detected in active smokers. ETS-exposed non-smokers had a slight but non-significant increase in median nicotine hair levels. Neonatal hair samples did not show a similar trend between smokers and non-smokers exposed or unexposed to ETS. Maternal and neonatal hair nicotine levels did not correlate ($r = -0.03$, $p = 0.78$).

Based on maternal report, the OR for an SGA baby for non-smokers exposed to ETS was 1.0 (95% CI 0.4-2.1) compared to no ETS. For calculations of risk based on nicotine levels, hair nicotine of <0.75 μg/g was the referent. For non-smokers with nicotine levels between 0.75 and 4 μg/g, the OR for SGA was 3.4 (95% CI 1.3-8.6). Among non-smokers with nicotine hair levels above 4 μg/g, the OR for an SGA baby was 2.1 (95% CI 0.4-10.1). However, this estimate was based on only three SGA babies. Based on self-report, the OR for an SGA baby was not elevated, but when non-smokers were stratified by maternal nicotine hair levels, there was a significant increase in the OR if the hair level was above 0.75 μg/g. Either non-smokers had more ETS exposure than they realized or they were light or occasional active smokers, or both.

A strength of this study is the objective measure of ETS exposure through hair nicotine analysis. This approach worked well for maternal hair, but insufficient hair was available for the analysis from some neonates (43% of cases, 37% of controls). This problem was exacerbated by the small size of the study and may have contributed to the lack of correlation between maternal and neonatal hair nicotine levels. Nevertheless, measured as hair nicotine, ETS exposure was associated with an increased risk of SGA babies.

Ahluwalia et al., 1997. This is a study of ETS and BW data for 17,412 singleton births of low-income women reported to the CDC and Prevention Pregnancy Nutrition Surveillance System for the States of Arizona and North Dakota from 1989 to 1994. Home ETS exposure was self-reported as a yes/no response. Active cigarette smoking was defined as a yes/no response to having smoked any number of cigarettes asked at their initial prenatal care visit. Among the 17,412 mother/infant pairs, 3,817 were smokers of whom 67% were also exposed to ETS. Among the 13,497 non-smokers, 21.2% were exposed to ETS. The data were also stratified by maternal age. Among non-smokers less than 30 years of age, there was no difference in their babies' BWs between ETS exposed and ETS unexposed. However, after the age of 30, mean BW was 90 g lower in the offspring of non-smokers exposed to ETS (95% CI -0.8-181) compared to non-exposed nonsmokers. Among offspring of smokers, BWs were lower for those exposed to ETS with the greatest effect among smokers over 30 years of age.

Maternal non-smokers under the age of 30 did not have a significant increase in risk of LBW, SGA or PTD associated with ETS exposure. However, offspring of non-smokers over the age of 30 did have a significant increase in the risk of LBW and PTD after controlling for ethnicity, education, marital status, parity, geographic location, altitude, alcohol use, weight gain and pre-pregnancy BMI. For non-smokers over 30 years of age who were exposed to ETS, the OR for LBW was 2.42 (95% CI 1.51-3.87), and for PTD the OR was 1.88 (95% CI 1.2-2.88). For maternal smokers, ETS exposure was not associated with an additional increase in the OR for LBW, SGA, and PTD. However, there was an increase in the adjusted OR for LBW (OR = 1.39, 95% CI 1.0-1.93) if the mother was under 30 years of age, smoked and was exposed to ETS. .

The study population included only low-income women. The relationship between ETS exposure and these outcomes may differ by socioeconomic status. Also the intensity and duration of ETS exposure was not recorded and may have differed between the age groups possibly contributing to the apparent differential effects with age.

Wang et al., 1997. This is a prospective Boston study of gene-environment interactions in maternal smokers. The cohort included 740 pregnant women enrolled prior to 20 weeks GA of which 410 were non-smokers with no ETS and 73 with ETS. Maternal smokers numbered 257. Urine and plasma samples were obtained at each post-natal care visit and analyzed for cotinine. Urine cotinine was corrected for creatinine. Parental smoking status and ETS exposure were obtained by interview. Mean urine cotinine level for non-smokers with no ETS was 20 ng corrected for creatinine (95% CI 18.4-21.6), while for those with ETS it was 41 ng (95% CI 35-47) ($p<0.001$). The urine cotinine levels for the active smokers were generally above 1000 ng. At birth, the umbilical cord cotinine level correlated with both maternal serum cotinine ($r = 0.91$, $p<0.001$) and maternal urine cotinine ($r = 0.72$, $p<0.001$). Compared to non-smokers, babies of mothers who smoked daily had a mean BW that was 257 g lower, were 1.2 cm shorter, and had a 0.5 cm decrease in head circumference. For mothers who intermittently smoked, there was a mean decrease in their newborns' BW of 56 g, but the BW and head circumference were similar to babies of non-smokers. After adjustment, each 1000 ng increase in urine cotinine concentration was associated with a 59 ± 9 g decrease in BW ($p < 0.01$), 0.25 ± 0.05 cm decrease in birth length ($p < 0.01$), and a 0.12 ± 0.03 cm decrease in head circumference ($p < 0.01$). The authors stated that there was a small but detectable negative effect on BW, birth length, and head circumference when the maternal urinary cotinine level was 31-100 ng cotinine/mg creatinine in

comparison to those with urine levels below 31 ng. "These results were suggestive" that ETS exposure of non-smokers affects fetal growth.

There are other concerns with this study. The participation rate was on the low side (75%) and no comparison with the women who did not participate was given, nor were the reasons for their exclusion. The authors' selection of urine cotinine levels of <31 ng/ml for the reference group is problematic since this level may include active smokers. In addition, the limit of detection of 3 ng/ml may be too high to discriminate truly non-exposed from exposed individuals. This study is not included in the tables.

Horta et al., 1997. This is a retrospective Brazilian study of 5,166 live singleton babies without malformations. Mothers were interviewed during the birthing hospitalization regarding their smoking habits and if their partner was a smoker. Among the mothers, 65.2% were non-smokers and 57% of their partners were non-smokers. No quantification of ETS exposure was done, nor were the sizes of the various cohorts given (non-smokers with and without ETS, smokers with and without ETS). Odds ratios were adjusted for social class, prior LBW, maternal height, maternal pre-pregnancy weight and prenatal care. Few BW data were reported. In the analysis of the effects of paternal smoking, the ORs were adjusted for maternal smoking. Babies born to mothers whose partner smoked had a 30 g decrease in BW ($p<0.05$). The adjusted OR for LBW if the partner smoked was 1.18 (95% CI 0.94-1.48). The adjusted OR for PTD if the partner smoked was 1.25 (95% CI 0.99-1.57); this was greater than the adjusted OR if the mother was a smoker during the whole pregnancy (OR 1.02, 95% CI 0.80-1.29). The adjusted OR for IUGR if the father was a smoker was 1.33 (95% CI 1.05-1.68). A strength of this study was the large number of live births. However, there was no quantification of ETS exposure as the only history elicited was maternal and paternal smoking status.

Lodrup Carlsen et al., 1997. This Norwegian study examined lung function in newborns and the association between maternal smoking, both active and passive, with newborn tidal flow-volume ratio and compliance of the respiratory system. A cohort of 3,754 newborns was established in Oslo, Norway, to prospectively study asthma. This study reported data for 803 healthy neonates with BWs >2,000 g, who underwent pulmonary function testing. ETS exposure in the mother did not appear to have an effect upon the pulmonary functions studies in the newborn. Birth weight data were also collected between January 1992 and March 1993. Questionnaire data were used to determine smoking status. The mother was classified as exposed to ETS based on the presence of daily smoking by a family member. The mean BW of 483 newborns of non-smokers with no ETS exposure was 3.6 kg (SD 0.49 kg). For mothers with ETS exposure, the mean BW was 3.5 kg (SD 0.46 kg); this was a significant difference from unexposed ($p=0.04$). For active smokers, the mean BW of their babies was 3.4 kg (SD 0.49 kg), also different from unexposed ($p <0.001$). The focus of this study was not BW, and BW data were not adjusted for covariates and confounders such as GA. Thus it is not known whether the changes in BW associated with ETS exposure would remain following adjustment.

Jedrychowski and Flak, 1996. This is a Polish retrospective study of ETS and BW of 1,165 school age children, half recruited from a polluted area of Krakow and half recruited from a clean area of Krakow. Data were available for 1,115. The mothers were interviewed for active and passive smoking during the pregnancy of the child in the study. Birth weight, GA at birth,

and other perinatal characteristics were also obtained from the mother. During the pregnancy of interest, there were 452 non-smokers without, and 512 with exposure to ETS. Among smokers, 23 had no ETS and 135 were exposed. The crude mean decrease in BW for babies of non-smokers exposed to ETS was 73 g. After adjusting for GA as reported by the mother, the effect of ETS exposure upon the BW of babies born to non-smokers was a decrease of 57.9 g (SE 31; p=0.004; 95% CI not reported). The OR of delivering an LBW baby for non-smokers with ETS was 1.46 (95% CI 0.83-2.6).

Data were presented for a validation study of the sensitivity and specificity of plasma cotinine to identify active smokers in 158 pregnant women. A plasma cotinine level of 25 ng/ml was used to separate smokers and non-smokers. This is a high plasma cotinine threshold, most likely allowing inclusion of active smokers. Nevertheless, based on the 25 ng/ml criterion, the authors found a significant misclassification (false negative) rate of 57%, reflecting women with plasma cotinine >25 ng/ml who claimed to be never or ex-smokers. Among the 142 women claiming to be never or ex-smokers, 5.6% had plasma cotinine above 25 ng/ml. Adjustment of the ORs for misclassification would lower the risk estimates.

3.2.2. Animal Studies of ETS and BW, IUGR

Animal studies reporting the effects of maternal ETS exposure during pregnancy on fetal and BWs are limited in number. In a study by Ji *et al.* (1998), pregnant rats were exposed to aged and diluted sidestream smoke for 6 hr/d, 7 d/wk starting on gestation day 5. While smoke exposure was seen to alter specific protein expression in fetal lung, the weights of fetuses collected at gestational days 14, 18 and 21 were not significantly different between exposed and control animals. In contrast to these results, Nelson *et al. (*1999b) found that BWs in rats were decreased by 41% compared to unexposed controls following exposure of the pregnant dam to sidestream smoke from one cigarette per day for one week if the exposure occurred during the first week of pregnancy. The same exposure starting in the third week of pregnancy resulted in a 73% reduction in BW. A significant dose-dependent decrease in intrauterine growth and BW with smoke exposure was observed after exposure to 0-3 cigarettes per day ($p < 0.001$). The reasons for the discrepancy between these studies in BW data are not clear but are likely related, in part, to different exposure conditions. The exposure conditions are not well characterized in the study by Nelson *et al.* thus limiting comparison with the study by Ji *et al.*

3.2.3. Discussion of Fetal Growth

In this update, 18 studies were reviewed that investigate the relationship between maternal ETS exposure and fetal growth as measured by BW or the incidence of an adverse fetal growth outcome (LBW, SGA or PTD). These studies represent several geographically separated areas (North America, South America, Europe and Asia). Most studies done in the past decade controlled for confounders known to be associated with decreased fetal growth.

3.2.3.1. Birth Weight Data

There are numerous studies from the previous and current reviews that provide strong evidence for an association between ETS exposure and decrements in BW. The following conclusion appeared in the prevous review.

There appears to be sufficient evidence that ETS is associated with a decrement in birthweight (and fetal retardation), based on all sources of data with primary emphasis on the high quality epidemiological 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.

Those studies combined with the more recent ones indicate ETS exposure is associated with a decrease in BW (in the non-smoking mother) in the range of 10-100 g. This includes evidence of a dose-response down to very low levels of exposure (Kharrazi *et al.*, 2004). Studies from both the previous and current documents that reported BW data with statistics are shown in Figure 3.1 in chronological order.

Table 3.4 ETS and BW; Studies that Included Maternal Smokers

Reference	Total	MNS[1] no ETS	MNS[1] w/ ETS	Change in BW (g) (95% CI)	Confounder, Covariate Adjustments[2]
Dejmek *et al.*, 2002	6866	3,188	1,049	-41 g (-5- -77)[3]	Sex, Eth, Par, Alc, SES, MWt, MHt, Oth
Kukla *et al.*, 2001	4530	2987	1,178	ETS < 15 CPD –4g; n.s. ETS > 15 CPD –49g; p<0.063	None reported
Hruba & Kachlik 2000	1097	755	292	-64 g; no statistics given	GA
Luciano *et al.*, 1998	112	50	39	-254 g ; p < 0.013	None reported
Ahluwalia *et al.*, 1997	17412	10639	2,855	<30 yo +8.8 g (-26-+44) >30 yo -90.0 g (-181-+1)	Eth, Par, Alc, MWt, Oth
Horta *et al.*, 1997	5166			-30g; p<0.053	GA, MA, Eth, Par, SES, MWt, MHt, Oth
Lodrup Carlsen *et al.*, 1997	803	483	96	–100g; p=0.043	None reported
Wang *et al.*, 1997	740	403	80	data suggestive of ETS effect on BW	GA, Eth, Par, Alc, MWt, MHt, Oth
Jedrychowski & Flak 1996	1115	246	532	ETS=10 CPD, -57.9g p = 0.004	GA, Sex, Par, Oth

[1] MNS: maternal non-smoker (Blank – number not given); [2] Alc: alcohol use; Eth: ethnicity; GA: gestational age; MHt: maternal height; MWt: maternal weight; MA: maternal age; Oth: other; Par: parity; SES: socioeconomic status; Sex: sex of newborn.
[3] Statistically significant change.

Table 3.4 summarizes the eight studies that reported BW data for nonsmokers with ETS exposure, as well as for maternal active smokers. A decrease in BW was associated with ETS exposure in all eight studies although one (Ahluwalia *et al.*, 1997) reported a non-significant increase in BW for infants of mothers under 30 years of age. The BW decrements ranged from 4 to 100 g, and the results were statistically significant in three studies. Five studies (Jedrychowski and Flak, 1996; Horta *et al.*, 1997; Wang *et al.*, 1997; Hruba *et al.*, 2000; Kharrazi *et al*., 2004) considered GA in their analyses. For the studies that controlled for GA, the BW decrements

were 30 to 111 g. Other studies had larger decreases in BW, some of which were similar to those reported for active smokers. However, the lack of control for GA in some studies undermines the reliability of the magnitude of BW decrements reported by these studies.

Studies that excluded maternal smoking from their analysis of the association between BW and ETS exposure are summarized in Table 3.5. Six of the eight studies took GA into account. One study (Windham *et al.*, 2000) found an increase in BW of 8 g otherwise all studies found a decrease or no difference in BW. Of these, one study reported a statistically significant decrement in BW. This study by Kharrazi *et al.* (2004) was prospective and used cotinine to quantitate exposure to ETS. The reference cohort had plasma cotinine levels below 0.01 ng/ml. There were three cohorts above 0.01 ng/ml cotinine. The smallest cohort had the highest levels (1-10 ng/ml) and may have included light active smokers, but the levels of the other two cohorts (0.01-0.1 ng/ml and 0.1-1 ng/ml) are consistent with ETS exposure. There was a 20 to 40 g decrease in BW associated with maternal plasma cotinine levels between 0.01 and 1 ng/ml. This is similar to the difference in BW reported by Haddow *et al.* (1988) between those with plasma cotinine levels in the lowest group (<0.5 ng/ml) compared with those with cotinine levels between 1.1 and 9.9 ng/ml. Both Haddow and Kharrazi had similar magnitudes in the BW decrements between those with the lowest cotinine levels and those with the highest (104 g and 111 g, respectively). The study by Martinez *et al.* (1994) found a similar magnitude of BW decrement (34 g) associated with paternal smoking when compared to the Kharrazi study.

Included in the studies summarized above are two meta-analyses addressing the effects of ETS on BW. The pooled estimates of decrements in BW were statistically significant and similar between the studies: -24.0 g (95% CI -39.3--8.6) (Windham *et al.*, 1999a) and -31 g (95% CI -44--19) (Peacock *et al.*, 1998).

Table 3.5 ETS and BW; Studies that Excluded Maternal Active Smokers

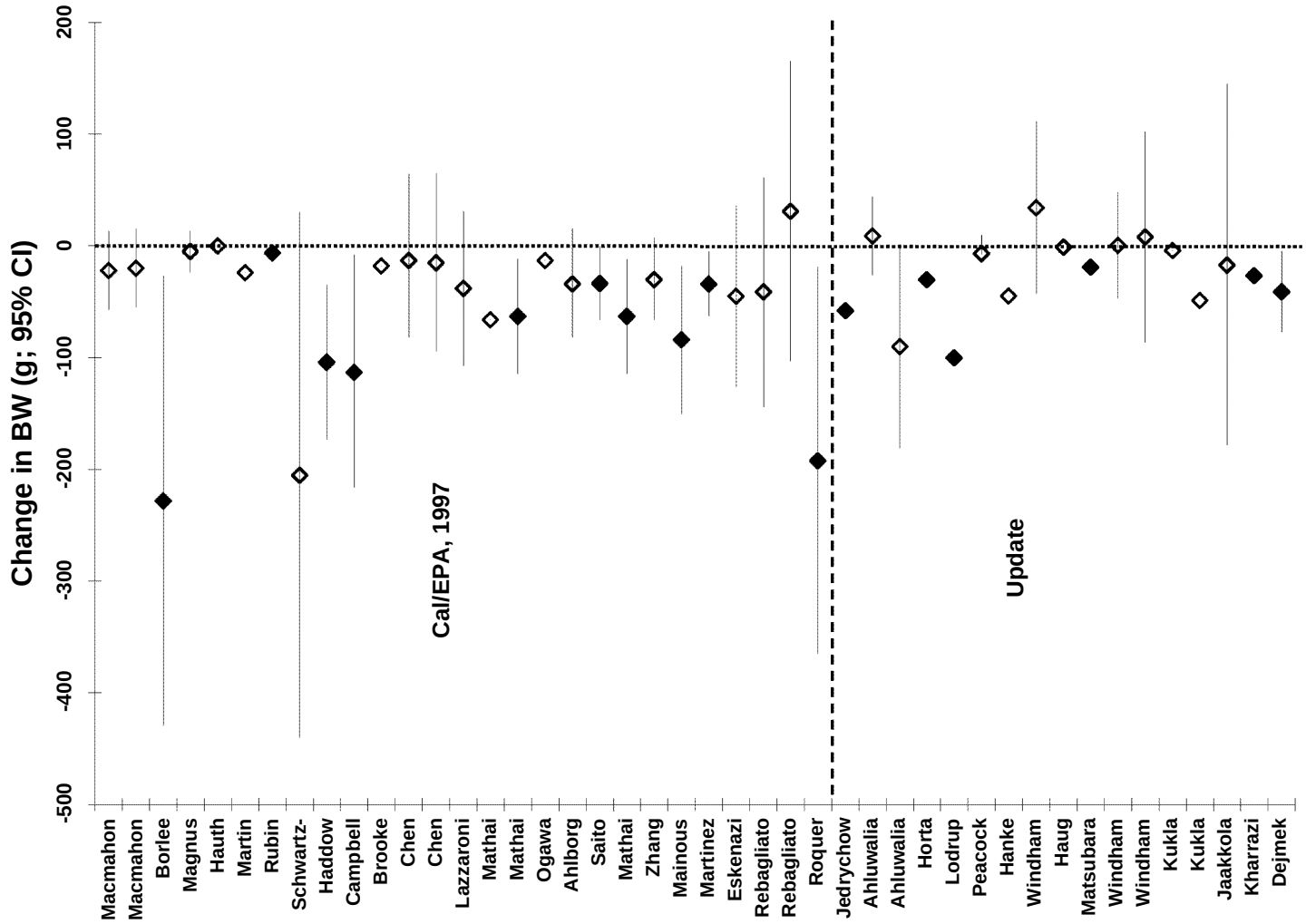
Reference	Total N	MNS[1] no ETS	MNS w/ETS	Change in BW (95% CI)	Confounder, Covariate Adjustments[2]
Kharrazi *et al.*, 2004	2796	951	1845	-20 to -111 grams; p = 0.04	GA, Sex, Eth, SES, Other
Jaakkola *et al.*, 2001	477	288	233	-17 g (-178- +145)	Sex, MA, MWt, SES, Alc, Other
Haug *et al.*, 2000	22883			-1 g; n.s.	
Matsubara *et al.*, 2000	8624	2693	3586	-11 g between ETS and no ETS; -22g between high ETS and no ETS, but both n.s.	GA, Sex, Par, Alc, MWt, MHt, MA
Windham *et al.*, 2000	4099	2887	759	low ETS +0.68 g (-47-+48) high ETS +8.2 g (-86-+102)	GA, MA, Eth, Par, Alc, SES, MWt, MHt
Hanke *et al.*, 1999	1751	924	827	n.s.	GA, MHt, Oth
Windham *et al.*, 1999a	992			+34 g (-43-+111)	GA, Eth, Alc, MA, Par, SES, Other
Peacock *et al.*, 1998	703	420	283	-6.7 g (-8.4- +9.7)	GA, Sex, Par, MHt

[1] MNS: maternal non-smoker; [2] Abbreviations: Alc: alcohol use; Eth: ethnicity; GA: gestational age; MHt: maternal height; MWt: maternal weight; MA: maternal age; Par: parity; SES: socioeconomic status; Sex: sex of the newborn.

In this update, there is a consistent finding of a decrease in BW associated with maternal ETS exposure that was substantiated in one of two animal studies. These findings are in the same range as that reported in the previous document (25-50 g) and lend further support for the previous suggestion of a causal association. Most of these studies considered pertinent confounders, as well as GA, in their analysis. One study was able to validate the ETS exposure and BW decrements with maternal plasma cotinine levels below 1 ng/ml. This magnitude of BW deficit may not seem clinically significant, but this is a mean deficit. As with fetuses of smokers (Wang *et al.*, 2002), some fetuses of maternal non-smokers with ETS exposure may be at greater risk than others based on genetic make up. Future studies may be able to elucidate this.

Figure 3.1 The Effects of ETS on Birth Weight.

The mean change in BW with maternal ETS exposure from studies reported in the previous document (Cal/EPA, 1997) and those included in this update. Statistically significant values are represented by solid diamonds; statistically non-significant values by open diamonds.



3.2.3.2. Adverse Fetal Growth Outcomes

There are 25 studies that investigated the association between maternal ETS exposure and an adverse fetal growth outcome (LBW, SGA, IUGR and PTD), ten of which were published since the previous document. Table 3.A (Appendix) presents data from all of the studies that reported outcomes for LBW, SGA, IUGR, and PTD. Pre-term delivered newborns are not necessarily fetal growth retarded, but PTD is included here because many pre-term delivered babies have a BW below 2500 g, the definition of LBW. Additionally, PTD, LBW, IUGR, and SGA are commonly studied together. Of the ten new studies, five excluded active smokers and three analyzed non-smokers exposed to ETS as a separate stratum. Six studies found an increased risk of an adverse fetal growth outcome while three found no increased risk (OR or RR is $\leq$1.0), or only reported the results as non-significant.

3.2.3.3. Low Birth Weight

In the previous document it was suggested that the studies supported a slight increase in risk for LBW in association with ETS. However, due to wide confidence intervals, the results were also consistent with no effect. The more recent studies provide evidence that strengthens this association. Included in this update are seven studies reporting LBW data. Six found an increased risk of LBW associated with ETS exposure with ORs ranging from 1.18 to 3.8 (Table 3.7), two of which were statistically significant. The study by Ahluwalia *et al.* (1997) is a large prospective study. ETS exposure was not associated with an increased risk for LBW among maternal non-smokers under the age of 30 years, but it did increase the risk of LBW if the mother was 30 years or older. This is consistent with studies of smokers that have found that the more years a woman has smoked, the greater the BW deficit. It is postulated that this is due to the accumulation of toxic heavy metals over the years of smoking (Kuhnert *et al.*, 1988). Cigarette smoke contains lead and cadmium and their elimination half-lives are measured in years. Smoking is the major determinant of plasma cadmium levels even among those residing adjacent to cadmium smelters (Lagerkvist *et al.,* 1993). Maternal non-smokers with ETS exposure, over the age of 30, may have been exposed to ETS and accumulating cadmium for years (Dempsey and Benowitz, 2001; Kuhnert *et al.*, 1988).

Table 3.6 ETS and LBW

Reference	Total N	MNS[1] no ETS	MNS[1] w/ETS	LBW OR, RR (95% CI)	Confounder, Covariate Adjustments[2]
Kharrazi *et al.*, 2004	2796	951	1845	Adverse Outcome 1.36 (1.06-1.72)[3] LBW: 1.42 (0.91-2.21)	Sex, Eth, SES, Oth, ExAS
Goel *et al.*, 2004	576	435	141	1.03 (0.65-1.65)	BO, Ed, MA, Occ, Par
Dejmek *et al.*, 2002	6866	3710	1797	1.51 (1.02-2.26)[3]	Sex, Eth, Par, Alc, SES, MWt, MHt, Oth
Jaakkola *et al.*, 2001	477	288	233	1.51 (1.02-2.26)	ExAS Sex, MA, MWt, Alc, Oth
Windham *et al.*, 2000	4099	2887	759	1.8 (0.82-4.1) high ETS 3.8 (1.5-9.8) " , non-caucasian	GA, MA, Eth, Par, Alc, SES, MWt, MHt, ExAS
Ahuwalia *et al.*, 1997	17412	10639	2855	0.97 (0.76-1.23) < 30yo 2.4 (1.5-3.9) ≥ 30yo[3]	Eth, Par, Alc, MWt, Oth
Horta *et al.*, 1997	5166			1.18 (0.94-1.48)	GA, MA, Eth, Par, SES, MWt, MHt, Oth
Jedrychowski & Flak 1996	1115	452	512	1.46 (0.83-2.6)	GA, Sex, Par

[1] MNS: maternal non-smoker (Blank – number not given); [2] Abbreviations. Alc: alcohol use; BO: birth order; Eth: ethnicity; ExAS: excludes active smokers; GA: gestational age; MA: maternal age: MHt: maternal height; MWt: maternal weight; Oth: other; Occ: occupation; Par: parity; SES: socioeconomic status; Sex: sex of newborn. [3] Statistically significant change.

The study by Dejmek *et al.* (2002) is a well-designed study. Smoking histories and ETS exposures were obtained during hospitalization for the birth and numerous covariates and confounders were included in the ETS model. The adjusted OR for LBW associated with ETS exposure among maternal non-smokers was 1.51 (95% CI 1.02-2.26). This is very similar to the risks reported by other studies given in Table 3.6. The OR for LBW associated with heavy smoking was 2.31 (95% CI 1.34-4.08).

The prospective study by Windham *et al.* (2000) limited their assessment of ETS effects to maternal non-smokers and stratified their data by ethnicity. They found a significant increase in the adjusted OR for LBW among non-Caucasian women. This is consistent with studies of maternal smokers that have found higher ORs for LBW, SGA and PTD among African-American smokers compared to Caucasians.

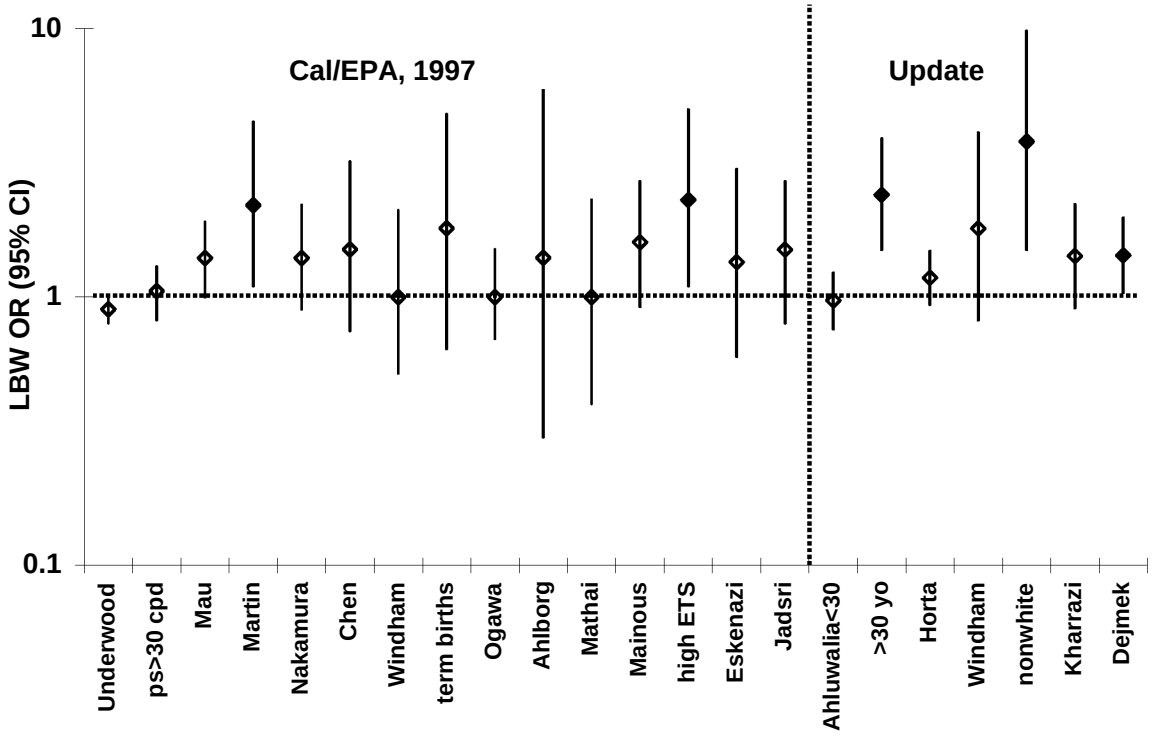
The study by Kharrazi *et al.* (2004) is also a prospective study limited to maternal non-smokers that showed an increased risk of an adverse pregnancy outcome (LBW, SGA or PTD) associated with ETS exposure. They did not find a statistically significant increase in LBW but their OR of 1.42 is similar to the larger study by Dejmek *et al.* (2002). The Kharrazi study is important because the ETS exposure was defined by maternal cotinine levels. Their assay method is state of the art and the lower limit of detection is well below all other published studies. The levels of cotinine for two of the three ETS exposure groups and the reference group were below 1 ng cotinine/ml plasma. It is unlikely that active smokers were among those whose levels are below 1 ng/ml.

Since the previous monograph there have been three studies that found a statistically significantly elevated risk of delivering an LBW baby associated with ETS exposure among women who were non-smokers during their pregnancies. These data indicate that ETS exposure is associated with an increased risk of delivering a LBW baby.

According to the California Dept Health Services (CDHS, 2000a), for 2000 there were 32,853 births in California classified as LBW. According to Gilpin *et al*. (2001), the level of ETS exposure among nonsmoking females during the two weeks prior to the survey in 1999 was 13.2%. Windham *et al* (1999a) estimated an OR for LBW of 1.38. The attributable fraction (a) is a = 0.132(1.38-1)/(0.132(1.38-1)+1 = 0.048. Thus in 2000, there were 1,577 (0.048 x 32,853) excess LBW newborns in California attributable to ETS exposure.

For the US, the National Vital Statistics Report (CDC 2002b) reported 4,025,933 live births in 2001 with a rate of LBW of 7.7%. There were 309,997 (4,025,933 x 0.077) LBW births in 2001. Adult females reporting ETS exposure in NHANES-III for 1995 was 22.7% (Pirkle *et al*., 1996). A = 0.227(1.38-1)/(0.227(1.38-1)+1) = 0.079. Thus: 0.079 x 309,997 = 24,500 excess ETS-attributable LBW newborns in the US in 2000. Since the categories of LBW and preterm delivery are not exclusive of each other the associated attributable risks are not additive.

Figure 3.2 ETS and Risk of Low Birth Weight



3.2.3.4. SGA, SFD and IUGR

Fetal growth retardation (SGA, SFD, IUGR) is intrinsically difficult to study compared to LBW, which is an easy outcome to document, or PTD, which is a relatively easy outcome to determine. An accurate measure of GA is required for SGA, SFD and IUGR because these measures are gestationally dependent. Late entry into prenatal care or poor prenatal care, which are associated with SGA, SFD and IUGR make it difficult to accurately estimate GA. Fetal or pregnancy conditions that result in PTD are often associated with poor fetal growth.

With respect to studies of ETS and IUGR, the previous document suggested that taken together "*they support a slight increase in* [risk of] *LBW or IUGR in association with ETS exposure.*" This association has been strengthened in this update. Eight studies have reported data regarding the adverse fetal growth outcomes of SGA, SFD, and IUGR. One study found a reduced risk of adverse growth outcome, four studies found no increase in the risk, while three studies found a statistically significant increased risk. The increased risks ranged from 1.08 to 3.9 (Table 3.7). Of the studies finding statistically significant increases in risk of SGA, SFD or IUGR associated with maternal ETS exposure, one is Brazilian (Horta *et al.*, 1997), one is Swedish (Dejin-Karlsson *et al.*, 1998), and the third Indian (Goel *et al*., 2004).

Table 3.7 ETS and SGA, SFD, IUGR

Reference	Total N	MNS[1] no ETS	MNS[1] /ETS	IUGR, SGA, SFD OR, RR (95% CI)	Confounder, Covariate Adjustments[2]
Goel *et al.*, 2004	576	435	141	SGA 2.10 (1.27-3.48)	BO, Ed, MA, Occ, Par
Dejmek *et al.*, 2002	6866	3710	1797	IUGR 1.08 (0.82-1.43)	Sex, Eth, Par, Alc, SES, MWt, MHt, Oth
Matsubara *et al.*, 2000	7411			IUGR 0.95 (0.72-1.26)	Sex, MA, Par, Ed, Alc, MHt, MWt,
Windham *et al.*, 1999a	992			SGA 1.4 (0.79-2.5)	GA, Eth, Alc, Oth, ExAS
Dejin-Karlsson *et al.*, 1998	854	247	345	SGA 3.9 (1.4-10.7)[3]	GA, MA, Eth, Par, Alc, Drg, SES, MWt, MHt, Oth
Nafstad *et al.*, 1998	163	68	54	SGA 1.0 (0.4-2.1)	GA, Sex, MWt, MHt, Oth
Ahluwalia *et al.*, 1997	17412	10639	2855	SGA 0.97 (0.8-1.3) <30yo 1.3 (0.8-2.2) ≥30yo	Eth, Par, Alc, MWt, Oth
Horta *et al.*, 1997	5166			IUGR 1.33 (1.05-1.68)[3]	GA, MA, Eth, Par, SES, MWt, MHt, Oth

[1] MNS: maternal non-smoker (Blank – number not given); [2] Abbreviations. Alc: alcohol use; BO: birth order, Ed: maternal education; Eth: ethnicity; ExAS: excludes active smokers; GA: gestational age; MA: maternal age; MHt: maternal height; MWt: maternal weight; Occ: occupation, Oth: other; Par: parity; SES: socioeconomic status; Sex: sex of newborn. [3] Statistically significant change.

The study by Horta *et al.* (1997) carefully investigated IUGR, LBW, and GA. This study comprised 80% of all births in one town for one year. Smoking histories were taken by study personnel during the postpartum hospital stay and newborns were prospectively examined for

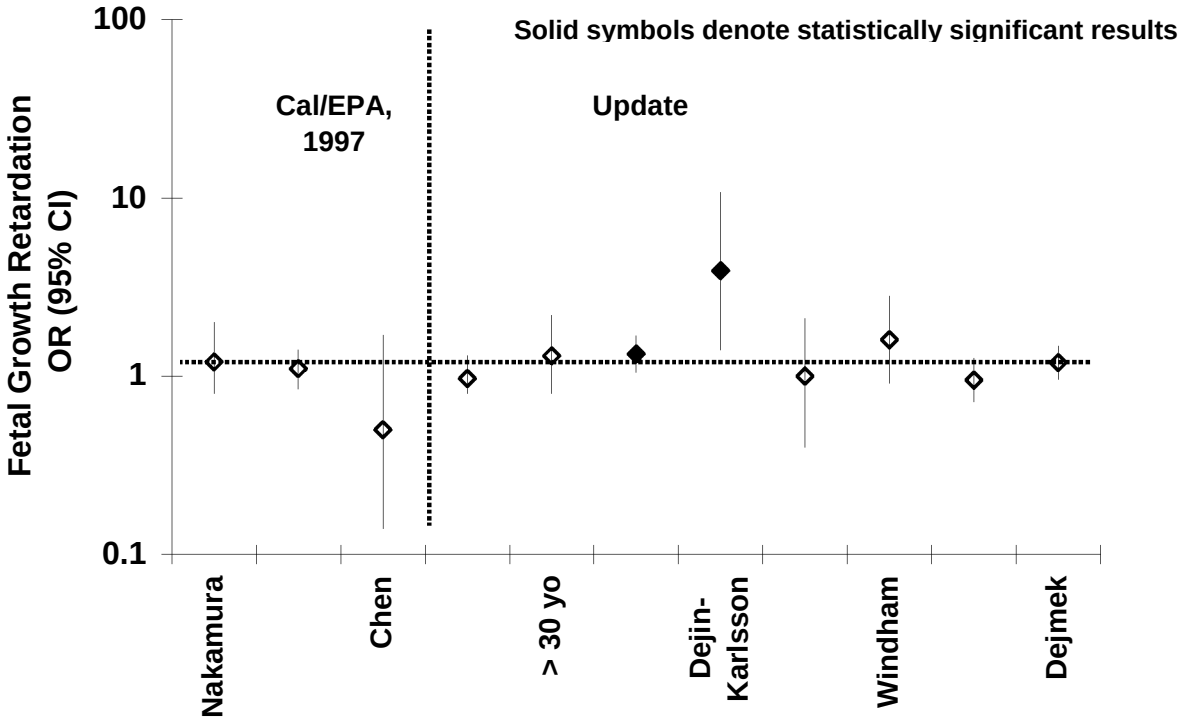
GA by trained study personnel using the Dubowitz method (the most widely used examination instrument to determine GA of newborns). Babies were assigned to four categories based on BW and GA: BW $\leq$ 2500 g and GA <37 weeks; BW $\geq$ 2500 g and GA $\geq$ 37 weeks; BW $\geq$ 2500 g and GA < 37 weeks; and BW $\leq$ 2500 g and GA > 37 weeks. Newborns were also evaluated for growth retardation. This was a thorough postpartum evaluation of growth, and the study controlled for most of the relevant confounders or covariates. They found an adjusted OR for SGA of 2.0 (95% CI 1.5-2.69) for light active smokers (1-5 CPD). It was 2.48 (95% CI 1.68-3.68) for heavy active smokers ($\geq$ 20 CPD) and, after controlling for maternal smoking, the OR for SGA associated with paternal smoking was 1.33 (95% CI 1.05-1.68).

The Swedish study by Dejin-Karlsson *et al.* (1998) also reported a significant increase in risk for SGA associated with ETS exposure (adjusted OR 3.9; 95% CI 1.4-10.7), while that for smokers was 6.0 (95% CI 2.1-17.5). Although this OR is about double that reported by other studies, this is a very well designed prospective study that controlled for most of the relevant covariates and confounders. The study population was 87.7% of all nulliparous mothers who delivered in one town during one-year interval. Gestational age was confirmed by sonographic exam at 20 weeks gestation. Growth curves were based on Swedish and Danish ultrasonographic data.

Both of these are thorough studies in which fetal growth was the primary outcome of interest. In one study, all newborns had a Dubowitz exam by a trained examiner to determine GA and fetal growth retardation. In the other study, GA was confirmed using sonography, and newborns that weighed 2.5 standard deviations below the age-related means were classified as SGA. These studies strongly indicate that there is an increased risk to fetal growth retardation associated with maternal ETS exposure.

Evidence for significant fetal growth restriction was also observed by Nelson *et al.* (1999b) in rats after exposure to sidestream smoke from 1, 2 or 3 cigarettes per day.

Figure 3.3 ETS and Risk of Fetal Growth Retardation (IUGR, SGA)



3.2.3.5. Pre-Term Delivery (PTD)

On the basis of five studies reporting data on PTD, two prospective, two retrospective, and one of uncertain type, the previous document concluded that there was little evidence of an association between ETS and PTD. In this update, there are seven new studies that reported data regarding PTD (Table 3.8). In contrast to the previous document, these studies all reported an increased risk of PTD associated with ETS exposure for at least some strata of the data with OR or RR ranging from 1.29 to 6.12, six of which were statistically significant.

Table 3.8 ETS and PTD

Reference	Total	MNS[1] no ETS	MNS[1] w /ETS	PTD OR, RR (95% CI)	Confounder, Covariate Adjustments[2]
Kharrazi *et al.*, 2004	2796	951	1845	Adverse Outcome 1.36 (1.06-1.72)[3] PTD: 1.78 (1.01- 3.13)	Sex, Eth, SES, Oth, ExAS
Goel *et al.*, 2004	576	435	141	1.15 (0.69-1.92)	MA, Ed, Occ, BO, Par
Jaakkola *et al.*, 2001	389			1.30 (0.30- 5.58) maternal hair nicotine < 4.0 μg/g; 6.12 (1.31-28.7) maternal hair nicotine ≥ 4.0 μg/g	Sex, MA, MWt, SES, Alc, Oth
Windham *et al.*, 2000	4099	2887	759	1.6 (0.87-2.9) high ETS 2.4 (1.0-5.3) "very preterm, Ethnicity not Caucasian" 2.4 (1.1- 5.5) high ETS[3] 3.8 (1.3-10.7) "very preterm"[3] 2.8 (1.2-6.6) > 30 yr [3]	BMI, MA, Ed, Eth, Par, Alc, SES, ExAS
Hanke *et al.*, 1999	1751	924	827	1.86 (1.05-3.45) 7 hr ETS/day	MA, MHt, MS, Occ, Par
Ahluwalia *et al.*, 1997	17412	10639	2855	0.9 (0.8-1.1) < 30 yo 1.9 (1.2-2.9) ≥ 30 yo[3]	Eth, Par, Alc, MWt, Oth
Horta *et al.*, 1997	5166			1.25 (0.99-1.57)	MA, Ed, Eth, Par, SES, MHt, Oth

[1]MNS: maternal non-smoker (Blank – number not given); [2]Abbreviations. Alc: alcohol use; BO: birth order; Ed: education; Eth: ethnicity; ExAS: excludes active smokers; MA: maternal age; MHt: maternal height; MS: marital status; MWt: maternal weight; Occ: occupation; Oth: other; Par: parity; SES: socioeconomic status; Sex: sex of newborn. [3] Statistically significant change

One of the prospective studies reporting a significant risk for PTD used a state of the art assay method to determine cotinine levels, and two of the three ETS exposure groups had second trimester maternal plasma cotinine levels below 1 ng/ml (Kharrazi *et al.*, 2004). This study found a significant increase in PTD for the top 20% of ETS-exposed mothers compared to those whose cotinine levels were below the level of detection. An exposure-response was reported with an OR of 1.29 (95% CI 0.97-1.72) for each unit increase in log cotinine levels. Goel *et al.* (2004) reported a non-significantly elevated risk for PTD based on cumulative ETS exposure only in the home.

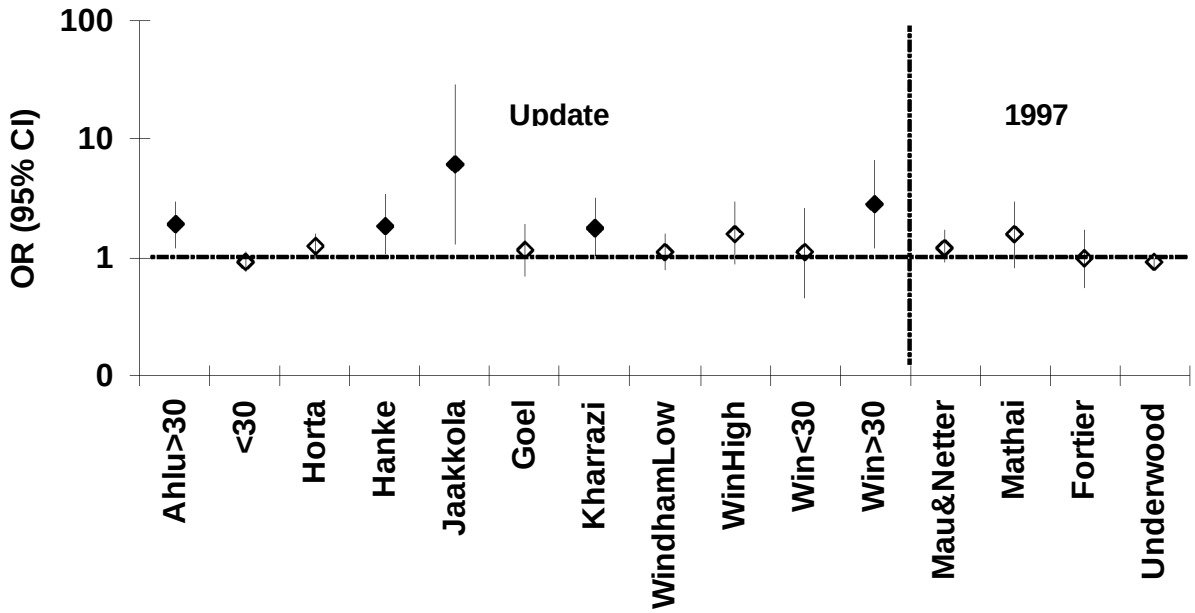
The study by Jaakkola *et al.* (2001) stratified their 389 nonsmoking subjects by maternal hair nicotine level in order to assign ETS exposures as low (<0.75 μg/g hair), medium (0.75 to < 4 μg/g), and high (≥ 4.0 μg/g). The OR for PTD comparing the low with the high exposure group yielded a statistically significant OR of 6.12 (95% CI 1.31-28.7), and there was some evidence of increasing response with increasing exposure as measured by maternal hair nicotine.

The study by Windham *et al.* (2000) stratified subjects by age and found that among all non-smoking women, there was no significant risk of PTD or very PTD with low exposure to ETS, but risk increased with high ETS levels. But among women 30 years and older, there was a significant risk of PTD (adjusted OR 2.8; 95% CI 1.2-6.6) associated with ETS exposure. This increased risk of PTD associated with older women (>30 years) was also previously seen by

Ahluwalia *et al.* (1997) in a very large study (n=17,412) in which the adjusted OR for PTD for women 30 years and older was 1.9 (95% CI 1.2-2.9). Windham *et al.* (2000) stratified subjects by ethnicity and found increased risk of PTD among non-Caucasians with high ETS exposure; the adjusted OR for PTD was 2.4 (95% CI 1.1-5.5) while for very PTD it was 3.8 (95% CI 1.3-10.7).

Hanke *et al.* (1999) found an exposure-dependent increase in PTD risk with daily duration of exposure to ETS with a significant risk at >7 hr/day (OR 1.86 (95% CI 1.05-3.45). While the retrospective study by Horta *et al.* (1997) found an elevated risk, it did not reach statistical significance (adjusted OR 1.25; 95% CI 0.99-1.57). These seven studies taken together provide evidence supportive of a causal association of maternal ETS exposure with PTD.

Figure 3.4 ETS and Risk of Preterm Delivery



OEHHA reviewed 11 studies that reported adjusted estimates of PTD risk associated with ETS exposure during pregnancy. From these studies a summary OR of 1.57 (95% CI 1.35-1.84) was found that indicates a robust association. The review included seven new studies, five of which reported statistically significant risks in one or more strata. The association of PTD with ETS exposure is coherent with the increased risk of PTD reported with active smoking and with exposure to polluted air (Ritz *et al.*, 2000). Evidence of an exposure-response was provided in the studies by Jaakkola *et al*. (2001) and Kharrazi *et al*. (2004) for ETS intensity, and by Hanke *et al*. (1999) for exposure duration. In consideration of the strength and temporality of the association, the consistency of findings in the more recent, better controlled studies, the coherence of the data with the effects of other forms of air pollution, biological plausibility, and the evidence of an exposure-response, OEHHA considers the evidence to be indicative of a causal association between ETS exposure during pregnancy and PTD.

In light of a causal association, the effects of ETS on PTD may be estimated as follows. According to the California Dept Health Services (CDHS 2000) for 2000 there were 52,522 preterm births in California. According to Gilpin *et al*. (2001), the level of ETS exposure among nonsmoking females during the two weeks prior to the survey in 1999 was 13.2%. Using the summary OR of 1.78 for PTD from the one California-specific study (Kharrazi *et al*., 2004), the attributable fraction a = 0.132(1.78-1)/(0.132(1.78-1)+1) = 0.09. Thus in California in 2000, there were 4,700 (0.09 x 52,522) excess cases of PTD attributable to ETS. This is probably a conservative estimate as the proportion of women with serum cotinine levels of 0.257-10 ng/ml was approximately 20% in the study by Kharrazi *et al*. (Kharrazi, pers comm).

For the US, the National Vital Statistics Report (CDC 2002b) reported 4,025,933 live births in 2001 with a rate of PTD of 11.9%. There were 479,086 (4,025,933 x 0.119) PTD births in 2001. Adult females reporting ETS exposure in NHANES-III for 1995 was 22.7% (Pirkle *et al*., 1996). A = 0.227(1.78-1)/(0.227(1.78-1)+1) = 0.15. For the U.S., ETS was responsible for 71,900 (0.15 x 479,086) excess PTD cases in 2001.

3.3. Spontaneous Abortion (SAB) and Perinatal Death

Perinatal death encompasses a wide variety of causes or diagnoses (e.g., abruptio placenta, premature rupture of membranes, severe malformation), which may result from different etiologic factors. Identification of confounders is particularly complex. As prematurity and LBW are risk factors for neonatal death, BW and GA 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. Pregnancy loss also occurs at the much earlier stage immediately post-implantation, when pregnancy is not observable by the usual clinical criteria but successful implantation is detectable by the rise in urinary human chorionic gonadotrophin (HCG). There is a substantial background rate of loss at this stage, even without obvious risk factors or harmful exposures, but the rate of loss may be further increased by factors that adversely impact the health of the mother or embryo.

Table 3.9. ETS Exposure, Early Pregnancy Loss and Spontaneous Abortion

Reference Country	Study description	Smoke exposure measure	Findings and OR (95% CI)	Comments
Kharrazi *et al.*, 2004 US	Prospective study of maternal serum cotinine and birth outcomes. n=2,777	Maternal cotinine Above 0.236 ng/ml	Spontaneous abortion: OR 3.36 (0.81-13.96)	Dose response for increased SAB associated with maternal serum cotinine. ORs adjusted for maternal age, ethnicity, parity, infant gender, gestational age, insurance.
Venners *et al*., 2004 China	Prospective study of ETS and early post-implanation pregnancy loss. n=310	Paternal smoking only (none, moderate <20 cigs/day or heavy, (≥ 20 cigs/day).	OR (early pregnancy loss in wives of heavy smokers) 1.81 (1.00-3.29) p = 0.049)	Study in Chinese women textile workers: first child, all women non-smokers. Early pregnancy loss detected via urinary HCG assay. Dose-response seen. ETS impact reduced later SAB: also had impact on fecundability.
Windham *et al.* 1999b US	Prospective study of ETS and spontaneous abortion. n=4,209	Maternal passive only	Spontaneous abortion OR 1.01 (0.8-1.27)	Study group comprised women in pre-paid plan seeking prenatal care; may not represent general population.
Chatenoud *et al.* 1998 Italy	Case-control study of parental smoking and spontaneous abortion n=354	Maternal exposure Paternal smoking	Spontaneous abortion OR 0.8 (0.7-1.0)	Non-significant effect of paternal smoking on spontaneous abortion but maternal smokers included with non-smokers in analysis of paternal effects.

Kharrazi et al. (2004). This study included 19 fetal deaths examined in detail in section 3.2.1. Elevated death rates were seen at the highest cotinine level (0.50-10 ng/ml) with some evidence of a dose response at lower levels. As cotinine levels rose, fetal deaths occurred at earlier gestational ages resulting in higher cumulative death rates (<0.05 ng/ml 0.6%; 0.05-0.10 ng/ml 0.9%; 0.10-0.50 ng/ml 1.1%; 0.50-10.0 ng/ml 1.8%). The risk of fetal death at a cotinine level above 0.236 ng/ml had an OR of 3.36 (C.I. 0.81-13.96). An increase in risk (OR) for each log unit increase in cotinine was noted to be 1.58 (C.I. 0.78-3.21). Although the ORs for individual exposure groups are not statistically significant for this endpoint, the apparent dose-response is suggestive of a real effect on fetal death.

Venners et al. (2004) describe a study of conception rates and early post-implantantion pregnancy loss in women whose husbands smoked moderately (< 20 cigarettes/day, n = 239) or heavily (≥ 20 cigarettes/day n = 71). The referent group consisted of women whose husbands were non-smokers (n = 216). All the women were non-smokers, did not drink alcohol, were nulliparous at the beginning of the study, and were employed full-time as textile workers in Anhui, China. Urinary human chorionic gonadotrophin was measured daily, using an immunoradiometric assay, to detect conception and early pregnancy losses, and pregnancies were followed to detect clinical spontaneous abortions.

Results are summarized in Table 3.10. For all conceptions in women whose husbands were heavy smokers, there was an elevated crude OR of early pregnancy loss (OR 2.18; 95% CI 1.18-4.02). This ratio was less elevated after adjustment for wife's and husband's ages, education, perceived life stress, and exposures to dust and noise; husband's use of alcohol, previous smoking, and exposure to toxicants, and wife's body mass index and tea drinking (OR 1.81; 95% CI 1.00-3.29), but still just achieved statistical significance (p = 0.049). Additionally, although results in subsets of first, first and second, or first, second and third conception, and for lower

smoke exposure, did not achieve statistical significance as individual values, there was a clear and consistent tendency towards higher pregnancy loss rates in smoke-exposed women, and a distinct dose response with higher rates of loss in more heavily exposed women.

There was also an overall tendency towards lower risk of conception and pregnancy in women with smoking husbands. However, the rate of clinically observable SAB was markedly reduced in women whose husbands smoked heavily. In spite of this the overall rate of pregnancy loss (early loss and clinical SAB) was apparently elevated in smoke-exposed women. The authors suggested that this effect reflected increased sensitivity to early smoke-induced loss for pregnancies that were in danger of later abortion.

This study is consistent with earlier findings of a lack of effect on later (clinically observable) SABs, but suggests instead that there may be an impact of ETS on early post-implantation pregnancy loss. Because the study design used the husbands' smoking behavior as the measure of exposure, it is not possible to determine whether the effect seen is a result of an impact of the husbands' active smoking on sperm (perhaps producing heritable genotoxic damage), or an impact of the women's passive smoking on their ability to establish and maintain pregnancy. Indeed, it is possible that both such effects may be present.

TABLE 3.10. Relative Odds of Early Pregnancy Loss by Husband's Smoking Amount for First, First Two, First Three, and All Conceptions in Anhui, China, 1996–1998 (from Venners *et al*., 2004)

			Crude			Adjusted*		
Cigarettes/day smoked by husband	**No. of women**	**No. of conceptions**	**OR of early pregnancy loss**	**95% confidence interval**	**Two-sided pvalue**	**OR of early pregnancy loss**	**95% confidence interval**	**Two-sided pvalue**
First conception								
Not current smoker	204	204	Referent			Referent		
<20 cigarettes/day	225	225	0.93	0.59-1.49	0.775	0.81	0.49-1.33	0.400
≥20 cigarettes/day	68	68	1.52	0.82-2.81	0.188	1.41	0.73-2.74	0.304
First and second conceptions†								
Not current smoker	204	240	Referent			Referent		
<20 cigarettes/day	225	266	1.10	0.71-1.70	0.674	0.97	0.62-1.52	0.899
≥20 cigarettes/day	68	85	1.78	1.00-3.17	0.052	1.55	0.85-2.81	0.153
First, second, and third conceptions†								
Not current smoker	204	245	Referent			Referent		
<20 cigarettes/day	225	281	1.14	0.75-1.74	0.547	1.00	0.65-1.54	0.990
≥20 cigarettes/day	68	93	2.04	1.14-3.65	0.016	1.73	0.95-3.13	0.073
All conceptions†								
Not current smoker	204	245	Referent			Referent		
<20 cigarettes/day	225	288	1.19	0.77-1.84	0.429	1.04	0.67-1.63	0.854
≥20 cigarettes/day	68	100	2.18	1.18-4.02	0.013	1.81	1.00-3.29	0.049

*Models adjusted for both wife's and husband's ages, education, perceived life stress, and exposures to dust and noise; husband's use of alcohol, previous smoking, and exposure to toxicants; and wife's body mass index and tea drinking.

† Standard errors for both crude and adjusted models estimated to accommodate correlations in pregnancy losses among conceptions from the same woman.

Windham et al., 1999b. This is a prospective study of over 5,000 pregnancies conducted in California. Women in a prepaid health plan who sought prenatal care during the first trimester were phone interviewed within two weeks of their first prenatal care visit, and their smoking habits and ETS exposure were obtained. Birth outcomes were obtained from computerized hospital records and medical charts. There were 499 SABs, 4,613 live births, and 32 stillbirths (outcomes for 198 could not be determined). ETS exposure was ascertained during interview as number of hours per day spent in the presence of smokers, and only examined among women who were non-smokers (n = 4,209) of whom 1,178 were ETS exposed. The adjusted OR for SAB among ETS exposed non-smokers was 1.01 (95% CI 0.8-1.27). The risk of SAB among ETS exposed non-smokers was increased if there was moderate alcohol consumption or heavy caffeine consumption, although it was statistically significant only for caffeine consumption greater than 300 mg/d. They also found an increase in the OR for SAB among active smokers, although the 95% confidence intervals included one.

As with other studies that rely exclusively on self-report for ETS exposure, there may have been some misclassification bias. Also, the amount of spousal smoking during pregnancy was not quantified. Thus any efforts by the parents to quit smoking, or prevent ETS exposure prior to conception or upon learning of the pregnancy, could have limited exposure to ETS. This would result in an under-estimation of the risk of ETS exposure.

Chatenoud et al., 1998. This is an Italian case-control study investigating parental smoking habits before and during the first trimester of pregnancy in 359 cases of spontaneous abortion (GA ≤ 12 weeks) and 685 control cases of term deliveries (GA > 37 weeks). Smoking behavior of the mother and father was based on maternal recall during interviews. Confounders included in the multiple logistic regression were: hospital, maternal age, education, marital status, maternal family history of SAB and miscarriages, and alcohol and coffee habits during the first trimester. The OR for SAB associated with paternal smoking was 0.8 (95% CI 0.7-1.0). However, maternal smokers and non-smokers were included in the analyses of the effect of paternal smoking and no adjustment for maternal active smoking was indicated. The inclusion of maternal smokers and non-smokers in the control group makes the significance of the risk calculation hard to interpret.

3.3.1. Discussion: ETS, Spontaneous Abortion and Perinatal Mortality

The following definition and conclusions from the previous monograph (Cal/EPA, 1997) remain unchanged by more recent studies:

> *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.*

> *In conclusion, there is some epidemiological 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 inconsistent findings.*

Three studies have been published since the previous monograph investigating the association between ETS exposure and pregnancy wastage using the criteria defined above (Windham *et al.*, 1999b; Chatenoud *et al.*, 1998, Kharrazi *et al.,* 2004). These studies did not find a significant association overall between maternal or paternal exposure to tobacco smoke and spontaneous abortion. Kharrazi *et al*. found an increased OR for fetal death in heavily exposed mothers, and a possible dose response. Overall, the limited new data do not support a causal association for an increased risk of the loss of a clinically observable pregnancy associated with maternal ETS exposure. However, the data continue to be suggestive of a possible effect. Gene-environment interactions may also affect the risk of pregnancy wastage. One Dutch study of women with recurrent early pregnancy losses found that the frequency of one glutathione-S transferases gene (GSTP1-1b1b alleles) was significantly higher among women with recurrent pregnancy losses compared to controls (Zusterzeel *et al.,* 2000). Glutathione transferases are involved in the metabolic elimination of some cigarette toxicants. Based on genetic susceptibility, it may be that some pregnancies are more vulnerable to maternal ETS exposure than others. Future research in this direction may help clarify this issue.

Although the evidence of an association between exposure to ETS and spontaneous abortion of clinically observable pregnancies remains merely suggestive, one recently published study (Venners *et al.*, 2004) examined pregnancy loss at the much earlier stage immediately post-implantation. At this time pregnancy is not observable by the usual clinical criteria, but successful implantation of the conceptus is detectable by the rise in urinary HCG. In contrast to some studies of later pregnancy loss, these authors found evidence suggestive of a positive association between paternal smoking and early post-implantation pregnancy loss.

There are difficulties in interpretation of the studies examining associations between pregnancy outcomes and paternal smoking (or where this is a factor in reported maternal exposure to ETS). While paternal active smoking may result in maternal ETS exposure, it may also affect sperm, so that any association between paternal smoking and fetal wastage may be unrelated to ETS exposure.

3.4. Human Studies of ETS and Congenital Malformations

Congenital malformations (specifically structural) 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 3 to 10 percent of births are affected depending upon the definition and method of detection. 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. The same malformation may be associated with different etiologies. Potential confounding variables are not well defined, but maternal age, prior reproductive history, socio-economic status, and nutritional intake should be considered.

The literature on the relationship of active maternal smoking to congenital malformations is inconsistent, and the 2001 Surgeon General's report found no association between congenital malformations and active smoking (U.S.DHHS, 2001). More recent research in the area of congenital malformations has focused on genetic predisposition (Romitti *et al.,* 1999; van Rooij *et al.,* 2001). Specifically, there has been a search for susceptibility genes which, in and of themselves, increase the risk of a particular malformation. Susceptibility genes may interact with teratogens, resulting in an even greater risk of a specific malformation (gene-environment interaction). This susceptibility gene may be nonspecific, such as the ability or inability to metabolize a teratogen to a nontoxic metabolite, or conversely, to a more toxic metabolite (Buehler *et al.,* 1990). Secondly, there may be gene or gene products that are specifically involved in a particular embryonic event that are impacted differently by a teratogen depending upon the gene variant.

Malformations comprise a large number of different anomalies (e.g. clubbed feet, cleft lip, transposition of the great vessels of the heart, etc.) and there may be several etiologies for the same malformation. Therefore, large studies looking at smoking may not detect an overall rise in incidence of a particular malformation associated with a given etiology, even though smoking may be associated with a doubling of the occurrence of malformations associated with a particular etiology. Furthermore, certain individuals may be both unable to detoxify a teratogen while also carrying a susceptibility gene variant that, when combined with the teratogen, results in the malformation. Thus, there may be a large increase in the incidence of a specific malformation among individuals with a particular genetic make up that may not be detectable in epidemiology studies.

Since the previous review, there have been few additional data regarding ETS exposure of non-smoking pregnant women and the risks of congenital malformations. The Surgeon General's report noted equivocal findings regarding maternal smoking and the risks of congenital malformations (U.S.DHHS, 2001). Studies that look at malformation rates for large numbers of births have found maternal smoking to both increase and decrease the risk of specific malformations.

Susceptibility genes for cleft malformations are an active area of research and there appear to be embryos, based on gene variants, at greater risks of developing cleft malformations if the mother is a smoker. The increased risk of isolated cleft lips and/or palates associated with maternal smoking appears to be due to a gene environment interaction. A number of candidate susceptibility genes has been identified, although there is a disagreement in the literature about this. Particular variants of these genes, when combined with maternal smoking, are associated with an increased risk of cleft malformation. Clefts are highly visible malformations and are one of the most common malformations, occurring in one in one thousand births. Visibility and commonness facilitate detection. Other malformations that may be impacted by smoking include single ventricles of the heart, anal atresia, limb abnormalities, gastroschisis and neural tube defects.

3.4.1. Human Studies of Congenital Malformations and ETS Exposure

Studies that have examined the potential association of prenatal ETS exposure and congenital malformations are given below. Generally maternal ETS exposure is 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.

Steinberger et al., 2002. This is a population based case control study of 55 cases of single ventricle type cardiac malformations derived from the Baltimore Washington Infant Study (BWIS) of cardiovascular malformations (1981-1989). Control infants (n = 3572) did not have cardiac defects and were randomly selected from the regional cohort of live births. Paternal cigarette smoking and paternal alcohol consumption were associated with all cases of single ventricle malformations (OR 2.4, 95% CI 1.1-5.1, and OR2.0, 95% CI 1.1-3.9, respectively).

Romitti et al., 1999. This is a population based case control study of 366 cases of cleft lips and palates identified through the Iowa Birth Defects Registry (1987-1994) and 393 controls without malformations. Data were collected regarding paternal smoking habits, as well as maternal smoking and drinking habits. Maternal smoking was associated with an increased risk of cleft palates (OR 2.3; 95% CI 1.1-4.6) compared to non-smokers; and this risk was higher for male infants than females. Paternal smoking was not associated with an increased risk of cleft.

Shaw et al., 1996. This is a California case control study of oral cleft (clefts of the lips, palate or both) identified by the California Birth Defects Monitoring Program. Control cases were drawn from the same county as the case, had a similar time of birth and had no reportable malformations during the first year of life. Otherwise, controls were not matched to cases. Mothers were interviewed three to four years after delivery regarding maternal and paternal smoking habits and ETS exposure prior to conception and during the first trimester. There were 731 cases and 734 controls. There was an increased risk of isolated oral cleft if the mother was a smoker. This risk was higher if the father was a smoker and the risks increased further if the baby carried one or two copies of the A2 allele for the TGFα gene (transforming growth factor-alpha).

Among non-smoking mothers there was no increase in the risk of a cleft defect if the father was a smoker or the mother was exposed to ETS. But, if the baby carried the A2 allele for TGFα, the risk of a cleft for a fetus of a maternal non-smoker was similar to that of babies who carry the A2 allele and whose mothers were smokers. Specifically, among smoking mothers the OR for isolated clefts ranged from 2.1 to 2.8 (range of 95% CI 1.1-7.2) depending upon the number of cigarettes smoked and the smoking status of the father. If the baby of the smoking mother carried an A2 allele for TGFα, the OR for isolated cleft lips with or without a cleft palate was 6.1 (95% CI 1.1-36.6) and the OR for isolated cleft palates was 9 (95% CI 1.4-61.9). Among non-smoking women exposed to ETS whose babies carried the TGFα-A2 allele, the risk of isolated cleft lip ± isolated cleft palate was 9.8 (95% CI 1.1-218) and the risk of isolated cleft palates was 5.3 (95% CI 0.55-124).

It does not seem plausible that smoking twenty cigarettes per day by a mother during the first trimester has approximately the same risk as ETS exposure during the first trimester. Possibly, the A2 allele, independent of smoking or ETS exposure, is responsible for the increased risk. On the other hand, the number of cases with the A2 allele was small and smoke exposure was determined retrospectively after three to four years, making recall bias a strong possibility. In addition, research has shown that when interviewed postpartum, mothers of babies that had fetal distress during delivery decreased their report of smoking when compared to smoking status data obtained during prenatal care visits (Wong and Koren, 2001), while mothers who had uneventful deliveries did not.

Wasserman et al., 1996. This California case-control study examined the effects of passive and active smoke exposure on congenital anomalies of the heart, limbs and neural tubes. Among 344,214 infants delivered in 1987-1988, 207 cases of conotruncal heart defect, 264 cases of neural tube defect, and 178 limb reduction defect cases were compared with 481 controls. While there were elevated risks associated with maternal passive exposure at work and/or at home for all defects examined, passive exposure was significantly associated only with Tetralogy of Fallot (OR 2.9, 95% CI 1.3-6.6) after maternal exposure to ETS at work.

Yuan et al., 1995. This is a Japanese case control study of anal atresia (both syndromic and isolated), which utilized a birth registry of 216,707 births and stillbirths between 1989 and 1994. There were 84 cases of anal atresia and 174 controls. Controls were selected from the same birth registry and did not have a malformation. The two consecutive births after the case that were matched to the case with respect to maternal age, sex, parity, and season of birth were selected. The methods for collecting parental smoking and drinking habit data were not given. Neither parent was exposed to specific chemicals or physical factors at work. Maternal ETS exposure was not associated with an increased risk of anal atresia. There was a non-significant increase in risk of anal atresia if the mother was a smoker and a significant increase in risk if the mother drank during the first trimester (OR 4.8; 95% CI 1.2-19.1). The strength of this study is the high prevalence of smoking among the fathers (approximately 50%) and the low prevalence of smoking among the mothers (approximately 10%). As with many studies of specific malformations, this study may be too small to detect differences in risks. This study does not support an increased risk of anal atresia associated with maternal ETS exposure.

3.4.2. Malformations Discussion and Conclusions

Given that the results of studies of active smoking have been inconsistent and the Surgeon General's report stated that there was no association between congenital malformations and active smoking (U.S. DHHS, 2001), a teratogenic effect of ETS is unlikely to be strong. It would be very difficult to detect a significant association of a weak teratogen 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. Indeed, in the previous document it was concluded that "*it is not possible at this time to determine whether there is an association of ETS exposure and birth defects.*" This conclusion remains unchanged by recent studies.

There are eleven studies that have investigated congenital malformations and maternal ETS exposure, five of which have been published since the previous monograph (Cal/EPA 1997). In

almost all studies, paternal smoking is used as a surrogate marker for ETS exposure. Cal/EPA (1997) noted that epidemiologic studies suggest a moderate association of severe congenital malformations with paternal smoking although none of the research presented compelling evidence that ETS exposure caused congenital malformations. The use of paternal smoking status as a surrogate for ETS exposure means that a direct effect of active smoking cannot be ruled out.

Only two studies (Shaw *et al.*, 1996; Wasserman *et al.,* 1996) investigated ETS exposure independent of paternal smoking. Shaw *et al.* found an increased risk of oral clefts (OR range = 9-9.8) in babies of non-smokers with ETS exposure if the baby carried the TGFα A2 allele. ETS-exposed non-smokers and active smokers had similar elevations on risk associated with TGFα A2 allele (OR range 6.1 – 9.0). It does not seem biologically plausible that active smoking and ETS exposure carry the same risk for isolated clefts in the presence of the TGFα A2 allele.

Two groups studied the association between oral clefts and parental smoking (Shaw *et al.*, 1996 and Romitti *et al.*, 1999). One study (Shaw *et al.*, 1996) found an increased risk of clefts if the mother was a non-smoker with ETS and the baby carried the TGFα A2 allele but otherwise there was no increase in risk of cleft in maternal non-smokers exposed to ETS.

The risks of various kinds of cardiac malformations were investigated in two studies (Wasserman *et al.*, 1996 and Steinberger *et al.*, 2002). The study by Wasserman found a significant increase in risk of tetralogy of Fallot associated with ETS exposure in non-smokers, although it was one of thirty odd ratios calculated for non-smokers with ETS, and it was the only one that was significantly elevated. The study by Steinberger *et al*. (2002) found that all cases of single ventricle, a rare type of cardiac defect, were associated with paternal smoking and paternal alcohol consumption. These studies do not provide compelling additional data for an association between maternal ETS exposure and cardiac defects.

Only one study not included in the previous monograph investigating neural tube defects (NTD) was located. This study (Wasserman *et al.*, 1996) found no increased risk or a non-significant increase in risk of NTD associated with parental smoking.

A variety of other malformations are presented in the synopses: multiple malformations, severe defects, major defects, minor defects, urethral stenosis, anal atresia and limb defects. In the previous monograph, Mau and Netter (1974) found a significant elevation in risk of severe malformations associated with paternal smoking. Otherwise all of these investigations found no elevation of risk or a non-significant elevation in risk associated with paternal smoking or ETS exposure of maternal non-smokers.

Facial clefts, cardiac malformations, and defects of the nervous system (CNS, NTD) are common congenital defects, irrespective of exposure to toxicants such as tobacco smoke. The data presented here do not support an increased risk of congenital malformation associated with ETS exposure in selected populations. The etiology of malformations is just beginning to be unraveled. Over the past decade the percentage of malformations classified as idiopathic has decreased from approximately 70% to 55% as some malformations are found to have a genetic etiology.

Although the research presented here does not support an association between maternal ETS exposure and an increased risk of congenital malformations, these data should not be construed to mean that there is no increased risk of congenital malformations associated with maternal ETS exposure. Just as there appears to be a gene environment interaction between BW and maternal smoking (Wang *et al.*, 2000), there may be gene-environment interactions for congenital malformations. It will be difficult to demonstrate a gene environment interaction for congenital malformation because there may be multiple etiologies for the same malformation, and there are so many malformations.

3.5. Animal Studies of Tobacco Smoke Exposure

There is a limited number of animal studies of mainstream and sidestream smoke. Data from the studies published since the previous monograph are given in Table 3.11. Animals exposed to tobacco smoke inhale the smoke as humans do, but smoke particulate matter also may deposit on their fur. Unlike humans, animals groom their fur by licking it, thus they may also ingest tobacco smoke particulate matter.

Information on perinatal mortality in animals is provided by endpoints such as numbers of resorptions, numbers of live and dead fetuses at term (in studies with term hysterectomy), and litter size (in studies with spontaneous birth). Studies using mainstream smoke presented in the previous monograph were not generally supportive of effects on these parameters. In the three available studies using sidestream smoke (SS), 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. No new studies examining perinatal mortality in animals were identified.

Regarding the association between fetal malformation and ETS exposure in animals, the previous monograph stated:

> "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 studies of mainstream smoke using one or more of these techniques, four did not find any effects (Wagner *et al.*, 1972; Reznik and Marquard, 1980; Peterson *et al.*, 1981; Bassi *et al.*, 1984) and two mentioned limited findings (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."

Table 3.11: Animal Studies of Mainstream or Sidestream Smoke

Reference	Animal	Gestational Cigarette Smoke Exposure Findings:
Elliot *et al.* 2001	Guinea pigs	Increased airway responsiveness, alteration in alveolar attachment points.
Slotkin *et al.* 2001	Rat	Increased adenylyl cyclase activity in brain and heart. Inhibition of coupling of beta adrenergic receptors to adenylyl cyclase in brain. Decrease in muscarinic - m2 receptor expression in heart. Level of prenatal ETS exposure consistent with active smoking.
Hasan *et al.* 2001	Rats	Selective reduction of fetal protein kinase C and nitric oxide synthetase in dorsocaudal brain stem.
Czekaj *et al.* 2000	Rats	The effect of tobacco smoke exposure on fetal rat CYP2B1 expression.
Florek *et al.* 1999	Rats	Decreased maternal weight, delayed lung maturation in offspring.
Florek and *Marszalek.* 1999	Rats	Three-generation study of fertility and reproduction. No significant differences found although there was a trend for a decrease in the number of pregnancies, in the mating index, and in the fertility index. At high cigarette smoke levels, this study approximated active smoking. At levels more consistent with ETS exposure, no differences were found.
Nelson *et al.* 1999a	Rats	Dose dependent reduction in birth weight. No macroscopic malformations. Widespread retardation of ossification.
Nelson *et al.* 1999b	Rats	Histopathologic changes noted in bronchial muscles, liver, kidneys, stomach, and intestines.
Jalili *et al.* 1998	Mice	Increased number of DNA deletions in mouse embryo.
Ji *et al.* 1998	Rats	Maternal prenatal exposure to aged and diluted sidestream smoke: No effect on fetal weight; there was a significant alteration in the developmental expression of pulmonary Clara cells.

No complete teratology studies conducted with sidestream smoke were found for this update. The recent animal studies summarized in Table 3.11 focused on histologic and/or biochemical end points. Among these a study by Nelson *et al.* (1999a) reported an increase in the rate of apoptosis in several tissues from fetuses after maternal exposure to sidestream smoke. This observation is consistent with their other report (Nelson *et al.*, 1999b) of decrements in fetal weights and intrauterine growth following smoke exposure and may suggest a mechanism for IUGR in human fetuses similarly exposed.

3.5.1. Animal Studies – Conclusion

The animal data presented in Table 3.11 do not materially affect the conclusions based on data in humans. Those studies that reported histologic and biochemical changes associated with exposure to tobacco smoke support the studies of prenatal exposure to parental nicotine (Dempsey and Benowitz, 2001).

3.6. Chapter Summary

In summary, data presented here indicate that ETS exposure of non-smoking pregnant women is associated with a 20 to 100 g decrease in BW. This is in agreement with that reported in the previous document, although the magnitude of the effect is larger, and strengthens the conclusion that ETS may be causally associated with decreases in BWs. This may be viewed by some as a modest reduction in BW, however, it is a mean value and may indicate a downward shift in the BW distribution curve so that there is an increase in the number of babies that are growth retarded. Data presented here indicate that there is a downward shift in the distribution as evidenced by an increase in the risk of delivering a growth-retarded baby (LBW, SGA, SFD or IUGR) associated with ETS exposure of non-smoking pregnant women (Table 3.12 below). Indeed, the more recent studies support the conclusion of the earlier report that ETS is causally associated with elevated risk of low birth weight, and are more strongly supportive of a causal association between ETS exposure and restricted fetal growth and especially PTD than was seen in the previous document. Recent research has demonstrated gene environment interactions involving cigarette smoking and drug metabolizing enzymes. Based upon genetic differences in drug metabolizing enzymes, subgroups of fetuses appear to be at much greater risk of adverse outcomes associated with maternal smoking, specifically increased risks of LBW and PTD. Similarly there appear to be subgroups of fetuses, which are more susceptible to the effects of maternal ETS exposure.

Birth weight decrements may also be a surrogate indicator for other fetal abnormalities. Research (Dempsey and Benowitz, 2001) has shown a myriad of molecular biological differences in the mother, newborn and placenta associated with maternal smoking. Similar differences may be found between ETS exposed and ETS unexposed pregnant non-smokers. Consistent with the previous document, the limited data presented here do not support a causal association for an increase in risk of pregnancy wastage associated with maternal ETS exposure; however, taken as a whole, the data continue to be suggestive of a possible effect. The studies to date do not support an increased risk of congenital malformations. Future research may be able to determine if there are subgroups that are at increased risk of pregnancy wastage or malformations based on genetic predisposition.

Table 3.12: ETS and Outcome: LBW, SGA, SFD, IUGR and PTD

Reference Date	Total N	MNS[1] no ETS	MNS[1] w/ETS	OR, RR (95% CI) for IUGR, LBW, SGA, SFD and PTD[2]	Confounders and Covariates Adjustments[3]
Underwood *et al.*, 1967	48,505	9,427	15,233	LBW : 0.9 (0.8-1.0) PS≥ 30CPD: 1.05 (0.82-1.3) PTD: 0.9 (0.8-1.0) PS≥ 30 CPD: 1.05 (0.8-1.3)	Sex, MWt, ExAS
Yershalmy *et al.*, 1971	13,083	8,286		LBW: 0.9 n.s.	Oth, ExAS
Mau & Netter *et al.*, 1974	5,183	2,070	1,626	LBW: 1.4 (1-1.9) PTD: 1.2 (0.9-1.7)	None reported
Martin and Bracken,1986	3,891	1,707	906	LBW OR 2.2 (1.1-4.5) PTD n.s.	GA, MA, Eth, Alc, Drg, SES, MWt, MHt, Oth, ExAS
Haddow *et al.*, 1988	1,231	376	855	LBW: RR 1.29 – no statistics	Eth, Par, MWt, MHt, Oth, ExAS
Nakamura *et al.*, 1988	2,005	561	1,444	LBW: 1.4 (0.9-2.2) SGA: crude 1.2 (0.8-2.0) PTD: crude 1.2 (0.8-1.8)	GA, MA, Par, Alc, SES, Oth, ExAS
Chen *et al.*, 1989	1,162	325	837	LBW: 1.5 (0.75-3.2)	Sex, Par, SES, Oth, ExAS
Saito 1991	2,713	1,311	1,402	SFD: 1.3; $p<0.05$ PS>20CPD: 1.4; $p<0.05$ PTD: n.s.	
Ogawa *et al.*, 1991	5,336	3,606	1,730	LBW: 1.0 (0.7-1.5)	GA, MA, Par, Alc, MHt, Oth, ExAS
Ahlborg & Bodin, 1991	4,701	2,170	1,703	High ETS - LBW: 1.4 (0.3-5.9) High ETS – SAB: 2.2 (1.2-3.8)	GA, Sex, Par, Alc, Oth
Mathai *et al.*, 1992	994	474	520	LBW: 1.0 (0.4-2.3) PTD: 1.6 (0.8- 2.9)	GA, MA, Sex, Par, SES, MHt, Oth
Zhang & Ratcliffe, 1993	1,765	1,033	732	LBW: 1.07, n.s. IUGR: 1.1, n.s.	GA, Sex, Par, MHt, Oth, ExAS
Fortier *et al.*, 1994	> 7,000	2,368	2,276	IUGR: 1.1 (0.85-1.4) PTD: 0.98 (0.56-1.73)	Par, MWt, Oth
Mainous & Hueston, 1994	3,253	743	2,510	LBW: 1.6 (0.92-2.7) high ETS LBW: 2.3 (1.1-5.0)	Eth, Par, SES, Oth, ExAS
Eskenazi *et al.*, 1995	2,292	2,129	114	LBW: 1.35 (0.6-3.0)	GA, MA, Eth, Par, Alc, MWt, MHt, Oth
Chen and Petitti, 1995	225	100	120	IUGR: 0.5 (0.14-1.7)	Eth, Par, Alc, Drg, SES, MWt, Oth
Jedrychowski & Flak 1996	1,115	452	512	LBW: 1.46 (0.83-2.6)	GA, Sex, Par

[1] MNS: maternal non-smoker (Blank – number not given); [2] CPD: cigarettes per day; IUGR: intrauterine growth restriction; LBW: low birth weight; PTD: preterm delivery; SFD: small for date; SGA: small for gestational age. [3] Abbreviations: ALC: alcohol use; Drg: drug use; Eth: ethnicity; ExAS: excludes active smokers; GA: gestational age; MA: maternal age; MHt: maternal height; MWt: maternal weight; Oth: other; Par: parity; SES: socioeconomic status; Sex: sex of the newborn.

Table 3.12: ETS and Outcome: LBW, SGA, SFD, IUGR and PTD

Reference Date	Total N	MNS[1] no ETS	MNS[1] w/ETS	OR, RR (95% CI) for IUGR, LBW, SGA, SFD and PTD[2]	Confounders and Covariates Adjustments[3]
Horta *et al.*, 1997	5,166			LBW: 1.18 (0.94-1.48) PTD: 1.25 (0.99-1.57) IUGR: 1.33 (1.05, 1.68)	GA, MA, Eth, Par, SES, MWt, MHt, Oth
Ahluwalia *et al.*, 1997	17,412	10,639	2,855	LBW: <30yo 0.97 (0.76-1.23) ≥30yo 2.4 (1.5-3.9) PTD: <30yo 0.9 (0.8-1.1) ≥30yo 1.9 (1.2-2.9) SGA: <30yo 0.97 (0.8-1.3) ≥30yo 1.3 (0.8-2.2)	Eth, Par, Alc, MWt, Oth
Dejin-Karlsson *et al.*, 1998	854	247	345	SGA: 3.9 (1.4-10.7)	GA, MA, Eth, Par, Alc, Drg, SES, MWt, MHt, Oth
Nafstad *et al.*, 1998	163	68	54	SGA: 1.0 (0.4-2.1)	GA, Sex, MWt, MHt, Oth
Windham *et al.*, 1999a	992			LBW 1.0 (0.52-2.1) Term LBW 1.8 (0.64-4.8) SGA 1.4 (0.79-2.5)	GA, Eth, Alc, Oth
Windham *et al.*, 2000	4,099	2,887	759	high ETS LBW 1.8 (0.82-4.1) high ETS PTD 1.6 (0.87-2.9) high ETS very PTD 2.4 (1.0-5.3) Ethnicity not caucasian high ETS LBW 3.8 (1.5-9.8) high ETS PTD 2.4 (1.1-5.5) high ETS very PTD 3.8 (1.3-10.7) Mat age >30y, PTD 2.8 (1.2-6.6)	GA, MA, Eth, Par, Alc, SES, MWt, MHt, ExAS
Matsubara *et al.*, 2000	7,411			IUGR 0.95 (0.72-1.26)	Sex, MA, Par, Ed, Alc, MHt, MWt,
Jaakkola *et al.*, 2001	477	288	233	LBW: 1.55 (0.55-4.43) PTD : 6.12 (1.31-28.7)	ExAS
Dejmek *et al.*, 2002	6,866	3,710	1,797	LBW: 1.51 (1.02-2.26) IUGR: 1.08 (0.82-1.43)	Sex, Eth, Par, Alc, SES, MWt, MHt, Oth
Goel *et al.*, 2004	576	435	141	1.15 (0.69-1.92)	MA, Ed, Occ, BO, Par
Kharrazi *et al.*, 2004	2,796	951	1,845	Adverse Outcome 1.36 (1.06-1.72) LBW: 1.42 (0.91-2.21) PTD: 1.78 (1.01-3.13)	GA, Sex, Eth, SES, Oth, ExAS

[1] MNS: maternal non-smoker (Blank – number not given); [2] CPD: cigarettes per day; IUGR: intrauterine growth restriction; LBW: low birth weight; PTD: preterm delivery; SFD: small for date; SGA: small for gestational age. [3] Abbreviations: ALC: alcohol use; Drg: drug use; Eth: ethnicity; ExAS: excludes active smokers; GA: gestational age; MA: maternal age; MHt: maternal height; MWt: maternal weight; Oth: other; Par: parity; SES: socioeconomic status; Sex: sex of the newborn.

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Chapter 4. Developmental Toxicity: II. Postnatal Manifestations of Pre- and/or Postnatal ETS Exposure

Infants and children are among the most critical subgroups for consideration of health inpacts of environmental pollutants. Due to their smaller body size and typically higher activity levels than adults, their intake of food, water and air per kilogram of body weight is greater than adults. These factors, along with child-specific behaviors, result in greater exposures to pollutants and food contaminants. Additionally, the biochemical and physiological processes of infants and children are not simply smaller scale copies of those found in adults. Organ systems are immature, especially in infants, and may not have the defensive functions and reserve capacity seen in the adult. Most importantly, there are crucial developmental processes taking place throughout infancy and childhood, resulting in growth and maturation. If these processes are interfered with by toxicity or other disease processes, the result may not be merely a temporary morbidity as might be seen in an adult, but frequently a failure of one or more organ systems to achieve its proper adult capacity and function, a deleterious outcome with lifelong consequences. These considerations are a key component of the concerns expressed by the California's Children's Environmental Health Protection Act ("SB25"), and have also informed the evaluation of postnatal developmental impacts of ETS reported in this chapter. A summary of the conclusions regarding the evidence of a causal association between ETS exposure and postnatal development, and ETS exposure and sudden infant death syndrome (SIDS), from the 1997 OEHHA report and from this update is provided below in Table 4.0. The findings are based on a weight of evidence approach and include both prenatal and postnatal exposures.

In summary, ETS exposure has been conclusively shown to harm infants; specifically, it is a cause of SIDS. Further, the available evidence suggests an association between ETS exposure and postnatal cognitive and behavioral effects, and possible associations with immunological, hematological, and cardiovascular effects, although the data for these last endpoints are inconclusive at this point. Impacts on the respiratory system are discussed in Chapter 6.

Table 4.0 ETS, SIDS, Postnatal Development: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	# Additional Studies in Update	Findings: OEHHA 1997 Evidence of causal association?	Findings: Update Evidence of causal association?
SIDS	10	9 (1 meta)	Conclusive	Conclusive (strengthened)
Cognition and Behavior	11	3	Suggestive	Suggestive (strengthened)
Postnatal physical development[b]	5	0	Inconclusive	Inconclusive
CNS changes[c]	0	2	Not assessed	Suggestive (animal model)
Cardiovascular[d] Hematological Immune	0	6	Not assessed	Inconclusive

[a]meta = # meta-analyses – not included in counts of studies [b]Measured as height gain
[c]Includes changes in brain structure and receptor numbers.
[d]Includes changes in cardiac receptor numbers, HDL-C, RBC type and count, and allergic sensitization.

4.0. Introduction

In the 1997 OEHHA report (Cal/EPA, 1997), passive and active maternal tobacco smoke exposure, as well as passive smoke exposure in children, were seen to have a deleterious effect on specific childhood outcomes. These included postnatal development, cognition and behavior, and the incidence of SIDS. This chapter examines the research in these areas published since that review. The chapter is subdivided into sections on SIDS and on other developmental effects of passive smoke exposure. In the studies included here, a child's exposure to ETS generally represents a continuation of the passive exposure it received *in utero* from maternal prenatal smoking. For this reason it is often not possible to ascribe specific outcomes exclusively to exposures from one versus the other route. Indeed it appears that the prenatal smoke exposure a fetus may or may not receive partly determines its response to subsequent ETS exposure as an infant. The situation is complicated further by the consistent association of smoke exposure with other risk factors for negative childhood outcomes. Thus appropriate study design and control for these confounding factors are critical to the delineation of the role of ETS. While the emphasis in these studies is on the child's passive exposure to smoke, studies that specifically examined the childhood consequences of a mother's passive exposure to ETS during pregnancy included persistent pulmonary hypertension in infants (Bearer *et al.,* 1997) and fetal hypoxia (Dollberg *et al.*, 2000).

4.1. Sudden Infant Death Syndrome (SIDS)

This review utilizes the following definition of SIDS from the previous document:

> "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 one month to one 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 birth weight, 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 & Bulterys 1991; Guntheroth & Spiers 1992).

The 1997 OEHHA report reviewed 10 epidemiological studies that examined the relationship between ETS exposure and SIDS. Although these studies vary in quality and size, they all support an association between passive smoke exposure and SIDS. In that review was the following assertion:

> "In conclusion, the strength of the Klonoff-Cohen *et al.*, 1995 and Blair *et al.*, 1996 studies, their consistency with two earlier well-conducted studies (Mitchell *et al.*, 1993 and Schoendorf & 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.

The studies published since that time generally reflect a heightened appreciation and control for various confounding factors while continuing to support this conclusion. While the difficulties associated with distinguishing the effects of pre- versus postnatal smoke exposure remain, demonstration of elevated cotinine and/or nicotine levels in SIDS victims compared to controls clearly supports a postnatal effect of ETS on SIDS (Milerad *et al*., 1998; Rajs *et al*., 1997; McMartin *et al.*, 2002). Described below are nine studies in humans, one meta-analysis, and one review published since the 1997 Cal EPA report that support an association of passive smoke exposure and SIDS. Animal studies include the study by Slotkin *et al*. (1999) in rats suggesting a mechanism by which passive smoke exposure may increase the risk of SIDS by altering the development of the heart and brain. Altered brain development was also observed by Gospe *et al*. (1996) in rats exposed to side stream smoke. In piglets, Froen *et al*. (2000) found evidence implicating nicotine in combination with infection as a cause of SIDS. These effects may be exacerbated by the higher levels of fetal hemoglobin (HbF) in neonates that are associated with prenatal smoke exposure (Fagan *et al.*, 1995) and tighter binding of CO, and with increased incidence of SIDS (Giulian *et al.*, 1987; Gilbert-Barness *et al.*, 1993; Cochran-Black *et al.*, 2001).

4.1.1. Newer Epidemiological Data

Table 4.1 ETS and SIDS

Reference Country	Study Description	Exposure to smoke	Outcome and OR (95% CI)	Comments
Meta-analysis				
Anderson & Cook 1997	Meta-analysis of studies on pre- and postnatal smoking SIDS	Maternal Postnatal	SIDS OR adj 1.94 (1.55-2.43)	5 of 8 studies that examined postnatal smoking and controlled for prenatal smoking found increased SIDS with postnatal ETS exposure.
Original studies				
Carpenter *et al.* 2004	20-city case-control of SIDS risk factors SIDS n = 745 Ctrl 2,411	Maternal <10 cig/d >10 cig/d +bedsharing By others 1-9 cig/d 10-19 cig/d 20-29 cig/d ≥ 30 cig/d	Adj. OR 1.52 (1.10-2.09) 2.43 (1.76-3.36) 17.7 (10.3-30.3) 1.07 (0.71-1.61) 1.54 (1.11-2.14) 1.73 (1.21-2.48) 3.31 (1.84-5.96)	Multicenter European study of 56 SIDS risk factors. Postnatal maternal smoking and smoking by others significantly associated with SIDS, especially with bedsharing. Couldn't distinguish contribution of prenatal smoking. Good confounder control.
McMartin *et al*. 2002 Canada, US	Case-control Measured cotinine and nicotine in lungs from victims of SIDS and non-SIDS death. n = 73	Postnatal SIDS Non-SIDS Smoking Non-smoking Smoking Non-smoking	Nicotine (ng/g) 19.64 ± 2.61 7.86 ± 1.63 (p=0.0001) 19.92 ± 2.63 7.86 ± 1.68 (p=0.0001) Cotinine (ng/g) 13.48 ± 2.41 5.04 ± 0.57 (p=0.0001)	Lungs from 44 SIDS and 29 non-SIDS victims for nicotine and cotinine measurements. Data stratified by household smoking status, also by SIDS vs non-SIDS. Study can't definitively distinguish pre- vs postnatal passive exposure due to possible reporting bias. Nicotine in lungs supports ETS exposure prior to death.

Table 4.1 ETS and SIDS

Reference Country	Study Description	Exposure to smoke	Outcome and OR (95% CI)	Comments
Dwyer *et al*. 1999 Tasmania	Prospective cohort of ETS and SIDS at 1 mo. n = 9,826	Maternal post 1-10 cig/d 11-20 > 20	SIDS OR adj 2.08 (0.79-5.48) 2.15 (0.85-5.47) 4.69 (1.74-12.58)	Good correlation of postnatal ETS and SIDS but not with cotinine. Postnatal effect may be continuation of prenatal maternal smoking.
Elliot *et al*. 1998 Australia	Case-control Compared airways of SIDS victims with vs without smoke expo. n = 36	Maternal > 20 cig/d No smoke	Ratio of inner wall area/Pbm[1] 0.07 ± 0.013 0.055 ±0.008	Smoke exposure increased thickness of inner wall ($p<0.05$) and epithelium ($p< 0.01$) of large airways. Can't separate pre- vs postnatal exposure.
Milerad *et al*. 1998 Scandinavia	Case-control: cotinine in peri-cardial fluid in victims of sudden death. n = 45	Post +/- prenatal . SIDS Accidental Infection	Cotinine (ng/ml) Median (range) 15.8 (3.5-110) 12.9 (2.1-114) 7.1 (1.2-15.4)	Cotinine reflected recent nicotine exposure prior to death in infants: 24 SIDS, 12 infection, 9 accidents No ETS: 0-0.4 ng/ml; when both parents smoke: 2.4-5.4 ng/ml
Alm *et al*. 1998 Scandinavia	Case-control: smoke exposure in SIDS victims. n = 218	Maternal Prenatal only Ceased while pregnant Pre+postnatal	SIDS OR 1.1 (0.5-2.4) 1.1 (0.4-3.2) 4.5 (3.1-6.5)	Assessed smoking habits before, during and after pregnancy by questionnaire in families of SIDS victims. If smoking stopped at delivery, risk of SIDS dropped suggesting postnatal ETS effect.
Mitchell *et al*. 1997 New Zealand	Prospective case-cohort of risk factors for SIDS n = 1,049	Maternal 1-19 cig/d > 20 cig/d Postnatal Maternal Shared bed Paternal	SIDS OR unadj: 5.84 (3.72-9.21) 14.89 (6.38-34.72) SIDS OR adj: 1.43 (0.58-3.51) 5.02 (1.05-24.05) 3.84 (2.49-5.92)	SIDS risk increased with more post-natal maternal smoking. No control for prenatal smoking. Increased risk with paternal smoking compared to maternal only, or bed sharing with smoking mother supports post-natal ETS effect.
Brooke *et al*. 1997 Scotland	Case-control of infant care practices and SIDS. n = 577	Smoking Both parents Mother only Paternal only	SIDS OR adj 5.19 (2.26-11.91) 5.05 (1.85-13.77) 2.12 (0.99- 4.56)	201 SIDS in 798 postnatal deaths. Good confounder control. Risks if both parents or father only smoked suggest postnatal ETS effect. Dose response ($p = 0.001$).
Rajs *et al*. 1997 Sweden	Cohort: cotinine and nicotine in pericardial fluid in victims of SIDS and non-SIDS death. n = 85	Postnatal +/- prenatal	SIDS assoc with cotinine > 30 ng/ml. In SIDS nicotine incr. with age.	Pericardial fluid taken at autopsy from 50 male, 35 female SIDS (67) and non-SIDS (18) infants. Suggests SIDS assoc. with elevated cotinine or nicotine.

[1] Pbm = perimeter of basement membrane

4.1.1.1. Meta-analysis

Anderson & Cook (1997) conducted a meta-analysis of the effects of prenatal and postnatal smoke exposure on incidence of SIDS. Nine studies included data on postnatal maternal smoking of which four controlled for maternal prenatal smoking. The adjusted pooled OR for postnatal ETS exposure and SIDS from these studies was 1.94 (95% CI 1.55-2.43). To more directly assess the effects of pre- versus postnatal ETS exposure, several studies examined the SIDS risks associated with other smokers in the household. The number of such studies was small and the results more variable so no meta-analysis was attempted. In a study by Mitchell *et al*. (1993), no effect of paternal smoking (OR 1.00) was found when the mother did not smoke, consistent with prenatal exposure making the infant more susceptible to subsequent ETS exposure. However, when the mother did smoke prenatally, an OR of 1.37 (95% CI 1.02-1.84) was calculated for paternal postnatal smoking after adjusting for maternal smoking and other confounders. Similarly Blair *et al.* (1996) found an OR of 2.50 (95% CI 1.5-4.2) for paternal smoking after adjusting for maternal smoking and other confounders. In 5 of 8 reviewed studies for which smoke exposure *in utero* was controlled or excluded there appeared to be an increased risk of SIDS associated with postnatal ETS exposure independent of prenatal exposure.

4.1.1.2. Original Studies

Carpenter et al. (2004) analyzed data from 20 case control studies conducted in 20 centers throughout Europe in 1992-1996 to determine current risk factors for SIDS. In all, 745 cases of SIDS and 2,411 controls, matched for age and survey area, were analyzed. The study sought to collect data on 56 risk-related variables, however, data for 24 of them were not collected by all centers. Multivariate analyses were used to derive ORs adjusted for all the other variables, among which were maternal smoking habits, number of other smokers in the household, sleeping position, birth weight, mother's age, marital and employment status, previous live births, use of pacifier, bed sharing, alcohol use, and drug use.

Compared to mothers who neither smoked nor shared the bed, maternal smoking in the absence of bed-sharing significantly elevated risk in an exposure-dependent fashion (Table 4.2). While bed-sharing alone was associated with a non-significant increase in SIDS risk (OR 1.56, 95% CI 0.91-2.68), the combination of maternal smoking and bed-sharing resulted in a substantially elevated risk of SIDS (OR 17.7, 95% CI 10.3-30.3). In addition, there was an exposure-dependent increase in risk associated with smoking by others in the household.

Table 4.2 Adjusted Odds Ratios for SIDS for Maternal Smoking and/or Bed-Sharing

Bed-sharing/ maternal smoking	Cases/ Controls	Adjusted OR (95% CI)
No/No	249/1624	1.00
Yes/No	32/139	1.56 (0.91-2.68)
No/<10 cig/day	133/328	1.52 (1.10-2.09)
No/>10 cig/day	194/247	2.43 (1.76-3.36)
Yes/Yes	111/56	17.7 (10.3-30.3)
Smoking by others		
None	259/1465	1.00
1-9 cig/day	64/215	1.07 (0.71-1.61)
10-19	131/297	1.54 (1.11-2.14)
20-29	110/203	1.73 (1.21-2.48)
≥ 30	55/41	3.31 (1.84-5.96)

While maternal smoking around an infant posed a substantial risk, it was not possible to separate the effects of an infant's exposure to smoke products *in utero* versus postnatally. Given the usual continuity of maternal pre- and postnatal smoking, the high OR of 17.7 for maternal smoking and bed-sharing probably reflects the adverse effects of maternal smoking during pregnancy as well as the direct effects of postnatal ETS. That postnatal ETS exposure *per se* is an independent risk factor for SIDS is supported by the exposure-dependent increase in risk associated with smoking by others in the household. This was a well-designed study that represented a geographically diverse area and controlled for a large number of variables.

McMartin et al., 2002. Nicotine and cotinine levels were measured in the lungs of 44 SIDS and 29 non-SIDS victims with the results stratified according to reported household smoking status. Significantly higher nicotine levels were found in SIDS cases (19.64 ± 2.61 ng/g) compared to non-SIDS cases (7.86 ± 1.63 ng/g)(p=0.0001) irrespective of reported smoking status. Cotinine levels, however, were not significantly different between these two groups (10.87 ± 2.32 vs 8.71 ± 1.47 ng/g)(p=0.2). When all cases were compared, nicotine and cotinine levels were significantly higher in infants from identified smoking vs nonsmoking households: nicotine 19.92 ± 2.63 vs 7.86 ± 1.68 ng/g (p=0.0001); cotinine 13.48 ± 2.41 vs 5.04 ± 0.57 ng/g (p=0.0001). Probable bias in the reporting of smoking history limits this study's ability to correlate SIDS with prenatal vs postnatal smoking. Nevertheless, elevated nicotine levels in the lungs of SIDS vs non-SIDS victims strongly indicate an involvement of postnatal ETS in SIDS. In addition, the elevated nicotine levels in the presence of cotinine levels that were not elevated indicate that the relevant exposure occurred during a very short time before death, namely, during the half-life of nicotine.

Dwyer et al., 1999. This was a prospective study of ETS exposure at one month of age in relation to SIDS. The data came from the Tasmanian Infant Health Survey from 1988-1995, a prospective cohort study involving 9,826 infants assessed as being at high risk of SIDS. The analysis included 35 SIDS deaths. At the same time, a population-based retrospective case-control study was also conducted that provided retrospective data on SIDS cohort infants for whom prospective data were not available at 1 month of age. For the prospective study, initial interviews, conducted when the infants were 4 days old, collected data on maternal smoking

habits during pregnancy, whether the mother lived with someone who smoked, number of cigarettes smoked in the mother's presence per day inside and outside the house, and time spent in the same room with someone smoking. Infant and home environment measurements were taken during a home visit during the fifth postnatal week. At this time the number of cigarettes smoked per day, number of adult smokers in the house and whether the mother or others smoked in the same room as the infant was assessed. A follow-up interview was conducted when the infants were 12 weeks of age. Infant urinary cotinine levels were measured on samples collected during the home visits.

Maternal prenatal smoking was associated with reduced birth weight (p=0.0001) and reduced placental weight (p=0.02). After adjustment for prematurity, birth and placental weights, prenatal smoking was associated with an OR for SIDS of 2.76 (95% CI 1.18-6.46). For postnatal exposure, univariate analysis gave an OR among infants in a home where the mother and others smoked of 2.83 (95% CI 1.09-7.37) which was not higher than the OR of 4.48 (95% CI 1.65-12.13) found in homes where only the mother smoked. It is not clear whether this unexpected result is related to the inclusion of women who smoked prenatally as well as postnatally. Smoking by other residents reportedly increased an infant's urinary cotinine by 63%, but did not appear to be related to SIDS incidence. After adjustment for socioeconomic variables (education, marital status, paternal employment, health insurance), and for such variables as season of birth, sleeping in a prone position, sex, low birth weight, bottle feeding, mother's age, delayed first immunization and family history of asthma, the OR for SIDS from maternal postnatal smoking was 3.44 (95% CI 1.49-7.94). A dose response was suggested as the adjusted OR for maternal postnatal smoking of 1-10 cigarettes per day was 2.08 (95% CI 0.79-5.48); 11-20 cigarettes per day, OR 2.15 (95% CI 0.85-5.47); >20 cigarettes OR 4.69 (95% CI 1.74-12.58). Analysis of these data along with those from the retrospective case-control study reportedly gave similar estimates of risk from maternal and other resident's smoking. It gave an OR for postnatal smoking of 3.61 (95% CI 1.88-6.93) and a significant trend for increased risk with increasing number of cigarettes smoked (p=0.047). Interestingly, overall there was no evidence of an increase in SIDS incidence associated with the presence of other smokers (adjusted OR 0.72; 95% CI 0.48-1.46) even though there was an association between other smokers and urinary cotinine. However other smokers significantly raised the risk for SIDS in households of older mothers (>19 yrs; OR 2.38; p=0.058) versus younger mothers (OR 0.32; p=0.0064). The reason for this effect is not clear.

Since maternal smoking habits tended not to change from before to after birth, the size of this study prevented clear separation of the effects of pre- versus postnatal smoke exposure. Nevertheless, these results were similar to the findings of the Tasmanian case-control study where maternal postnatal smoking was strongly associated with SIDS (OR 3.96; 95% CI 1.91-8.24) but smoking by other household residents was not (OR 1.31; 95% CI 0.70-2.44).

Elliot et al. (1998) asked whether the airways from infants who had died of SIDS and had been exposed to high levels of maternal smoking were structurally different from those who had died from SIDS and were not exposed. Data were collected by interview from mothers of SIDS infants on smoking history before, during and after pregnancy. During postmortem examination of transverse sections of lungs from SIDS victims, the perimeters of the internal epithelium, basement membrane, outer smooth muscle and outer airway were measured. This allowed estimation of the total, epithelial, inner and outer wall areas, and epithelial thickness.

Some 228 airways from 19 infants in the high-smoke exposure group (mother smoked >20 cigarettes per day) were compared with 158 airways from 19 infants with no exposure. To compare similar-sized airways from different subjects, airways were divided into three arbitrary size groups. The means of pooled measurements for each size group were compared between exposure groups. Inner wall areas were calculated by subtracting the area of a circle whose perimeter is that of the basement membrane from the area of a circle whose perimeter is that of the outer smooth muscle layer. For comparisons, the mean inner wall area (± SD) was expressed as a ratio to the basement membrane perimeter (Pbm). In the Pbm 2-4 mm group, this ratio was significantly greater in the smoke-exposed versus the unexposed infants (0.07 ± 0.013 vs 0.055 ± 0.008; $p<0.05$). The epithelial thickness in relation to Pbm was also significantly greater in the smoke-exposed group (0.03 ± 0.007 vs 0.02 ± 0.003; $p<0.01$). In the two smaller airway size groups (Pbm < 1 mm and Pbm 1-2 mm) there were no significant differences in the measured wall thicknesses. This study suggested that smoke exposure alters airway morphometry, increasing the wall thickness of the larger airways. Due to the small size of this study, it was not possible to assess the relationship between histologic changes and smoking history in the 45 cases where the infants were exposed to varying levels of smoke. The authors thus restricted their analysis to the 38 cases where smoke levels were constant before, during and after pregnancy. This comprised 19 mothers with no smoke exposure and 19 who smoked >20 cigarettes per day for the duration. It was thus not possible to distinguish the effects of exposure *in utero* versus postnatal exposure to ETS nor to discern a possible dose response. It has been suggested that a direct toxic effect of postnatal ETS exposure on lung growth may occur secondary to altered lung growth from *in utero* exposure. This may predispose the infant to impaired lung function and increased risk of SIDS.

Milerad et al., 1998. This study compared levels of cotinine in pericardial fluid from all cases of sudden death of children in southeastern Norway during 1990-1993. Included were 24 infants who died of SIDS, 12 who died from infections and were matched for age and sex with the SIDS cases, and 9 who died from accidents. Cotinine was used as an objective measure of recent nicotine exposure. Due to the rate of metabolic conversion of nicotine to cotinine and the fact that nicotine metabolism ceases after circulatory arrest, cotinine levels in pericardial fluid obtained at autopsy were taken to reflect nicotine exposure 4-8 hrs before death. In this study pericardial cotinine levels >5 ng/ml were used to identify infants significantly exposed to nicotine shortly prior to death.

The median and range of cotinine concentrations for SIDS infants was 15.8 (3.5-110) ng/ml. This was significantly higher than the 7.1 (1.2-15.4) ng/ml for the deaths by infection ($p<0.003$) but not significantly different from the levels found in the accidental deaths (12.9; 2.1-114 ng/ml). Of the SIDS victims, 92% (22/24) had cotinine levels exceeding 5 ng/ml of which 6 (25%) had levels > 20 ng/ml. Among the infants who died of infection, 67% (8/12) had cotinine levels above 5 ng/ml and none above 20 ng/ml. In the 9 accident victims, 78% had cotinine levels above 5 ng/ml and 33% were above 20 ng/ml. Since smokers have a significantly increased risk of being involved in automotive accidents (Brison, 1990), children of smoking parents may be over-represented in traffic accident fatalities. In addition, exposure to ETS in the car prior to the accident would increase pericardial nicotine.

Based on the objective measure of cotinine in a body fluid, this study strongly supports a connection between an infant's recent exposure to ETS and SIDS. It is not clear to what extent

prenatal exposures to tobacco smoke may have contributed to the infant's susceptibility to SIDS, however the high levels of cotinine in the SIDS victims are consistent with intense ETS exposure as a precipitating event.

Alm et al., 1998. This case-control study in Scandinavia used postal questionnaires to examine the association between maternal and paternal smoking habits before, during and after pregnancy in 218 families of SIDS victims. Cases and controls were matched for gender but controls were slightly older (21.4 vs 16.1 wks). Odds ratios were adjusted for maternal and infant ages, and birth weight. SIDS risk was elevated with maternal smoking before (OR 2.5, 95% CI 1.7-3.7), during (3.6, 95% CI 2.4-5.3), and after (3.7, 95% CI 2.5-5.5) pregnancy. The effects of smoking cessation and its timing were also examined and crude ORs reported for the comparison with never smokers. If smoking stopped prior to pregnancy the OR was 0.7 (95% CI 0.3-1.4). Cessation at parturition gave an OR of 1.1 (95% CI 0.5-2.4) while cessation during pregnancy with resumption after birth gave OR 1.1 (95% CI 0.4-3.2). This compares to an OR of 4.5 (95% CI 3.1-6.5) for continuous maternal smoking during pregnancy and after. The drop in the risk for SIDS when the mother stopped smoking at parturition compared to that for continued smoking suggests that postnatal ETS is associated with SIDS. This effect may be partially due to other changes in maternal behavior of which smoking cessation was a part. The low risk seen if the mother stopped only during pregnancy supports the importance of prenatal exposure and is consistent with postnatal ETS being more deleterious if the infant was also exposed prenatally. If mothers who stopped smoking during pregnancy and resumed smoking postnatally are more likely to not smoke around their children, then the additive effect of prenatal to postnatal smoking may be overstated.

Mitchell et al., 1997. This was a prospective case-cohort study to identify risk factors for SIDS following a national campaign to prevent SIDS. Data from all SIDS cases plus a random sampling of control infants from births occurring between 10/1/1991 and 9/30/1993 in New Zealand were used with a case-control methodology. During the initial interview, and again when the infants were two months of age, data were collected on such variables as parental smoking during the previous 24 hrs, type of infant feeding, infant sleeping position and whether infant slept with the mother. Additional information obtained in the initial interview included infant's gender, birth weight, and gestation length, as well as maternal age, marital status, education, ethnicity, parity, antenatal care, and smoking habits.

Maternal smoking during pregnancy was associated with elevated incidence of SIDS with an OR of 6.05 (95% CI 3.90-9.40). After birth, the risk of SIDS increased with increasing levels of maternal smoking in the previous 24 hrs. At the initial interview, when mother and child did not share the bed, the SIDS risk associated with postnatal maternal smoking of 1-19 cigarettes/day had an unadjusted OR of 5.84 (95% CI 3.72-9.21) that increased to 14.89 (95% CI 6.38-34.72) with 20 or more cigarettes. At the two-month visit, these ORs were 4.90 (95% CI 2.65-9.06) and 21.42 (95% CI 6.89-66.52), respectively. After adjusting for maternal age, marital status, age mother left school, parity, infant gender, ethnicity, birth weight, sleep position and breastfeeding, the OR for SIDS associated with maternal smoking at two months of age was 1.43 (95% CI 0.58-3.51) which increased to 5.02 (95% CI 1.05-24.05) with bed sharing (Table 4.3). The increased SIDS risk when a child shares the bed with a smoking mother may be due to more concentrated ETS exposure. By comparison, there was no significant increase in SIDS when a nonsmoking mother and child shared the bed (OR 1.03; 95% CI 0.21-3.51). Paternal smoking was also

associated with an increased risk at both the first (OR 3.84; 95% CI 2.49-5.92) and second (OR 3.21; 95% CI 1.81-5.71) visits. These data support postnatal ETS exposure as a risk factor for SIDS independent of prenatal smoke exposure.

Table 4.3 Risk of SIDS with Maternal Postnatal Smoking and Bed-sharing

Bed-sharing/ Maternal smoking	SIDS OR adjusted (95% CI) 1st visit	SIDS OR adjusted (95% CI) 2 month visit
No/No	1.00	1.00
No/Yes	1.68 (0.84-3.34	1.43 (0.58-3.51)
Yes/No	0.55 (0.17-1.78)	1.03 (0.21-3.51)
Yes/Yes	5.01 (2.01-12.46)	5.02 (1.05-24.05)
Paternal smoking	3.84 (2.49-5.92)	3.21 (1.81-5.71)

Brooke et al. (1997) examined the relationship between infant care practices and the incidence of SIDS in Scotland from 1992 to 1995. Of the 798 post-perinatal deaths recorded with the Scottish registrar general, 201 were diagnosed as SIDS. Controls were matched for age, season of birth and maternity unit. Questionnaires were completed by the mothers during a home visit and provided core medical and social data as well as information on prenatal factors, feeding regimen, sleeping habits and environment, illnesses, and exposure to smoking. Odds ratios were calculated from both uni- and multivariate analyses, with the latter adjusted for a large number of factors including specifics of sleeping position and habits, gender, maternal age and education, birth weight, breast feeding, social class, parity, drug use, and parental smoking. Parental smoking was significantly associated with SIDS (p= 0.0001). If both parents smoked, the adjusted OR for SIDS was 5.19 (95% CI 2.26-11.91) while the OR for maternal only smoking was 5.05 (95% CI 1.85-13.77). Paternal-only smoking had an OR of 2.12 (95% CI 0.99-4.56). A dose response was associated with increased smoking by the mother (p=0.0001), father (p=0.0001), and other household members (p=0.001). Due to the size of this study and the continuity of maternal smoking during and after pregnancy, it was not possible to distinguish the effects of pre- versus postnatal maternal smoke exposure. However, an effect of postnatal ETS is suggested by the OR of 2.12 for paternal only smoking, and an elevated risk from other household members smoking.

Rajs et al., 1997. Pericardial fluid was collected at autopsy from 85 infants (50 male, 35 female) under the age of 1 year who died from SIDS (n=67) and non-SIDS (n=18) causes. Infant exposure to tobacco smoke was investigated by questionnaire in 18 cases (61% of the questionnaires sent out). The data collected included prenatal exposure, number of cigarettes smoked per day, smoking in infant's presence, and breastfeeding. Whereas in non-SIDS infants pericardial nicotine decreased with increasing age (p=0.014), in SIDS victims there was a tendency towards increasing nicotine with increasing age (p=0.071). While cotinine levels appeared not to change with age in both groups, for victims under 4 months of age, all infants with cotinine concentrations exceeding 30 ng/ml in the pericardium died of SIDS. Otitis media was noted in 12 of 85 deaths with the highest incidence (33.5%) in infants with high nicotine levels in the pericardium. The incidence of cardiovascular alterations (of unspecified nature) reportedly increased with increasing nicotine and cotinine levels. Foci of mononuclear leukocytes in the pancreas were associated with high cotinine levels (p=0.012). Pathological findings in the upper and lower respiratory tract were associated with intermediate levels of

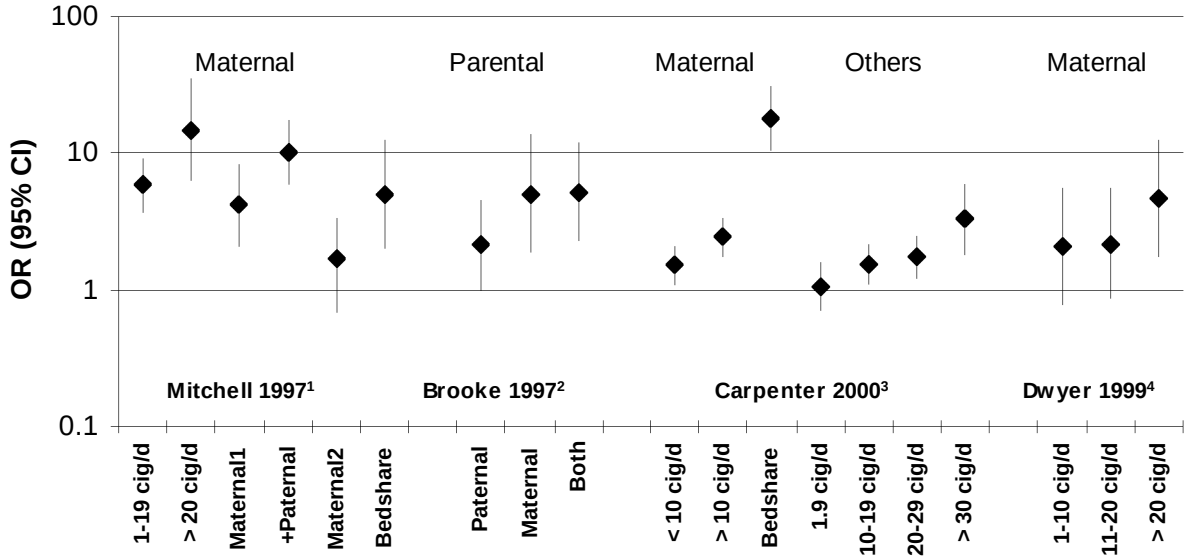
cotinine perhaps indicating that the alterations developed after the metabolism of nicotine to cotinine. Thus, there appeared to be an association between SIDS and levels of nicotine and cotinine in the infant.

This was a small study and the response rate to questionnaires smaller still. Control for other potential contributors to SIDS, such as prenatal alcohol and drug use, presence of infectious agents, diet, etc. was not uniform across subjects. There was likely bias in the smoke exposure data as the highest nicotine and cotinine levels were found in infants whose parents failed to return the questionnaires. Since there was no control for mother's prenatal smoke exposure, it is not possible to separate postnatal effects of ETS from prenatal exposure which may have predisposed the infant to SIDS. However the correlation between SIDS and high current nicotine and cotinine implicates postnatal ETS exposure in elevated SIDS risk.

4.1.1.2.1. ETS exposure-response gradient for SIDS

A causal role for ETS in SIDS is supported by the exposure-response gradient evident in the results from several studies. As shown in Figure 4.1 below, the risk of SIDS increases with increasing numbers of cigarettes smoked in the infant's environment. Mitchell *et al*. (1997) in their prospective case-cohort study demonstrated increased risk when both parents smoked, and increased risk with bedsharing when the mother smoked, but not when she was a nonsmoker. In their case-control study in Scotland, Brooke *et al*. (1997) noted higher risks with maternal smoking than paternal smoking. Carpenter *et al*. (2004) demonstrated increasing risks with increasing cigarette consumption as well as bedsharing with a smoking mother. The substantial increase in risk seen when a smoking mother and infant share a bed presumably reflects the effects of intense ETS exposure. In this study household smoking was related to SIDS risk in a dose-dependent fashion. Dwyer *et al.* (1999) also report increasing risk with increasing maternal cigarette consumption.

Figure 4.1 ETS and SIDS: Exposure-Response Effects



[1] Maternal2 and bedsharing adjusted for maternal age, marital status, education, previous pregnancies, infant sleep position, age, ethnicity, gender, breast feeding. Other values, unadjusted. [2] Adjusted for maternal age, sleep position, bed sharing, gestation, parity, maternal education, infant gender, SES, marital status, drug treatment, breast feeding, used mattress, position change at night. [3] Adjusted for maternal age and study centers. [4] Adjusted for infant gender, birth weight, maternal age, season of birth, parity, breast feeding, duration of second stage of labor.

4.1.1.3. Reviews

Thornton & Lee (1998a) reviewed 28 prospective and case-control studies on the relationship between parental smoking and SIDS published from 1966 to 1996. Where available, adjusted and unadjusted relative risk values were extracted from the studies and the factors for which adjustment was made were indicated. An attempt was made to evaluate whether the risk attributed to smoke exposure was in fact attributable to other factors by analyzing the amount by which the risk values were changed after adjustment for confounders.

For maternal smoking during pregnancy, 28 of the 29 unadjusted risk values extracted were above 1.00, many significantly so. Moreover, the extracted adjusted values were also significantly above 1.00 indicating an effect of prenatal smoking on SIDS. However from four of the studies examined (Malloy *et al.*, 1988; Blair *et al.*, 1996; Mitchell *et al.*, 1993; Wierenga *et al.*, 1990) the adjustments reduced the relative risks of SIDS by as much as 59-80%. This was interpreted as indicating that a large portion of the excess risk of SIDS associated with maternal prenatal smoking may be due to other risk factors. Indeed, a large number of pre- and postnatal factors have been found to contribute to the risk of SIDS, many of which, such as lower socioeconomic and education levels, are also correlated with maternal smoking. Thus maternal smoking may well be a marker for some of these risk factors as well as a contributor in its own right.

Similar to the studies of maternal prenatal smoking, the nine studies reporting risks associated with postnatal maternal smoking reported unadjusted risk values significantly above 1.00 with variable and, in some cases, large reductions in risk estimates after adjustment (Table 4.4). This again reflects that multiple factors contribute to SIDS incidence.

Table 4.4 SIDS Risk and Maternal Postnatal Smoking

Study	Unadjusted RR	Adjusted RR	Adjustment factors
Bergman & Wiesner (1967)	2.42 (1.22-4.82)	2.38 (1.17-4.83) 2.05 (1.00-4.24)	Maternal age Education
Blair *et al.* (1996)	5.19 (3.57-7.55)	--	--
Cameron & Williams (1986)	4.04 (2.63-6.20)	--	--
Dwyer *et al.* (1999)	3.13 (1.06-9.26)	Became non-sig.	Maternal age
Klonoff-Cohen *et al.* (1995) Any Same room	 3.13 (1.75-5.60) 6.17 (2.60-14.61)	 2.28 (1.04-4.98) 4.62 (1.82-11.77)	Antenatal classes, breast feeding, birth weight, medical condition, maternal smoking prenatally, sleep position.
McGlashan (1989)	1.92 (1.26-2.92)	--	--
Mitchell *et al.* (1993) Any In house Never in house	 4.24 (3.35-5.36) 2.20 (1.38-3.51) 5.07 (1.50-15.41)	 1.79 (1.30-2.48) -- --	Postnatal age, antenatal classes, breast feeding, bed sharing, birth weight, gestational age, neonatal intensive care, maternal age and age at first pregnancy, medical condition, months pregnant, pregnancy smoking, race, region, season, education, socio-economic status, sleep position, time of day.

Data from Thornton and Lee (1998a).

Table 4.5 SIDS Risk and Paternal Smoking

Study	Unadjusted RR	Adjusted RR	Adjustment factors
Bergman & Wiesner (1976)	1.53 (0.78-3.01)	-	-
Blair *et al.* (1996)	3.04 (2.13-4.36)	2.50 (1.48-4.22)	Maternal alcohol use, breast feeding, bed sharing, birth weight, illegal drug use, gestational age, maternal age, marital status, parity, socioeconomic status, sleep position, type of birth.
Cameron & Williams (1986)	1.85 (1.32-2.60)	-	-
Klonoff-Cohen *et al* (1995) During pregnancy After birth After birth in same room	 3.56 (2.11-6.00) 3.53 (1.99-6.27) 9.20 (3.66-23.15)	 3.46 (1.91-6.28) 8.49 (3.33-21.63)	Antenatal classes, breast feeding, birth weight, medical condition, maternal smoking in pregnancy, sleep position.
Lewak *et al.* (1979)	No association	-	-
McGlashan (1989)	1.73 (p = 0.05)	-	-
Mitchell *et al.* (1993)	2.41 (1.92-3.02)	1.37 (1.02-1.84)	Postnatal age, breast feeding, birth weight, maternal age, marital status race, region, sex, socioeconomic status, sleep position, time of day.
Nicholl & O'Cathain (1992)	-	1.63 (1.11-2.40)	Birth weight, maternal age, parity, state of major accommodation.

Data from Thornton and Lee (1998a).

Smoking by the father or other partner was investigated in only eight studies (Table 4.5). Two of these studies reported either no or a non-significantly elevated association with SIDS. The rest of the studies reported a significant association including one by Klonoff-Cohen that reported a greater association of SIDS with paternal than with maternal smoking.

After recognizing the limitations of the studies, alternative interpretations and the possible confounding factors, the authors concluded that "for all the indices of exposure considered, there does appear to be evidence of an increase in SIDS risk in relation to an increase in the extent of exposure to tobacco smoke."

4.1.2. Animal Studies of SIDS and Tobacco Smoke Exposure

Slotkin et al., 1999. SIDS is thought to be evoked by episodes of hypoxia; the mammalian response to hypoxia is mediated by the autonomic system acting through cholinergic receptors. Rats were used to model the role of pre-and postnatal nicotine exposure on the expression of cholinergic receptors in neonatal brain and heart. Pregnant rats were implanted with osmotic minipumps to provide continuous delivery of buffer (controls) or nicotine bitartrate to give doses of 2 or 6 mg/kg/day, levels which approximate moderate and heavy smoking in humans. For experiments involving postnatal exposure, pups were given subcutaneous injections of nicotine or vehicle corresponding to 0.3 or 3 mg nicotine, twice daily for 4 days. These injections

occurred on days 1-4, 11-14, or 21-24 with the animals necropsied on days 5, 15 or 25 and the hearts and brains removed for receptor determinations.

In cardiac tissue, acetylcholine decreases contraction rate via its activation of cardiac muscarinic type 2 receptors (M2) and the subsequent inhibition of adenylyl cyclase. In the heart, prenatal but not postnatal nicotine exposure at both doses caused a significant overall increase in M2 receptor numbers and binding at 18 days of age ($p<0.03$) as shown by receptor binding assays. Nicotine exposure has been shown previously to cause a decrease in ß-adrenergic receptors (Navarro *et al.,* 1990). These changes in receptor numbers altered cellular function as manifested in the ability of muscarinic and adrenergic agonists to modify adenylyl cyclase activity in cardiac membrane preparations. As would be expected from an increase in the inhibitory M2-receptors concomitant with a decrease in ß-adrenergic receptors, isoproterenol, a ß-adrenergic agonist, showed an impaired stimulatory response with nicotine treatment while carbachol, a muscarinic receptor agonist, showed enhanced inhibition of adenylyl cyclase.

In contrast to the heart, prenatal nicotine exposure did not enhance M2 receptor numbers in the brainstem. Instead the entire pattern of receptor acquisition and loss was delayed so that deficits were seen early in postnatal development. Also, unlike the heart, administration of nicotine immediately after birth caused a deficit in brainstem M2 receptors similar to that seen with prenatal exposure that was significant at the higher dose (3 mg/kg/day; $p<0.02$). While nicotine decreased M2 receptors in the brainstem, both doses increased nicotine receptors on day 5 after 4 days of postnatal nicotine exposure. However, on days 11-14, this up regulation was seen only at the higher dose and was not seen with either dose after treatment on days 21-24. The authors suggest that these data indicate a late prenatal to early postnatal window of sensitivity to these effects of nicotine in rats, the timing of which is developmentally equivalent to the last trimester in humans.

The maintenance of cardiac function, and thus cerebral perfusion, are dependent on catecholamine release and on the transduction of the adrenergic signal via cardiac ß-receptors. In contrast, the inhibitory vagal innervation is competent earlier, can be activated by stress, and operates on the cardiac signaling pathway mediated by M2 receptors. Thus the reduction in the stimulatory ß-adrenergic receptors and the increase in inhibitory M2 receptors induced by nicotine exposure will impair cardiac performance during periods of hypoxic stress. In addition, the observation in this study of a nicotine-induced reduction in brainstem muscarinic receptors parallels that seen in infants who have died from SIDS. In these infants there was decreased binding in brainstem areas associated with cardiorespiratory functions (Kinney *et al.,* 1995). Thus via nicotine, ETS exposure may contribute to the risk of SIDS by impairing the ability of the brain and heart to respond appropriately to periods of hypoxia. The hypoxia in turn may be caused by elevated HbCO, also resulting from ETS exposure.

Froen et al., 2000. Insufficient autoresuscitation following apnea in infancy is associated with SIDS. In addition, at the time of death SIDS victims frequently have a slight infection and a stimulated immune system. Froen *et al*. exposed piglets to nicotine and/or interleukin-1ß (IL-1ß) to simulate the effects of ETS exposure with and without simultaneous infection on autoresuscitation following induced apnea. IL-1ß was used as it is a prototypic inflammatory cytokine released in the inflammatory response accompanying an infection. In these experiments, intravenous administration of IL-1ß (10 pmol/kg) simulated IL-1ß release during

infection. Nicotine exposure (5 µg/kg) was in the same range as that received by an infant exposed to ETS and breastfed by a smoking mother (0.1-6.5 µg/kg). In untreated animals, induction of apnea resulted in a drop in heart rate and blood pressure followed by autoresuscitation and a rapid increase in heart rate, blood pressure and respiration rate. Nicotine treatment resulted in more and repeated spontaneous apneas that prevented the compensatory increase in respiration rate following induced apnea. IL-1ß treatment caused prolonged apneas and an inability to hyperventilate. The effects of nicotine and IL-1ß combined were additive with more spontaneous and longer lasting apneas, loss of normal hyperventilation after induced apnea, and dramatically decreased respiration rates. This resulted in lowered arterial pH and pO_2, and elevated pCO_2 up to 5 minutes after induction of apnea. Thus, in this piglet model, nicotine exposure at levels obtainable in infants exposed to ETS or through breast milk from a smoking mother interferes with normal autoresuscitation after apnea. This effect is significantly worsened in the presence of an underlying infection, both of which predispose to SIDS.

Gospe et al., 1996. This study in rats examined whether ETS exposure *in utero* and/or postnatally altered the biochemical composition of rat brains. Side stream smoke (SS) was used as a surrogate for ETS and had a total suspended particulate concentration of 1.00 ± 0.07 mg/m^3, CO of 4.9 ± 0.7 ppm, and nicotine of 344 ± 85 µg/m^3. The CO concentrations were typical of smoky bars but the nicotine and particulate concentrations were 30 and 10 times higher, respectively. Four scenarios were designed which gave control (filtered air), prenatal only, postnatal only, and prenatal with postnatal exposures. Exposures were for 4 hr/d, 7 d/wk from day 3 of gestation until delivery for prenatal exposure, and from birth to 9 weeks of age for postnatal. At necropsy the brains were removed and divided into fore- and hindbrains. Levels of protein, DNA and cholesterol were assayed in the respective brain halves as indices of brain development.

Prenatal exposure to SS did not alter these three biochemical indices of brain development (protein, DNA and cholesterol levels) whereas postnatal exposure caused a decrease in DNA concentration. No interaction between pre- and postnatal exposures was detected so the data were pooled into two groups: animals with and without postnatal exposure. Postnatal exposure to SS significantly increased mortality during the first 18 days of life (43% of SS vs 14% of controls; $p<0.001$) and decreased body weights at 9 wks ($p=0.012$). In the brains, the SS effect on DNA was more pronounced in the hindbrain which contains the cerebellum and which in the rat undergoes significant postnatal development. The decrease in DNA was significant ($p=0.008$) and indicated a reduction in cell density in this region although the weights of the brain halves were not changed by SS exposure. Compared to the unexposed group, postnatal SS exposure reduced DNA in the forebrain by 2.2% ($p=0.034$) and in the hindbrain by 4.4% ($p=0.001$). This effect was accompanied by an increase in the protein/DNA ratio of 8.4% ($p=0.001$), which is taken as an indication of cell size. These data suggest that in the rat, postnatal but not prenatal SS exposure decreased brain cell numbers but increased cell size. The neurodevelopmental consequences of this change are not known nor is it clear whether these findings apply to humans. This period of postnatal neurodevelopment in the rat is thought to be equivalent to that seen during the last trimester in human fetuses. Nevertheless this study provides a plausible explanation for some of the smoke-associated neurobehavioral decrements reported in other studies.

4.1.3. Summary of SIDS Epidemiological Data

Of the additional ten studies reviewed here, all support an association between maternal postnatal smoking and SIDS with five providing adjusted odds ratios ranging from 1.43 to 5.05 (95% CIs in all cases exclude unity). Three studies found an effect for paternal smoking as well (ORs 1.37-3.84), while a fourth (Dwyer *et al*., 1999) found an association between paternal smoking and cotinine levels but not SIDS. Two studies (Milerad *et al*., 1998; Rajs *et al*., 1997) examined pericardial fluid from SIDS victims and found a strong association between death by SIDS and elevated pericardial cotinine levels indicating substantial exposure to nicotine shortly prior to death. One study (McMartin *et al.,* 2002) found elevated nicotine in pericardial fluid associated with SIDS indicating exposure occurred just prior to death. Pathophysiological changes associated with smoke exposure included thickening of the walls of the large airways in smoke-exposed, but not unexposed, SIDS victims (Elliot *et al.,* 1998). While the association between ETS and SIDS in these studies is often complicated by maternal prenatal smoking, a postnatal ETS effect is indicated by the association of paternal smoking with SIDS, and the evidence of high cotinine levels in SIDS victims relative to infants who died of other causes.

These data as well as research in animals suggest that ETS has pleiotropic effects in developing systems. In rats postnatal passive smoke exposure alters brain structure. Gospe *et al*. (1996) observed decreased cell numbers in the hindbrain, while Slotkin *et al*. (1999) found altered numbers of muscarinic and nicotinic receptors in the brainstem similar to the alterations seen in the brainstems of SIDS victims. The brainstem areas affected are involved in cardiorespiratory function, and changes in this area could potentially compromise the normal neonatal response to hypoxia. In addition, in piglets, postnatal nicotine depresses normal autoresuscitation following apnea, an effect that is exaggerated in the presence of infection (Froen *et al*., 2000).

4.1.4. Attributable risk

In their meta-analysis of studies controlling for prenatal smoke exposure, Anderson and Cook (1997) derived a pooled adjusted OR for SIDS associated with postnatal ETS of 1.94 (95% CI 1.55-2.43). According to the California Tobacco Control Program (Gilpin *et al*., 2001), 11.4% of children 1-17 years were exposed to ETS at home. Assuming a similar exposure for neonates, and assuming, as the data suggest, that ETS has a causal role in SIDS, a population attributable risk may be calculated. Where *p* is the exposure prevalence of 11.4%, the attributable fraction (a) is given by a = p(R-1)/(p(R-1) + 1) (Lilienfeld & Lilienfeld, 1980b)

$$a = 0.114(1.94-1)/(0.114(1.94-1)+1) = 0.097.$$

In California in 2000 there were a reported 222 deaths due to SIDS (CDHS, 2000b; Table 4-10 for 2000). Thus in 2000 there were an estimated 21 (95% CI 13-31) excess cases of SIDS attributable to ETS exposure in California (222 * 0.097 = 21).

4.2. Cognition and Behavior

4.2.1. Summary of Previous Findings

Some evidence supportive of an association between maternal smoking during pregnancy and impaired cognitive development of the offspring was described in OEHHA's 1997 report. The

evidence of an association with maternal ETS exposure was found to be limited. Evidence suggesting a link between postnatal ETS exposure and impaired cognition and behavior was found to be suggestive, although not entirely consistent.

4.2.2. New Epidemiologic Studies

With respect to behavior, assessing the effects of passive smoke exposure on outcomes as complex as human behavior is problematic at best. Bearing this in mind, two studies are presented that purport to examine the association between a child's prenatal and/or postnatal exposure to passive smoke and the subsequent development of behavior problems.

A recent study by Yolton *et al*. (2005) found that postnatal ETS exposure, as measured by serum cotinine, was significantly inversely correlated with cognitive development in children 6-16 years old as assessed by performance on tests of reading, math and block design. In the prospective study by Maughan *et al*. (2001), following boys and girls from birth to age 16, the childhood onset of behavior problems was associated with both pre- and postnatal maternal smoking in a dose-dependent fashion. The highest risks were associated with heavy prenatal smoking especially when the mother continued to smoke postnatally. When the mother stopped smoking at childbirth, the risks dropped significantly, suggesting an independent postnatal effect of ETS exposure. In the study by Williams *et al.* (1998), externalizing behaviors in 5-yr olds occurred at a higher rate among the offspring of women who smoked during pregnancy and/or after childbirth than among children of nonsmoking mothers.

Yolton et al. (2005). This cross-sectional study used data from NHANES III to analyze the association between serum cotinine levels and results on tests of cognitive and academic performance in 4,399 6-16 year old children. In this analysis, results on the reading and math subtests of the WRAT-R and the block and digit span subtests of the Wechsler Intelligence Scales for Children-III were compared with serum cotinine. There was a significant inverse relationship between serum cotinine levels and performance on cognitive tests. After adjustment for gender, race, region, poverty, parent education, marital status, ferritin and blood lead, as log serum cotinine increased from 1 to 10 ng/ml, there were significant decrements in scores for reading (-2.69 pts, $p < 0.001$) and math (-1.93 pts, $p < 0.001$, $b = -0.76$. $p=0.01$) based on a standardized mean of 100, and block design (-0.55 pts, $p < 0.001$) but not digit span (-0.08 pts, $p > 0.05$), based on a standardized mean of 10. The mean reading score among children with serum cotinine levels < 0.1 ng/ml was 94.7. Decrements in this score were seen at higher cotinine levels: -2.6 pts at 0.1-1 ng/ml, -2.8 pts at 1-3 ng/ml, and –7.4 pts at > 3 ng/ml. Using population estimates with appropriate sampling weights, the authors estimated that over 33.3 million children are at risk for ETS-related reading deficits. Similar trends were observed for math and block design scores. This study was limited in that neither the cognitive ability of the parents nor the quality of the home were assessed.

Maughan et al., 2001. The prospective 1970 British birth cohort study (BCS70) was the source of data for this study on pre- and postnatal maternal smoking and the incidence and age at onset of antisocial behavior in both male and female offspring. The study followed 2,969 boys and 2,801 girls from birth to age 16. Follow-up was by questionnaire at ages 5, 10 and 16 years. Data from medical examinations, parental interviews, and cognitive tests and questionnaires completed by the children were included in the study. The study measures collected when the

children were one month of age included gestational age, birth weight and maternal age, maternal smoking and drinking habits, parental education and social status, family structure and stability, and home environment. In addition, mothers and adolescents at age 16 completed the Malaise Inventory to provide an index for depression. At age 5, the children's abilities and attainments were assessed with the English Picture Vocabulary Test (EPVT). Conduct problems at ages 5 and 10 were assessed by the parents with the Rutter A2 behavior rating scales, a modified form of which was used when the children were 16.

Over 40% of the mothers smoked during pregnancy and their offspring were of lower birth weight, had significantly lower vocabulary scores at age five ($p<0.05$) and lower reading scores at age 10 ($p<0.05$). Compared with nonsmokers, and after controlling for gender, socioeconomic status, maternal age, family instability, maternal depressive symptoms, child ordinal position in the family, hyperactivity, and poorer vocabulary and reading skills, logistic regression analysis showed that children whose mothers smoked 5-14 cigarettes per day prenatally had an OR for conduct problems of 1.48 (95% CI 1.18-1.85). For the heaviest smokers the adjusted OR was 1.53 (95% CI 1.17-2.00). With heavy maternal prenatal smoking, conduct problems also tended to persist into adolescence with an OR of 1.69 (95% CI 1.08-2.63). Among sons of heavy smokers, 30% with childhood-onset conduct problems showed persistent conduct problems by age 16 compared with 21.5% of sons of nonsmokers. Among daughters of heavy smokers the persistence rate at age 16 was 29.2% versus 13.2% for girls of nonsmokers.

To determine to what extent postnatal maternal smoking contributed to the observed effects, the authors repeated the logistic regression analysis but with a 3-point cumulative index of postnatal smoking reflecting how many times (0, 1, 2) the mother reported smoking at the 5 and 10 year assessments. Controlling for the factors above, this index was significantly associated with an increased risk for conduct problems (OR 1.17; 95% CI 1.04-1.32). However, this effect was primarily associated with persistent smoking. That is, the adjusted OR for children of mothers who reported smoking at only one of the follow-ups was 1.20 (95% CI 0.88-1.62), not significantly different from nonsmokers' children, while for children of persistent smokers, the adjusted OR was significant at 1.37 (95% CI 1.07-1.74) with the effect becoming more pronounced as the number of cigarettes smoked increased. A weakness of this study was the estimation of smoke exposure from self-reports with no independent biochemical verification.

Overall this study supports an effect of both prenatal and postnatal smoking on the development of conduct problems. The highest risks were among children whose mothers smoked heavily during pregnancy and after. However, if the heavily smoking mother quit after pregnancy, the risk dropped to slightly above that for nonsmokers. This unexpected result suggests a significant postnatal effect of ETS exposure.

Williams et al., 1998. This was a prospective study of behavior in 5,342 5-year old children whose mothers had been recruited early in pregnancy into the Mater University of Queensland Study of Pregnancy. Information regarding social characteristics of the family and psychological characteristics of the mothers was collected at enrollment, 1 or 2 days after birth, and again at 6 months and 5 years after delivery. At each time point, data were collected on the mother's smoking behavior. At the visit right after birth, this included smoking behavior during the last trimester, while at the 6 month and 5 year visits, smoking behavior for the previous 7 days was recorded. At the 5-year follow-up, mothers completed a modified Child Behavior Check List

(CBCL; Achenbach & Edelbrock, 1981), and developmental, behavioral and health information was collected on the child.

Externalizing behavior problems (destructive behaviors, tantrums, mood swings, etc.) at 5 years of age, as assessed by the mothers on the CBCL, were classified progressively according to maternal smoking status before, during and after pregnancy. Never smoking mothers had the lowest rate of child behavior problems (7.9%, n = 2457) compared to mothers who smoked throughout (14.7%, n = 1364). Women who had never smoked until after childbirth and who were smoking at the 5-year follow up also reported increased rates of behavior problems (13.3%, n =113; p = 0.04). After adjustment for smoking at other times and numerous potential confounders such as maternal age at child's birth, education, marital status, social class, parity, child's gender, employment, etc., the relative risks for externalizing behaviors associated with postnatal maternal smoking suggested a dose-dependent increase with numbers of cigarettes smoked per day: none, RR = 1; 1-9, RR = 1.65; 10-19, RR = 1.87; ≥ 20, RR = 1.54. Although not presented, the authors claim the 95% CIs excluded unity in all cases. After further adjustment for maternal mental health, these estimates were reduced somewhat (none, RR = 1; 1-9, RR = 1.52; 10-19, RR = 1.87; ≥ 20, RR = 1.29) and only the estimate for 10-19 cigarettes per day had a 95% CI reportedly excluding unity. Assuming a cause and effect relationship, the authors calculate that maternal smoking during pregnancy may account for 25% of the reported behavior problems while maternal smoking when the child was 5 years of age may account for an additional 16%.

One of the strengths of this study is the control for a wide variety of potentially confounding and intervening variables. While this included the more commonly controlled variables of maternal and gestational ages, educational level, social class, marital status, employment, child's gender, and age at follow-up, it also included parent's country of birth and ethnicity, mother's religiosity, and number of other children. More importantly the mother's mental health was measured using the Delusion-Symptoms Status inventory in an attempt to control for the potential influence of maternal anxiety or depression on the child's behavior.

4.2.3. Conclusions

There is some suggestive evidence that both behavior and cognition are adversely affected by postnatal ETS. Due to the tendency of smoking mothers to smoke both during and after pregnancy, prenatal smoke exposure is likely to have contributed to the observed effects. However, the correlation of cognitive test scores with serum cotinine levels in children (Yolton *et al*., 2005), the observation that the risk of externalizing behaviors drops to near control levels if heavily smoking mothers stop smoking after childbirth (Maughan *et al*., 2001), and the increase in rates of childhood conduct problems among children whose mothers start smoking after pregnancy compared with never smoking mothers (Williams *et al*., 1998), all indicate a postnatal effect of ETS.

4.3. Postnatal Physical Development

No new studies were found that addressed postnatal physical development in terms of altered height and weight gain. Recent studies have focused on more subtle effects of ETS on a variety of endpoints that impinge on development of specific organ systems. These include the

cardiovascular system and depressed HDL-C levels, allergic sensitization in the immune system, middle ear disease which affects auditory development, elevated nucleated RBCs reflecting effects on the developing hematopoietic system, and dental caries.

4.3.1. Auditory Effects (and Secondary Neurodevelopmental Effects)

Bennett & Haggard, 1998. In this study, data from a large birth cohort of 9,000 to 11,000 children in the United Kingdom were analyzed to examine the various risk factors for childhood middle ear disease (MED) including passive smoke exposure. For children in this cohort, medical and social background data were collected from the mothers by questionnaire at birth and periodically thereafter until age 21. Two markers for inner ear disease were employed: whether or not the child had suspected or confirmed hearing difficulty up to 4 years of age, and similarly for ages 4-5; and whether or not there had been any purulent ear discharge during these two time periods. Potential confounders such as non-specific ear-nose-throat (ENT) disease and the child's general health were controlled. Potential risk factors for MED such as gender, day care, length of breastfeeding, parental smoking habits, birth weight and mother's age, were treated as independent variables.

Preliminary analyses indicated little difference in the reported rates of ear discharge or hearing difficulties between the two age groups so the data for both time periods were combined. In a multiple logistic regression model controlling for social status and non-specific ENT disease, only maternal smoking was significantly associated with ear discharge with an adjusted OR of 1.28 (95% CI 1.13-1.45). The percentage of children with ear discharge also showed a dose response associated with the number of cigarettes smoked (no cigarettes, 10.5%; 1-14, 11.6%; ≥ 15, 12.1%). After inclusion of the mother's smoking habits, none of the other independent variables was significant. Similarly maternal smoking was associated with hearing difficulties with an OR adjusted for social index and mouth breathing/snoring of 1.31 (95% CI 1.14-1.51). For the combined outcome of ear discharge and hearing loss, adjusted for social index and infant general health score, maternal smoking was associated with an OR of 1.60 (95% CI 1.21-2.11). Male gender and attendance in day care were also significant risk factors for MED.

Smoking during pregnancy showed a significant dose response relationship for ear discharge at 5 years, but it was not included as a separate entry in the regression model due to the inter-relation with postnatal smoking. Mothers who smoked prenatally tended to smoke postnatally as well. However, whereas the percentage of children with both discharge and hearing loss was 2.4% for non-smoking mothers, this rate was 2.9% if the mother stopped during pregnancy, but 3.8% if she smoked 1-14 cigarettes per day ($p = 0.001$) during pregnancy and after. This suggests that ETS exposure postnatally had a deleterious effect on hearing on top of that seen from *in utero* exposure to maternal smoking. In this study, paternal smoking was not seen to have an effect. It is possible that the presence and severity of the manifestations associated with postnatal ETS reflect an interaction with conditions created by prenatal exposure, conditions which render the infant more susceptible to postnatal ETS. The significance of an ETS effect on hearing derives from observations that children with mild hearing loss associated with otitis media show deficits in higher order auditory processing (Gravel *et al.,* 1996) which in turn may cause delays in language acquisition and academic development.

4.3.2. Cardiovascular, Hematological and Immune Effects

The role of passive smoke exposure in the development of cardiovascular disease in adults is the subject of another chapter. However children may also be at risk as suggested in the following study by Moskowitz *et al*. (1999) in which children persistently exposed to ETS had significantly lower serum levels of high density lipoprotein cholesterol (HDL-C), a risk factor for coronary heart disease (CHD). This effect was exacerbated if the family had a history of heart disease. Although no control for diet was evident, these results suggest a potential interaction between ETS and other risk factors for CHD in children. In addition, normal cardiac development in rats appears to be disrupted by prenatal nicotine exposure (Slotkin *et al*., 1999), and this effect may also apply to children and have consequences for SIDS incidence.

Moskowitz et al., 1999. Most investigations of the association between coronary heart disease (CHD) and ETS focus on adults. In this study, Moskowitz *et al*. examined how CHD risk factors, passive smoking, sex and race are related in pubertal children. Data were collected during four visits at 18-month intervals from 408 twin pairs from 11-15 years of age. Information on family and health histories, smoking, alcohol use, blood pressure, and anthropometrics was collected by questionnaire and during interview. Biochemical assays provided data on blood HDL-C, LDL-C, and cotinine. HDL-C subfraction 2 (HDL_2) was also assessed as most of the variation in HDL-C is due to this subfraction and others have shown that CHD deaths occur more frequently in families with low levels of HDL_2-C (Bodurtha *et al.,* 1987). Children with long-term passive smoke exposure had lower HDL-C than kids from nonsmoking families (visit 1: 1.21 ± 0.26 vs 1.31 ± 0.26 mmol/L; $p \leq 0.01$); similar results were observed for HDL_2 (0.31 ± 0.18 vs 0.41± 0.19 mmol/L, $p \leq 0.001$). The deleterious effects of passive smoke exposure on HDL-C levels were more pronounced in children of families with a history of cardiac disease versus those without as reflected in lower HDL-C levels (visit 1: 1.18 ± 0.23 vs 1.25 ± 0.23 mmol/mL; visit 4: 0.98 ± 0.10 vs 1.19 ± 0.18 mmol/mL; $p<0.001$). It is not clear to what extent these results are confounded by diet. Nevertheless, this study suggests that in children also, ETS exposure has a deleterious effect on HDL-C levels. Whether these effects persist into adulthood and/or increase the incidence of CHD later in life is not known.

Dollberg et al., 2000. The effects of maternal ETS exposure on absolute RBC counts were assessed in newborn infants of 55 mothers exposed and 31 not exposed to passive tobacco smoke during the last trimester. This study included only infants who were appropriate for gestational age and excluded infants of women with gestational or insulin-dependent diabetes, pregnancy-induced hypertension, placental abruption or placenta previa, any maternal heart, kidney, lung or other chronic condition, drug or alcohol abuse, perinatal infections, or infants with low Apgar scores. Complete blood counts were performed on venous blood collected within 12 hrs of birth.

There were no significant differences between exposed and unexposed groups for birth weight, gender, maternal age, gravidity or parity. However, gestational age in the smoking groups was slightly but significantly longer than in controls (< 1 week; $p=0.046$). While there were no significant differences between groups in counts for total RBCs, white blood cells, platelets or absolute lymphocytes, the counts of absolute nucleated RBCs were significantly elevated in the passive smoke-exposed group ($p = 0.02$). The mean counts (range) were 357 (0-5100) for children of passive smokers versus 237 (0-1700) in controls.

Elevation of nucleated RBCs in the neonate is a marker of fetal hypoxia. The authors have previously reported elevated nucleated RBCs in infants of actively smoking mothers in which, as in this study, the hematocrit was not significantly different between exposed and control groups. Although the mechanism(s) by which smoking may cause elevated nucleated RBCs is not known, it is thought to be related to hypoxia associated with smoke-induced fetal HbCO and/or nicotine-induced placental vasoconstriction. Periods of hypoxia may stimulate bone marrow to increase the hematocrit possibly in concert with a smoke-induced more rapid RBC turnover. This study suggests that maternal passive smoke exposure has qualitatively similar effects on the fetus as active maternal smoking.

This study was relatively small. Smoking history was obtained from the mother only and not verified by biochemical measures or by other family members. On the other hand, the prospective design of this study facilitated control of potentially confounding health conditions and minimized recall bias.

Kulig et al., 1999. The incidence of allergic sensitization associated with prenatal and postnatal smoke exposure during the first three years of life was examined in this study. Sensitization was indicated by the detection of specific IgE antibodies by immunoassay. Smoke exposure was assessed by questionnaire at birth, 18 months and 3 years of age. There were four exposure categories: 178 children were not exposed; 63 were exposed only postnatally and only to the father; 28 were exposed postnatally to the mother and possibly the father; and 74 were exposed both pre- and postnatally by the mother and possibly the father. Sensitization to food, outdoor, cat or mite allergens was assumed if specific IgE antibodies were detected at least once during the first three years. Data were gathered on gender, family history of atopy, duration of breastfeeding, and parental education. Diet was not evaluated although it might be expected to have a significant effect on the development of allergies to specific foods.

After adjusting for gender, parental education and study center, and compared with children never exposed to ETS, children exposed to mother's smoking both pre- and postnatally were much more prone to developing food allergen sensitivities with an OR of 2.3 (95% CI 1.1-4.6). Postnatal only ETS exposure from the mother was associated with an OR for food allergen sensitivity of 2.2 (95% CI 0.9-5.9). There were no significant associations between ETS exposure and sensitivity to outdoor, cat or mite allergens, nor between any allergen group and exposure to ETS from the father only. This study suggests that both prenatal maternal smoking and postnatal ETS exposures, separately or combined, have the capacity to adversely affect the developing immune system and render the child more susceptible to food allergies. That this effect was not observed for inhalant allergens may be related to the fact that allergic sensitization in infancy generally occurs first to food. Smoke exposure appears to act early in development and, in combination with food allergens, may interfere with the normal development of immunological tolerance.

4.3.3. Miscellaneous Effects – Dental Caries

Aligne et al., 2003. Dental records and serum cotinine levels, collected during NHANES III for 3,873 children, 4-11 years old, were used in this retrospective cross-sectional study of the association between ETS exposure and dental decay. In a logistic regression analysis adjusted for age, ethnicity, education of the household head, poverty, blood lead, time since last dental

visit and geographic region, serum cotinine level was a significant predictor of caries in deciduous teeth. The adjusted OR for decayed surfaces was 1.8 (95% CI 1.2-2.7) and 1.4 (95% CI 1.1-2.0) for the presence of fillings. Sugar consumption and gender were not included as they were not significant factors in bivariate analyses. A significant association of ETS with dental decay was seen only for deciduous teeth but not permanent teeth. This suggests that ETS exposure has a deleterious effect on dental health that is most pronounced if it occurs early in life, perhaps during the formation of tooth enamel.

4.4. Respiratory Development and Function

Respiratory development and function is covered in Chapter 6 (6.2.3)

4.5. Chapter Summary and Conclusions

This update presents data that strengthen the conclusion in the 1997 report that ETS is causally associated with elevated SIDS risk. In its examination of the association between smoke exposure and SIDS, the 1997 Cal-EPA report reached the following conclusion:

"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 posnatal 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."

This conclusion is substantiated by the more recent research reviewed here. While the ability to clearly separate the effects of prenatal from postnatal smoke exposure is limited in most studies, the meta-analysis by Anderson and Cook (1997) included four studies reporting postnatal effects of ETS on SIDS after controlling for prenatal maternal smoke exposure (pooled OR 1.94: 95% CI 1.55-2.43). In addition, the finding of elevated cotinine (Milerad *et al*., 1998; Rajs *et al*., 1997) and/or nicotine (McMartin *et al*., 2002) in tissues of infants who died from SIDS compared to non-SIDS deaths supports a postnatal effect of ETS. It could be argued that these levels merely reflect a continuation of smoke exposure that started prior to birth. However, the observation by Alm *et al*. (1998) that cessation of maternal smoking at parturition is associated with a dramatic drop in the risk of SIDS compared to that seen with continued smoking argues for a postnatal ETS effect. So too do the studies that find increased risks for SIDS associated with paternal smoking (Brooke *et al*., 1997; Mitchell *et al*., 1997).

The association of ETS with SIDS is further strengthened by the delineation of several probable mechanisms based on tobacco-related changes in the brainstem regions controlling cardio-respiratory responses, the muscarinic and adrenergic receptors in the heart, and thickening of the airways in the lungs noted in animal studies. In the animal models, the noted changes in muscarinic and adrenergic receptors inhibit autoresuscitation following apnea. Infants exposed to tobacco smoke also tend to have inflamed airways and are at higher risk of developing allergies and pulmonary infections. These conditions in combination with an infant's potentially ETS-compromised ability to resuscitate in response to smoke or apnea-induced hypoxia

significantly increase the chances of SIDS occurring in ETS-exposed infants. Indeed we estimate that in California in 2000, despite the low exposure of infants to secondhand smoke compared to the rest of the country, approximately 10% of the SIDS deaths (21/222) were attributable to ETS.

With respect to neurobehavioral effects, there is epidemiological evidence suggesting that maternal smoking during pregnancy has deleterious effects on neurodevelopment. Behavioral outcomes as manifested in childhood conduct problems appear to be negatively influenced by ETS exposure. However, the role of postnatal ETS exposure in cognitive development has been less extensively studied and, as a result, it is not clear to what extent ETS exposure may directly modify a child's cognitive development. The studies in this area are limited in number but suggest that pre- and/or postnatal passive smoke exposures may increase the risk for conduct disorders in the children so exposed.

ETS exposure has negative effects on diverse systems and exacerbates underlying conditions. Its effects on the immune system likely increase the development of allergies in exposed children. ETS-associated decreases in HDL-C in children may predispose to the subsequent development of heart disease, while the increase in middle ear disease associated with ETS influences auditory and neural development. The risks associated with each of these effects individually may be cumulative and the large and diverse number of effects increases the likelihood that ETS exposure will have a significant negative impact on exposed individuals.

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Chapter 5. Reproductive Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and reproduction from the 1997 OEHHA report (Cal/EPA, 1997) and this update are provided below in Table 5.0. The conclusions are based on a weight of evidence approach. In summary, there is evidence suggestive of an association between ETS exposure and fertility and menstrual cycle disorders.

Table 5.0 ETS and Reproduction: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	# Additional Studies in Update	Findings: OEHHA 1997 Evidence of causal association?	Findings: Update Evidence of causal association?
Fertility or fecundability	8	7 [1]	Inconclusive	Suggestive
Lower age at Menopause	2	1	Inconclusive	Inconclusive
Male reproductive Dysfunction [2]	0	1	Not assessed	Inconclusive

[1] Includes 2 studies suggestive of menstrual cycle disorders.

[2]. The one new study evaluated male reproductive function in adults of mothers who smoked during pregnancy.

5.0. 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 prior to the 1997 review (Cal/EPA, 1997) or since have investigated the effects of ETS exposure on male and female reproductive function. Of these, most have examined delay to conception in women who eventually achieve pregnancy as an indication of sub-fecundability. Many of these studies were designed to look at the woman's active smoking, not ETS exposure, but also reported the husband's smoking status, a surrogate for ETS exposure used in studies of other outcomes. It should be noted that although husband's smoking can be a surrogate for ETS exposure of the wife, the direct effects of active smoking on sperm complicate the analysis of effects on female reproductive function. Three of the studies reviewed for the 1997 report and one published since then (Table 5.1) 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. Unlike the 1997 review, this report also includes two studies of the effect of ETS on pregnancy rates in women enrolled in assisted reproductive technology programs such as in-vitro fertilization and gamete intrafallopian transfer (GIFT).

The discussion below 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 provides 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.

5.1. Female Fertility and Fecundability

In epidemiological studies, measurement of female fertility (ability to reproduce, as measured by actual live births) 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 and timing of coitus relative to ovulation, 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 multigeneration study in rodents are the fertility index, the fecundity index, the mating index and the parturition index; prior to 1997 multigeneration studies had not been conducted with tobacco smoke. However, a newer study is reviewed in this report. 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.

5.1.1. Findings on Human Studies of Female Fertility and Fecundability and Active Smoking from the 1997 OEHHA Report

The following finding was included in the 1997 report:

"Active smoking by women has been found to be associated with decreased fertility in a number of studies (reviewed in Stillman *et al.*, 1986; Spira *et al.*, 1987; Westhoff, 1990). 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 which 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."

5.1.2. Human Studies of Female Fertility and Fecundability and ETS Exposure

5.1.2.1. Summary of Previous Findings

The 1997 report reviewed three studies that examined conception delays (in women who eventually became pregnant) with respect to spousal smoking habits. Two of the studies (Suonio *et al.*, 1990; Olsen, 1991), both conducted in Scandinavia, found significantly increased risks (about 30%) of conception delays (of six to twelve months). This approaches the magnitude of increased risk reported for active smoking by Suonio *et al.* (1990) (50%) and by Olsen (1991)

(67% to 89%). 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). 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 was defined as spousal smoking in these studies, the association seen may have been due to direct effects on the husband's sperm or reproductive function. The authors of the report concluded that it was not possible to determine from the studies conducted to date whether ETS exposure as an adult is associated with female fertility.

The 1997 report also reviewed three studies that 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 was associated with a statistically significant increase in the fecundability ratio, or likelihood of conceiving; the third study did not confirm this finding. No mechanism to explain this increased fecundability has been suggested by the data collected to date. The 1997 report concluded that the data were inadequate to determine whether there is an association of ETS exposure with effects on fertility or fecundability.

Table 5.1 ETS Exposure and Infertility or Fecundability: Adult and In-utero Exposure

Authors (yr) Location	Design (study size)	Exposure Definition/Measure	Results[1]	Comments
Hull *et al.* (2000) United Kingdom	Retrospective study of pregnant women (n=8,559)	Partner or other household members smoking. Exposure to cigarette smoke at work	OR of delay to conception > 6 months for passive exposure only, at home or at work = 1.17 (1.02-1.37). OR of delay to conception >12 months for passive exposure only, at home or at work =1.14 (0.92-1.42)	Adjusted for several important confounders.
Jensen *et al.* (1998) Denmark	Prospective study of couples planning a pregnancy, followed for 6 menstrual cycles or until pregnant (n = 430)	Husband smoking, exposure *in utero* and during childhood	FR 0.70 (0.48-1.03) for nonsmoking women exposed *in utero*. Present smoking in husbands exposed *in utero* reduced FR to 0.83 (0.53-1.30), but was not statistically significant.	Eliminated cycles where no intercourse occurred during ovulation period. Controlled for BMI, alcohol intake, and reproductive diseases.
Chung *et al.* (1997) United States (Florida)	Prospective study of women undergoing gamete intrafallopian transfer (GIFT). (n=98)	Any household member smoking, including husband	No difference in pregnancy rates between passive smokers and nonsmokers. Live birth rates were 23.1% in passive smokers and 33.3% in nonsmokers. This difference was not statistically significant ($p > 0.05$).	Small sample size (only 13 passive smokers), limited power to detect effect. Looked at possibly confounding variables such as age and diagnosis, but did not adjust for these. Pregnancy and live birth rates significantly lower in active smokers.
Sterzik *et al.* (1996) United States	Prospective study of women attending an in-vitro fertilization program (n=197)	Cotinine concentration in follicular fluid.	No difference in fertilization or pregnancy rates among nonsmokers, passive smokers and smokers.	No adjustment for confounders.
Bolumar *et al.* (1996) Several European countries	Retrospective interview of pregnant volunteers (n = 2,587). Population-based sample of women who had planned a pregnancy (n=3,553)	Husband smoking	No association of male smoking with delay to conception (> 9.5 months) after adjustment for confounders.	Large sample size and control for several confounders, including frequency of sexual intercourse. Prospective analysis in a population based sample. Husband's smoking only asked as yes/no.

1OR = odds ratio:, BMI = Body Mass Index , FR = fecundability ratio, which indicates probability of conception at each cycle. FR >1 indicates improved fecundability, whereas FR <1 indicates sub-fecundability, when comparing 2 groups

5.1.2.2. Newer Epidemiologic Data

Hull et al. (2000) studied pregnant women enrolled in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) in the United Kingdom whose date of expected delivery was between April 1, 1991 and December 31, 1992, and whose pregnancies were at least 24 weeks. Analysis was limited to cases in which the woman's partner was the father of the child, and to women who had conceived intentionally (n=8,559). The authors studied fecundability by measuring time to conception in these women. Time to conception was categorized as < 6 months, 6-11 months, 1-3 years, or > 3 years. Several measures of exposure to tobacco smoke at the time when conception was being attempted were ascertained from a questionnaire: amount of active smoking by the woman, and by her partner (as reported by the partner), and the woman's exposure to ETS from her partner, other household members, or at work. No data were collected on the actual amount of cigarette smoke exposure from other household members or at work.

Information was also collected on a large number of potentially confounding variables including number of previous pregnancies, number of previous live births, ages of the mother and her partner at conception, their ethnic origins, highest education level of the mother and her partner, duration of oral contraception use, mother's and her partner's alcohol consumption, home ownership status, housing type, crowding at home (number of persons per room), years of cohabitation, and the woman's BMI before pregnancy. Stepwise regression was used to determine which of these variables to include in an adjusted logistic regression model of the smoking and passive smoking variables for two outcomes (conception beyond 6 or 12 months of trying).

After controlling for confounders, delayed conception was statistically significantly associated with both active smoking by the woman and by her partner and with passive smoking by the woman (including active smoking by her partner). Passive smoking was not evaluated in the partners. For active smoking by both the mother and her partner there appeared to be a trend in the number of cigarettes smoked and increased odds of taking longer than 6 or 12 months to conceive. In the mother the adjusted odds ratio (OR) for taking longer than 6 months to conceive increased from 1.22 (95% CI 0.92-1.62) for 1-4 cigarettes per day to 1.59 (95% CI 1.28-1.99) for $\geq$ 20 cigarettes per day compared with no active smoking (but women with passive exposure were included in the reference group). A similar trend was seen for smoking by the father and conception by 6 months, and the overall effect of smoking was statistically significant.

The authors also analyzed the woman's exposure to active and passive smoking using nonsmokers not exposed to tobacco smoke as the reference group. In this analysis the adjusted OR for only active smoking (all levels of smoking combined) was 1.23 (95% CI 0.98-1.49) for conception after 6 months and 1.54 (95% CI 1.19-2.01) for conception after 12 months. For passive-only exposure these ORs were, respectively, 1.17 (95% CI 1.02-1.37) and 1.14 (95% CI 0.92-1.42). Finally, for both active and passive smoke exposure these adjusted ORs increased to 1.51 (95% CI 1.27-1.78) and 1.57 (95% CI 1.26-1.96), for conception after 6 months and after 12 months, respectively. The authors also looked at exposure to passive smoke separately at home and at work and found an equally strong effect in both. However, statistical significance was lost when the subgroups were analyzed separately.

This study confirmed the established observation of reduced fertility in women who smoke cigarettes and provided new evidence of delayed conception if the man smokes or the woman is exposed to passive smoking at home or at work. The authors stated that "the fact that a woman's exposure to her partner's smoking did not exert a greater effect than exposure to smoking at work suggests a real effect of passive smoking on the woman that was not confounded by the likely effect of her partner's smoking on his sperm quality." The strengths of this study include very large sample size, detailed information on active and passive smoking and control of several important confounding variables. Limitations of this study include its restriction to one geographic area and its retrospective design. Also there were no data on coital frequency. However, recollection of time to conception has been found to be reliable, and information was collected early in pregnancy. The authors note that the effect of smoke exposure may be a critical factor in women attempting to conceive in later life or those who require treatment for distinct subfertility.

Jensen et al., 1998. This was a prospective study investigating the effects of active smoking and exposure *in utero* and during childhood to tobacco smoke on fecundability in 430 Danish couples recruited during 1992 to 1995. Recruitment occurred via a nationwide mailing of a letter to 52,255 trade union members (metalworkers, office workers, nurses, and day-care workers) who were 20-35 years old, lived with a partner, and had no children. The couples were enrolled when they discontinued birth control, and were followed for six menstrual cycles or until a clinically recognized pregnancy occurred. Both partners completed a questionnaire on demographic, medical, reproductive and lifestyle factors at enrollment and reported changes in occupational exposures and lifestyle factors (including smoking habits) in a monthly questionnaire. Smoking habits were reported as the number of cigarettes, cigars, or pipes smoked per day. Exposure to tobacco smoke *in utero* was ascertained by asking each partner "Did your mother smoke when she was pregnant with you." The men provided a semen sample at enrollment and once during the menstrual period of each cycle. Unlike the women in the Hull (2000) study, who did not report coital frequency, the women in this study recorded sexual intercourse daily. If couples had no intercourse from day 11 to 20 in the cycle, the cycle was excluded from analysis.

Survival analysis was used to determine the cycle-specific association between smoking exposure and fecundability. This was equivalent to logistic regression on the total number of observed cycles with the outcome "pregnant/not pregnant." The reference group was no current smoking or exposure *in utero*. Since passive smoking during childhood was not associated with fecundability in bivariate analyses, this exposure was not included in the final models. They examined several potential confounders and excluded those that changed the association between the smoking variable and fecundability by less than 10%. They performed separate models for women and their partners. The model with male smoking included female smoking but did not include semen quality because this may have masked an effect of male smoking on fecundability.

After adjustment for female body mass index and alcohol intake, diseases in female reproductive organs, semen quality, and duration of the menstrual cycle, the fecundability OR for smoking women who were also exposed to tobacco smoke *in utero* was 0.53 (95% CI 0.31-0.91) compared with unexposed nonsmokers. Fecundability OR for nonsmoking women exposed *in utero* was 0.70 (95% CI 0.48-1.03) and that for female smokers not exposed *in utero* was 0.67 (95% CI 0.42-1.06). If a woman stopped smoking within a year prior to the attempt to conceive,

her fecundability OR was similar to the women who never smoked (1.06, 95% CI 0.63-1.81). Exposure *in utero* was also associated with a decreased fecundability in nonsmoking males (OR 0.68, 95% CI 0.48-0.97). However, present smoking in males did not reduce fecundability significantly.

This study had several strengths, including its prospective design. This allowed the authors to investigate the effects of tobacco exposure on women whose fertility was undetermined at the start of the study, unlike retrospective studies of women who have become pregnant. In addition, detailed exposure information was collected as soon as the women began trying and in each cycle prior to the knowledge of the outcome of the cycle, reducing recall bias and obtaining more accurate measures of exposure. Data on sperm parameters and coital frequency were collected in this study, unlike the other studies of fecundability and exposure to tobacco smoke. Cycles where no intercourse occurred during the period of ovulation were excluded, thus eliminating a possible source of bias. Finally, the authors carefully examined and controlled for a variety of potentially confounding variables. However, excluding semen quality from the confounders included in the adjusted analyses of male fecundability may have affected the validity of those analyses because semen quality could certainly have been a factor independent of the effect of smoking. An analysis stratified by semen quality (good vs. poor) was not performed.

Chung et al., 1997. This study investigated the effects of active and passive smoking on the reproductive outcomes of patients undergoing gamete intrafallopian transfer (GIFT) because of infertility. A total of 98 women who underwent their first GIFT procedures at the University of South Florida from April 1991 to December 1994 were included in the study.

A detailed smoking history, including duration and amount of smoking, was obtained from chart review and an additional telephone survey. Passive smokers were patients who had at least one household member (e.g., husband) who smoked. There were 66 nonsmokers, 19 smokers and 13 passive smokers. The authors also looked at possible confounding variables such as age, diagnosis (unexplained infertility, endometriosis, anovulation, slight male factor, corrected tubal factor or cervical factor), levels of estradiol, total amount of hMG required and number of oocytes transferred. They did not control for these variables in the analysis, but they compared nonsmokers, active smokers and passive smokers with respect to these variables. Active smokers had a higher incidence of anovulation as compared to nonsmokers and passive smokers, and they required a significantly higher amount of hMG for controlled ovarian stimulation (COH). No statistically significant difference was found in the other variables between the groups. The analysis of the pregnancy data was done using a chi-square test of the unadjusted difference in proportions. Active and passive smokers were compared individually to nonsmokers. Pregnancy and live birth rates for active smokers (15.8% and 10.5%, respectively) were significantly lower than those for passive smokers (46.2% and 23.1%) and nonsmokers (45.5% and 33.3%). The authors stated that no difference was noted between the latter two groups. However, there were few passive smokers and the ability to detect a statistically significant difference may have been limited. The observed differences between active smokers and passive or nonsmokers in pregnancy and live birth rates could be caused by a decreased fertilization rate, abnormal tubal transport or decreased implantation rate in smokers.

Sterzik et al., 1996. The purpose of this study was to look at the association between cotinine concentration in follicular fluid (FF) recovered by follicle aspiration and the fertilization and

pregnancy rates in an in vitro fertilization (IVF) program. A total of 197 patients (age range 23 to 39 years) were recruited into the study. Entry criteria were a pathological tubal factor as the cause of sterility, normal spermiogram in the male partner, duration of sterility > 1 year, and positive follicle aspiration (recovery of an oocyte) after hormonal stimulation. The authors assessed history of smoking with a questionnaire but used FF cotinine concentrations to classify women as non-smokers ($\leq$ 20 ng/mL, n = 68); passive smokers (> 20 ng/mL and $\leq$ 50 ng/mL, n = 26); and active smokers (> 50 ng/mL, n = 103), based on a German study of active and passive smoking in pregnancy and serum cotinine levels (Grab *et al.*, 1988). The authors stated that FF cotinine concentrations correlate well with serum concentrations. Fertilization was diagnosed 18 to 24 hours after insemination when two pronuclei were visible. Pregnancy was defined by sonographic detection of positive fetal heart movement $\geq$ 28 days after embryo transfer. The fertilization rate per cycle was 67.6% for nonsmokers, 57.7% for passive smokers, and 67.9% for active smokers. The pregnancy rates were 32.6%, 33.3%, and 32.9%, respectively. None of these differences was statistically significant. However, the authors found a significant difference between active smokers and nonsmokers ($P < 0.025$) for serum concentration of estradiol (E_2), the primary estrogen produced by the ovaries. Between passive and nonsmokers, no significant E_2 level differences were found. Overall a negative correlation was found between cotinine and E_2 values for all patients ($r = -.065$, $P < 0.01$).

The authors concluded that the absence of association between active, passive and nonsmoking and the rates of fertilization and pregnancy in women attending an IVF program was valid only for the specific cohort of patients who were young, had a pathological tubal factor, unimpaired ovarian function, and male partners with a normal spermiogram. They postulated that a reduced quality of the oocytes due to smoking may be compensated by a morphologically and functionally intact spermatocyte. The cutoff they used to distinguish active smokers from nonsmokers and passive smokers (> 50 ng/mL) is higher than the currently accepted cutoff (< 10 or 15 ng/mL) for serum cotinine. Therefore, some of the women they designated as nonsmokers may have had passive smoke exposure. However, they still did not see a difference in fertilization and pregnancy rates between active smokers and nonsmokers. IVF does not mimic natural conception, and this is a serious limitation of this study in terms of generalizing the results.

Bolumar et al., 1996. This study examined the effect of female and male smoking on time to pregnancy in a very large sample of couples from several European countries. Smoking by the male partners was the only measure of passive smoke exposure for the women. Two types of sample were used: population-based samples of women aged 25-44 randomly selected from census registers and electoral rolls who had a planned pregnancy in the past and/or had been attempting to conceive more than 9.5 months prior to interview and were not pregnant (n=3,553); and samples of pregnant women (at least 20 weeks pregnant) who had planned their pregnancies and were recruited during prenatal visits (n=2,587). The outcome studied was subfecundity, defined as time to pregnancy > 9.5 months. Data on smoking were obtained for the time when the women started trying to become pregnant. Women were asked the number of cigarettes they usually smoked per day, and the male partners were only asked whether or not they smoked at this time. In addition to the smoking data, the authors collected data on the following potential confounders: mother's education, paid work, age, parity, alcohol and coffee consumption, use of oral contraceptives within 12 months prior to the starting time, and frequency of sexual intercourse.

The authors found a strong association between female smoking of more than half a pack of cigarettes per day and subfecundity in the population sample for both the first planned pregnancy (adjusted OR 1.7, 95% CI 1.3-2.1) and the most recent attempt to become pregnant (adjusted OR 1.6, 95% CI 1.3-2.1). Similar results were seen in the women recruited during their prenatal visits (adjusted OR 1.7, 95% CI 1.3-2.3). However, no significant association was seen with male smoking in the population sample, (OR 0.9, 95% CI 0.1-1.1, first pregnancy and OR 1.0, 95% CI 0.9-1.3, most recent attempt to become pregnant); or in the prenatal visit sample (OR 0.9, 95% CI 0.7-1.1).

This study had several strengths. First, it included a large population-based sample from several countries and found consistent results across countries. Second, it collected smoking data at the time of the start of the waiting period. Third, it included several important confounders in the analysis such as past use of oral contraceptives and frequency, but not timing, of sexual intercourse. The main limitation of this study was that passive exposure was indicated only by smoking (yes/no) in the male partner. The failure to find an effect of male smoking may have been due to the imprecise measure of cigarette smoke exposure. The Hull (2000) study found an effect of male smoking only for the highest category of smoking.

5.1.3. 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, had not apparently been conducted with tobacco smoke before the 1997 report. However, more recently Florek and Marszalek (1999) studied the influence of exposure to tobacco smoke on mating, fecundity and fertility in rats. They found that the mating index and the fertility index (number of females giving birth/number of mating females) decreased with increasing concentrations of carbon monoxide in the cigarette smoke. However, the fecundity index (number of pregnant females/number of females with evidence of mating) actually increased with increasing exposure. Although trends were present, none of the differences were reported to be statistically significant. However, the authors did not conduct a test for trend in their results.

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.

5.1.4. Discussion and Conclusions – Female Fertility and Fecundability

The human studies published since the 1997 OEHHA report continue to support the association of active smoking in the woman with reduced fertility and fecundability. However, the association with ETS is less clear. Most of the studies used smoking in the male partner as the measure of passive exposure in the woman and did not ascertain number of cigarettes smoked by the male or other measures of possible ETS exposure. Only Hull *et al.* (2000) collected

information on number of cigarettes smoked per day by the male partner. After controlling for several confounders they did find a statistically significant delay to conception if the father smoked, and there was a trend of increasing odds ratios with increasing number of cigarettes smoked per day. These authors also found an effect of exposure to smoke at work by the woman, but the number of women so exposed was too small for this to be statistically significant. The main weakness of that very large study (n=8,559) was that they failed to collect information on frequency of sexual intercourse. In the Bolumar (1996) study smokers in Spain and Italy had less frequent sexual intercourse, while the opposite was true in the Danish and German samples. Thus, coital frequency may have confounded the relationship between ETS exposure and delay to conception. The rest of the studies, which recorded yes/no for male smoking, failed to find a statistically significant delay to conception or reduced fecundability ratio with male smoking. In the Jensen (1998) study present smoking in the husbands resulted in a fecundity ratio of 0.83, but this reduction was not statistically significant. However, exposure to tobacco smoke *in utero* in nonsmoking husbands was associated with a statistically significant reduction in fecundity in that study. There was also a similar, almost statistically significant, reduction in fecundity for nonsmoking women exposed to tobacco smoke *in utero*.

In conclusion, there is suggestive evidence of an association of ETS exposure with effects on female fertility and fecundability. Large, carefully designed studies, including more quantitative measures of ETS exposure, are needed to conclusively verify these effects.

5.2. 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.

5.2.1. 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 two years less than that of nonsmokers. This reduction may be due in part to the anti-estrogenic effect of active smoking (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986). Some studies have also suggested increases in menstrual disorders associated with cigarette smoking (Brown *et al.*, 1988; Sloss and Frerichs, 1983).

5.2.2. Human Studies of Other Female Reproductive Effects and ETS Exposure: Summary of Previous Findings

In its 1997 report, OEHHA reviewed two studies examining the effects of passive smoking on age at menopause. 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. The mean age at menopause was reduced by 2 years among nonsmoking women whose spouses smoked, compared to those whose spouses did not smoke. Whether the decrease of 2 years in the age at menopause was statistically significant was not discussed. After adjusting for some confounders (age, race, education, and alcohol intake) the risk of “early menopause”, which was not defined, was elevated in nonsmokers exposed to ETS compared to

those not exposed (OR 2.1, 95% CI 1.04-4.5). The authors found that childhood exposure to maternal, but not paternal smoking was associated with early menopause. However, only four subjects had mothers who smoked, so the estimate (OR) of the maternal association was probably imprecise. The other study (Tajtakova *et al.*, 1990) provided data on age at menopause and exposure to ETS, but it was published in Slovak. According to the English abstract, those exposed to ETS had a mean age at menopause that was slightly younger than nonexposed nonsmokers. A difference of -0.7 years (95% CI -1.9-0.51) was calculated from data presented in a table. This difference was unadjusted for confounders.

5.2.3. Human Studies of Other Female Reproductive Effects and ETS Exposure: Newer Epidemiologic Data

Table 5.2 ETS Exposure and Other Female Reproductive Effects

Authors (yr) Location	Design (study size)	Exposure Definition/Measure	Results	Comments
Chen *et al.* (2000) China	Prospective study of dysmenorrhea in newlywed, nulliparous nonsmokers (n=165)	Average cigarettes smoked per day by regular household member.	Adjusted ORs of dysmenorrhea for tertiles of exposure Low: 1.1 (0.5-2.6), Medium: 2.5 (0.9-6.7) High: 3.1 (1.2-8.3).	Adjusted for district, body mass index, education, passive smoking at work, and several other work exposures.
Cooper *et al.* (1999) Minnesota	Prospectively collected data on age at menopause. Retrospective smoking information (n=543)	Living with a smoker.	Mean age at menopause 0.6 (-0.2 - 1.4) years higher for never smokers with passive exposure vs. never smokers without passive exposure.	Only 62% of original cohort of college students recorded menstrual data for 5 or more years.
Hornsby *et al.* (1998) Illinois	Prospective study of menstrual function using a daily menstrual diary for 6 months (n=358)	Living with or sharing a workplace with a smoker.	Mean duration of menses 5.8 days in nonsmokers and 5.5 days for passive exposure. Duration of dysmenorrhea (painful menses) 2.0 days for nonsmokers and 2.6 days for passive exposure. P values for trend test (including 2 active smoking categories) = 0.01 for duration of menses and 0.003 for duration of dysmenorrhea.	Controlled for exercise, body mass index, caffeine index, alcohol use, history of tubal ligation, stress and duration of menses.
Cooper *et al.* (1995) North Carolina	Cross-sectional study of follicle stimulating hormone (FSH) (n=290)	Smoking by any household member and *in utero* exposure[1]	FSH concentrations 66% (27%-116%) higher among current smokers (Mean FSH 14.0 mIU/mL), and 39% (4%-86%) higher among nonsmokers with passive exposure (11.7 mIU/mL) compared to nonsmokers without passive exposure (8.4 mIU/mL). *In utero* exposure was not related to FSH levels.	Controlled for age, body mass index, dietary galactose consumption. Evaluated other variables not found to be confounders. Women were ages 38 to 49 years.

1 *In -utero* exposure indicates that the mother of the target participant smoked during her pregnancy

Chen et al. (2000) conducted a prospective study of the effects of ETS on dysmenorrhea in 165 women living in two districts of Shenyang, China. The women were part of an established cohort of newly wed couples recruited to participate in a comprehensive study of the effects of various environmental and occupational exposures on reproductive outcomes. Women with a history of dysmenorrhea were excluded from the study in order to examine the effects of ETS on the incidence of dysmenorrhea. This study had unique advantages over previous studies of menstrual dysfunction. In China, few women smoke cigarettes, but exposure to ETS is high because of the high prevalence of smoking among men. Parity is suggested to be associated with menstrual pain (nulliparous women have a higher prevalence of dysmenorrhea than multiparous women). In this study all the subjects were newly wed, nulliparous, nonsmokers who intended to conceive and thus used no contraceptives during the follow-up period. They completed daily diaries on menstrual bleeding and associated symptoms, exposure to tobacco smoke and other occupational exposures and were followed up until the occurrence of clinical pregnancy or up to 1 year. Dysmenorrhea was defined as 2 or more days of menstrual pain (abdominal or low back pain) during menstrual bleeding. For each menstrual cycle, ETS exposure at home was characterized by the average number of cigarettes smoked per day by regular household members indoors while the subject was present; four ETS subgroups were formed: no exposure and low, medium and high tertiles of exposure. Occupational exposure to ETS was recorded as a yes/no variable.

The 165 women contributed a total of 625 prospectively followed menstrual cycles. ETS exposure was reported in 77% of the cycles. The crude incidence rate of dysmenorrhea in these cycles was 9.7% for the unexposed and 9.4%, 13.8% and 16.9% respectively for the low, medium and high tertiles of ETS exposure. This dose response was also seen when the incidence of dysmenorrhea was adjusted for district, BMI, education, occupation, area of residence, shift work, perceived stress, occupational exposure to chemical hazards, noise and dust, passive smoking at work, and season. Adjusted ORS for low, medium and high tertiles of ETS exposure were 1.1 (95% CI 0.5-2.6), 2.5 (95% CI 0.9-6.7) and 3.1 (95% CI 1.2-8.3), respectively. Generalized estimating equations were used to account for multiple cycles per woman. In this study the authors found a significant dose-response even though the levels of passive smoking were not particularly high. The average daily exposures per cycle ranged from 0.02 to 10.3 cigarettes. The “middle” tertile was 0.8 to 2.5 cigarettes per day.

Cooper et al. (1999) studied active and passive smoking and the occurrence of natural menopause among female college students who enrolled in a reproductive health study in Minnesota between 1934 and 1939 and recorded menstrual data for 5 or more years while in their 20’s. In 1990-1991, 943 of these women were successfully located. A total of 716 self-respondents and 158 proxy respondents (most often husband, daughter or other relative) completed a questionnaire which included active smoking status (yes/no) for each age between 10 and 79 years and cigarettes per day by decade. Passive smoking was defined as living with a smoker, and women were placed into categories of no adult passive smoking, passive exposure only more than 5 years before menopause and passive exposure within the 5 years before menopause. The analysis was limited to 543 women who had undergone natural menopause (i.e. not surgically or medically induced). As has been reported in previous studies the authors found a decrease in age at menopause of 0.8 years (-0.8, 95% CL -1.5-0.0) among current smokers compared to never smokers [note reference group includes 362 never active, but those include 117 with passive smoking]. Adjusting for BMI at age 30 did not substantially change the results.

The authors did not find a lower age at menopause with passive smoke exposure. The mean age at menopause among the 117 never-smokers with passive smoke exposure was 0.6 years higher (95% CL -0.2-1.4) compared with the 198 never-smokers without passive smoke exposure. These results are not in agreement with the Everson *et al.* (1986) paper described below, which found a decrease of 2 years in age at menopause among nonsmoking women whose spouses smoked compared to those whose spouses did not smoke. However, there were only a total of 261 women in that study, so that estimate was probably imprecise. The strength of Cooper *et al.* (1999) is that it included prospectively collected data on age at menopause and a high response rate among women who recorded menstrual data for 5 or more years (1,134 of the 1,807 college students who entered the cohort in 1934-1939). However, there may have been some selection bias because only 62% of the original cohort recorded menstrual data for 5 or more years. If those women who recorded this data were healthier than those who did not, this could have reduced the difference in age at menopause between smokers and nonsmokers. Although 51% of the women in the analysis worked outside the home during ages 40-44, workplace exposure to passive smoke was not included.

Hornsby et al. (1998) studied menstrual function in 358 women 37-39 years old whose mothers had participated, while pregnant with them, in a randomized clinical trial of diethylstilbestrol (DES) from 1950 to 1952. The women, who were interviewed in 1990, were eligible for study if they were still menstruating and not taking exogenous hormones or other medication known to affect menses. Study participants were asked to keep a daily menstrual diary for 6 months. Smoking exposure was categorized as none (n=211), passive (nonsmokers who reported living or sharing a workplace with a smoker, n=64), light (up to ½ pack per day, n=35), or moderate/heavy (greater than ½ pack per day, n=48). Prenatal exposure to DES was equally distributed in smokers and nonsmokers. Menstrual endpoints included cycle length (days), duration of menstrual bleeding (days), daily amount of bleeding (based on a subjective score from 1 = spotting to 4 = heavy), and dysmenorrhea (days of premenstrual and/or menstrual pain). For each of these endpoints, a mean was generated for each woman, and means of these means were then compared across smoking categories. The means were adjusted for potentially confounding variables that altered the coefficient for smoking by 10% or greater. These variables included exercise, body mass index, caffeine index, alcohol use, history of tubal ligation, stress and duration of menses.

The authors found that active smoking was associated with decreased duration of bleeding, increased daily amount of bleeding, and increased duration of dysmenorrhea. The duration of bleeding was also reduced in women with passive smoke exposure compared with nonsmokers. After adjusting for a history of tubal ligation, the mean duration of menses was 5.8 days in nonsmokers and 5.5 days in women with passive smoke exposure. In addition, the mean duration of dysmenorrhea, adjusted for exercise, stress and duration of menses, in women with passive smoke exposure was 2.6 days compared with 2.0 days for nonsmokers. Both these differences were statistically significant in the exposure trend test which included all categories of smoke exposure (p=0.01 and p=0.003, respectively).

Cooper et al., 1995. This cross-sectional study examined the effects of several forms of tobacco exposure on ovarian status, as reflected by early follicular phase follicle stimulating hormone (FSH) levels in serum. A high serum level of FSH is a recognized clinical index of menopausal status and significant increases in FSH occur before menstrual cycles cease. Study subjects, 290

highly educated women ages 38-49 years, who had not had a hysterectomy or oophorectomy, were recruited through posters and advertisements in Durham and Orange Counties, North Carolina. FSH levels were measured in blood on the second, third or fourth day of the menstrual cycle or at her earliest convenience if she had not menstruated in the past two months. Active smoking was defined as having smoked at least one cigarette per day for at least 3 months of the year, and passive smoking was defined as currently living with anyone who regularly smokes cigarettes at home. Prenatal exposure was assessed by asking whether the mother had smoked regularly while pregnant with the participant or the father had smoked regularly at home during this time.

The authors created a smoking status variable with three categories: current smokers (smoked during the past two years, n=31), nonsmokers (never- and ex-smokers) with passive exposure (n=25), and nonsmokers without passive exposure (n=232, the reference group). After controlling for age, body mass index, and dietary galactose consumption, the geometric mean FSH was 14.0 mIU/mL in current smokers, 11.7 mIU/mL in nonsmokers with passive smoke exposure and 8.4 mIU/mL in the reference group. These differences were statistically significant ($p < 0.05$). Other variables such as race, education, parity and caffeine consumption were evaluated and found not to be confounders in the analysis. The authors stated that similar results were seen when current hormone use was in the analysis, and the passive smoke effect was seen even when the analysis was limited to women who had never smoked. They also stated that prenatal exposure to smoking was not related to FSH levels, and no effect of ex-smoking was seen in this study. These data were not presented in the paper.

5.2.4. Discussion and Conclusions – Other Female Reproductive Effects

The one new study of age at menopause and ETS exposure failed to find a lower age at menopause in women exposed to ETS from living with a smoker. These results are not in agreement with the Everson *et al.* (1986) paper, which found a decrease of 2 years in age at menopause among nonsmoking women whose spouses smoked compared to those whose spouses did not smoke. Neither paper recorded cigarettes smoked per day by the spouses or workplace exposure to ETS. A study of women ages 38 to 49 years did find higher FSH levels in current smokers and nonsmokers with passive exposure compared to nonsmokers without passive exposure after controlling for age, body mass index and dietary galactose consumption (Cooper *et al.*, 1995). This may indicate an effect on ovarian function, and increased FSH level is a clinical indication of peri-menopause. Other evidence from studies in active smokers demonstrates that cigarette smoke is anti-estrogenic (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986). A number of studies have measured decreased levels of circulating estrogens in smokers reltive to nonsmokers (e.g., Sterzik ert al., 1996), or altered profile of active and less active estrogen metabolites (Terry and Rohan, 2002). This anti-estrogenicity would provide a plausible basis for earlier menopause in women exposed to cigarette smoke, although this effect may only be relevant for active smokers.

Two recent studies found an effect of ETS on dysmenorrhea (Chen *et al.*, 2000; Hornsby *et al.*, 1998). The Chen study actually found a dose response for tertiles of cigarettes smoked per day by a household member in a cohort of Chinese women who were nonsmokers. Both studies controlled for potential confounders such as body mass index.

There continues to be inconsistency in results and very few studies evaluating the effect of ETS exposure on female reproductive function other than fecundity and fertility. There is, however, suggestive evidence of biochemical effects of ETS on measures that affect age at menopause and female reproductive organ health, as well as suggestive evidence of dysmenorrhea from exposure to ETS. Menstrual cycle disorders may lead to decreased fertility and fecundability.

5.3. Male Reproductive Toxicity

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

5.3.1. Overview of Human Studies of Male Reproductive Toxicity and Active Smoking

The following review is from the 1997 OEHHA report. "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% lower than that of nonsmokers. The 1980 Surgeon General's Report (U.S. DHHS, 1980) stated, "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."

5.3.2. Human Studies of Male Reproductive Toxicity and Exposure to ETS

5.3.2.1. Summary of Previous Findings

The following is the summary of the findings for male reproductive toxicity from the 1997 report:

"No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. A study which examined the effects of early exposure to maternal smoking (both in utero and postnatal ETS exposure) found significant differences in sperm motility and oligospermia 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 sub-fecundability in women exposed to ETS by 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."

5.3.2.2. Newer Epidemiologic Data

No published studies were found that were designed to examine the association between ETS exposure of males and altered sperm parameters or fertility. However, evidence that the male reproductive system is affected by passive smoking was provided by Pacifici *et al.* (1995), who

found that exposure to ETS in nonsmokers results in measurable nicotine and cotinine levels in seminal plasma. Furthermore, seminal plasma cotinine concentration showed a significant positive correlation with degree of reported exposure. An in-vitro study of the effects of nicotine and cotinine on motility of sperm from nonsmokers usually not exposed to passive smoking (Gandini *et al.*, 1997) found that nicotine and cotinine at the average levels found in smokers' seminal plasma did not affect sperm motility, while a second experiment using aspirated cigarette smoke demonstrated a sharp reduction in all the sperm kinetic parameters. This study suggests that constituents of tobacco smoke other than nicotine or cotinine are responsible for the effects on semen quality.

The study by Jensen *et al.* (1998) described above in section 5.2.2.2 found that exposure to tobacco smoke in utero was also associated with a statistically significant decreased fecundability odds ratio in males (0.68, 95% CI 0.48-0.97). The other studies reported above in Section 5.2.2.2 did not collect information on passive smoking in the male partners.

5.3.3. Discussion and Conclusions – Male Reproductive Effects

There is only one new study that examined the effect of ETS exposure on reproductive dysfunction in males as part of a study of fecundity in couples. In this study exposure to tobacco smoke in utero was the measure of passive exposure for males. Further studies are needed which look at exposure to passive smoke outside of the home in nonsmoking males. Due to the paucity of data it is not possible to determine whether there is an association between ETS exposure and male reproductive dysfunction.

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Chapter 6. Respiratory Health Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and respiratory health from the 1997 OEHHA report and this update are provided below in Table 6.00.

Table 6.00 ETS and Respiratory Disease: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Finding OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
Lung development (children)	8	7 (1 meta)[a]	Suggestive	Suggestive (strengthened)
Asthma (children) exacerbation	8	14	Conclusive	Conclusive
Respiratory illness (children)	--[b]	9 (2 meta)	Conclusive	Conclusive
Otitis media ± effusion	22	7	Conclusive	Conclusive
Respiratory symptoms and other effects (children)	6	4	Conclusive	Conclusive
Asthma (children) induction	37	37 (1 meta)	Conclusive	Conclusive
Asthma (adults[c]) exacerbation	4	7	Suggestive	Conclusive
Sensory irritation and annoyance	18	14	Conclusive	Conclusive
Respiratory symptoms and other effects (adults)	20	6	Suggestive	Suggestive (strengthened)
Asthma (adults[c]) induction	2	15	Suggestive	Conclusive

[a] meta = # meta-analyses – not included in counts of studies. [b] A *de novo* review was not done in 1997 as this topic had been treated recently in reviews of nearly two dozen reports by the NRC, U.S. EPA and Surgeon General. [c] Some studies include adolescents as adults.

6.0. Introduction

The Children's Health Protection Act requires OEHHA to specifically evaluate adverse effects of candidate Toxic Air Contaminants on infants and children. ETS exposure has been shown to induce as well as exacerbate asthma in children, result in decreased lung function, and cause respiratory symptoms and illness (including otitis media) in children. There is evidence that postnatal ETS exposure impairs lung development, although the effect appears not to be as great as that from prenatal maternal smoking. ETS exposure also induces and exacerbates asthma in adults, and results in increased respiratory symptoms in adults.

The effects of ETS exposure on non-malignant endpoints of respiratory tract health were examined in the 1997 OEHHA report (Cal EPA, 1997). The conclusions of that report are examined here in light of more recent research on the induction and exacerbation of asthma, otitis media and middle ear effusion in children, lung development and respiratory infections in children, respiratory symptoms and changes in lung function in adults, and sensory irritation and

annoyance. The research examined includes both epidemiological and controlled exposure studies with the former representing geographically diverse populations. The more recent studies substantiate the association noted in the previous report between ETS exposure and deleterious respiratory health outcomes.

6.1. Lung Growth and Development (children)

6.1.1. New Epidemiological Findings

The effects of passive smoke exposure on the development of the pulmonary system were investigated in seven studies (Table 6.10). In six studies, spirometric measures showed decrements in lung function with ETS exposure consistent with the meta-analysis by Cook *et al.* (1998) of studies of forced expiratory volume (FEV). Mannino *et al.* (2001), Bono *et al.* (1998) and Rizzi *et al*. (2004) associated these decrements with high cotinine levels. Elevated neonatal serum cotinine and increased persistent pulmonary hypertension of the newborn were associated with maternal ETS exposure in the study by Bearer *et al.* (1997). As reported in Chapter 4, the study by Elliot *et al.* (1998) found passive smoke exposure to be significantly associated with structural changes in the large airways of SIDS victims. Finally, one study evaluated lung function and symptoms in adults who were exposed as children (Svanes *et al.*, 2004).

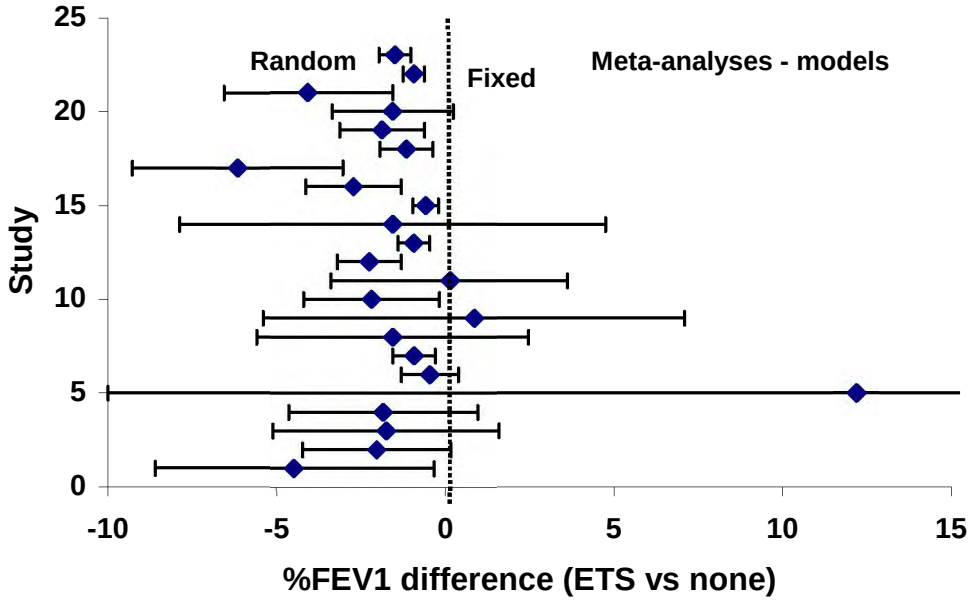
Table 6.10 ETS Effects on Lung Development

Reference Country	Study Description	Exposure To ETS	Outcome and OR (95% CI)	Comments
Meta-analysis				
Cook *et al* 1998 UK	Meta-analysis of 21 studies of lung function in school-age kids	Postnatal	FEV_1 -1.4% (-1.0--1.9) Mid exp flow -5.0% (-3.3--6.6) End exp flow -4.3% (-3.1--5.5)	Small but statistically significant decreases in lung function from maternal ETS. Adj for confounders but can't distinguish pre- and postnatal effects.
Original Studies				
Rizzi *et al.* 2004 Italy	Lung function in adolescent males n=80	Postnatal ETS only. Plus maternal pre-natal smoking	DLCO, Dm, KCO Significantly lower $p< 0.05$ Lower still with prenatal exposure also $p<0.0001$	ETS (as cotinine/creatinine ratio) inversely associated with decrements in lung function. Independent pre- and postnatal effects. Dose response noted.
Svanes *et al*. 2004 Europe	Lung function in adults after ETS in childhood. n=15,901	Parental ETS Maternal smoking	Wheeze OR 1.12 (1.02-1.23) Asthma symptoms 1.14 (1.02-1.26) FEV1 decrease $p = 0.012$	Significant risk of pulmonary symptoms in adults exposed in childhood to parental smoking. Effects from both maternal and paternal smoking.
Mannino *et al* 2001 US	Lung function vs. serum cotinine in 5400 8-16 yr-olds	Postnatal High vs. low cotinine	FEV_1 -1.8% (-3.2--0.4) MMEF -5.9% (-8.1--3.4)	Decrements in lung function associated with high vs. low cotinine.
Li *et al* 2000 US	Lung function in 5263 7-19 yr olds	Girls/asthma Past ETS only	MMEF -4%	Postnatal ETS exacerbates *in utero* exposure. Prenatal ETS-only effect seen in girls with asthma.
Bek *et al* 1999 Turkey	Cross-sectional study of lung function in 360 9-13 yr olds. Peak and forced expiratory flows and flow after expiration of 50 and 75% capacity.	Postnatal Paternal	FEV_{25-75} −7 % $p = 0.02$ PEF -6% $p = 0.03$ V_{max50} -7% $p = 0.008$ V_{max75} -9% $p =0.009$	Decrements in lung function associated with paternal but not maternal smoking due to unusually low maternal smoking and high paternal-child contact. Limited description of methods and confounder control limit utility of this study.
Bono *et al* 1998 Italy	Studied ETS and rate of change in FEV and FVC in 333 14-16 yr olds	Postnatal	FEV_1 -0.66% $p=0.05$ FVC -0.57% $p=0.082$	ETS as urinary cotinine slowed rate of FEV_1 increase over 1 yr
Bearer *et al* 1997 US	Maternal ETS exposure: persistent pulmonary hypertension of the newborn (PPHN)	Maternal ETS in pregnancy	Blood cotinine PPHN 3.5 ng/ml Ctrl 1.65 ng/ml ($p = 0.022$). OR: 4.68 (1.68-12.76)	Cotinine levels in newborns associated with ETS exposure and PPHN

CCR cotinine/creatinine ratio; DLCO diffusion capacity for carbon monoxide; Dm diffusion capacity of alveolar membrane; FEF_{25-27} forced expiratory flow at 25-75% of vital capacity; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; KCO carbon monoxide transfer coefficient; MMEF maximum mid-expiratory flow; PEF peak expiratory flow; PPHN persistent pulmonary hypertension in the newborn.

Cook et al., 1998. Part of a series on the health effects of passive smoking, this paper focused on the effect of ETS on spirometry. A meta-analysis was performed on 21 surveys of school-aged children. FEV_1 in children exposed to parental smoking was reduced by 1.4% (95% CI 1.0-1.9). Mid-expiratory flow rates and end expiratory flow rates were decreased by 5.0% (95% CI 3.3-6.6%) and 4.3% (95% CI 3.1-5.5%, respectively) when compared to controls. Adjustment for confounding reportedly had little effect on these estimates; however, other than age, gender and height, it is not clear what other factors were evaluated. Individually, these heterogeneous studies show a strong homogeneity of results with nearly all finding decrements in FEV_1 in exposed children (Figure 6.1). This analysis supports the association of maternal smoking with small, statistically significant deficits in spirometric studies in school-aged children. Due to the limitations of available studies, it is not possible to determine the relative effects of prenatal exposure to maternal smoking versus postnatal ETS exposure. In general, this review covers many of the same studies examined in the previous OEHHA document and supports the previous conclusions.

Figure 6.1 Percentage Difference in FEV1 Between Children of Smokers and Nonsmokers (Data from Cook *et al.*, 1998)



Rizzi et al.(2004) evaluated the effects of ETS exposure at home on 80 secondary school students free of chronic respiratory or cardiovascular health problems in Milan (16 ± 1 yrs of age). Questionnaires were given to students on their own and their parents smoking habits, respiratory health, sociodemographic factors, smokers living in the home, frequency of visiting smoky places, and the overall time exposed to ETS. Cotinine concentration and the cotinine to creatinine ratio of urinary samples were assayed. Lung function measurements and assessments of the diffusion capacity of the lung for carbon monoxide (D_{LCO}) were conducted on each student. The carbon monoxide transfer coefficient (KCO) and alveolar-capillary membrane diffusing capacity (D_M) were calculated. Lung function measurements were compared with predicted values.

Students were classified as smokers (21), passive smokers (29), and nonsmokers (neither parents nor students smoked, 30). There were no differences among the groups for height, weight or SES. Cotinine/creatinine increased significantly going from nonsmokers (18.6 ± 9.9 μg/mg) to passive smokers (65.5 ± 23.2 μg/mg) to active smokers (124.7 ± 41 μg/mg) (analysis of variance, $p<0.001$).

Exposure to ETS resulted in deficits in lung function compared to nonsmokers. Compared to nonsmokers, the maximum expiratory flow at 25% of FVC (MEF_{25}) was significantly lower, the residual volume and RV to total lung capacity ratio were significantly greater, and the D_{LCO}, KCO, and D_M were significantly lower in the ETS exposed adolescents. Comparing the three groups, smokers had less lung function than passive smokers who had less lung function than nonsmokers ($p<0.001$).

The authors also looked at those passive smokers whose mothers had stopped smoking during pregnancy and compared their lung function to those whose mothers had not stopped smoking during pregnancy. Their data indicate that *in utero* exposure resulted in larger negative effects than passive smoke exposure postnatally. Specifically, the MEF_{25}, D_{LCO}, KCO, and D_M values for passive smoking adolescents whose mothers smoked during pregnancy were statistically significantly lower than those parameters for passive smokers whose mothers had stopped during pregnancy (all $p<0.05$, unpaired t test).

Finally, comparing the passive smokers with only one household smoker to the passive smokers with more than one household smoker revealed a dose-response trend for MEF_{25}, D_{LCO}, KCO, and D_M all being significantly lower with multiple smokers than one smoker (all $p<0.01$, unpaired t test).

Thus, this study clearly demonstrated an effect of passive smoke exposure on residual volume and KCO, which suggests alterations in bronchiolar and alveolar structures. Lung function measures indicated mild airway obstruction in the passive smokers (and worse damage in active smokers). The study also found an independent effect of *in utero* exposure from a smoking mother and postnatal exposure to ETS on both spirometric measures and the measures of diffusing capacity.

Svanes et al. (2004) evaluated respiratory health of adults in relation to ETS exposure in childhood. Participating centers in the European Community Respiratory Health Survey randomly selected at least 1500 men and 1500 women from populations of at least 150,000 within defined geographic areas. Information was obtained from self-completed questionnaires as well as more detailed interviews, lung function tests, and blood tests. The paper included analyses of data from 18,922 subjects from 37 centers in 17 countries.

Spirometric data (FEV1 and FVC) were available for 15,901 subjects, and methacholine challenge was performed on 13,206 subjects. Atopy was defined as presence of specific IgE to dust mite, cat, timothy grass, and/or *Cladosporium* mold (available for 13,972 subjects). Information on parental smoking was collected at interview. Asthma was defined as medication use or asthma attacks in the previous 12 months. Information on respiratory symptoms in the previous 12 months and on chronic bronchitis was also obtained. The relationship between parental smoking in childhood and adult respiratory health was evaluated using logistic

regression models with adjustments for age, gender, body mass index, current smoking, current ETS exposure, occupation, and others.

Maternal smoking was statistically significantly associated with an increased risk of wheeze (OR 1.12; 95%CI 1.02-1.23), presence of more than 3 asthma symptoms in the previous 12 months (OR 1.14; 95%CI 1.02-1.26), chronic bronchitis (OR 1.19; 95%CI 1.05-1.35), decreases in FEV1 ($p=0.012$), and in the FEV/FVC ratio ($p<0.001$), when men and women were combined. Maternal smoking during pregnancy was also associated with statistically significant OR for wheeze (OR 1.24; 95%CI 1.09-1.42), more than 3 asthma symptoms (OR1.28; 95%CI 1.11-1.48; and chronic bronchitis (OR 1.32; 95%CI 1.11-1.57). In addition, there was a statistically significant decrease in the beta coefficient for FEV1/FVC ratio (-0.99; 95%CI –1.3--0.5). It should be noted that 40% of the subjects reported not knowing whether their mother had smoked during pregnancy, so this analysis includes only about 60% of the respondents. When only nonsmokers were evaluated (about 3000 men and 3500 women), there were similar elevations but most did not attain statistical significance.

When paternal smoking was evaluated, an association was noted between adult respiratory symptoms and lung function in men but not in women. The OR for wheeze in adult men associated with paternal smoking in childhood was 1.13 (95%CI 1.00-1.28), while that for more than 3 asthma symptoms was 1.20 (95%CI 1.03-1.39), and for chronic bronchitis was 1.22 (95%CI 1.02-1.45). The authors note that there is a convincing effect of postnatal exposure to ETS on lung health in adult men.

Maternal smoking was associated with both symptoms and lung function decrements in women, but less so in men. In women the odds ratios were 1.14 (95%CI 1.01-1.31) for wheeze, 1.16 (95%CI 1.01-1.33) for more than 3 asthma symptoms, and 1.22 (95%CI 1.01-1.46) for chronic bronchitis. Statistically significant decrements in FEV1 and in the ratio of FEV1 to FVC were noted.

This study also evaluated whether there was evidence of a dose-response by looking at the differences between results when only one parent smoked or when both parents smoked. For men and women combined, there was a significant trend upwards for both lung function decrement and symptoms when both parents smoked. This was also the case when men were considered separately, but only one trend test was positive when women were considered separately.

This study did not separate the effects of maternal postnatal exposure with intrauterine exposure to smoke constituents from maternal smoking. Paternal smoking appeared to have no effect on women's adult lung health, but did affect men's adult lung health. The authors speculate that there may be gender differences in the window of susceptibility for effects of tobacco smoke constituents on the lung, with females being more susceptible to prenatal damage and males more susceptible to postnatal damage. However, additional study would be needed to elucidate evaluate that hypothesis.

Mannino et al., 2001. This study from the Centers for Disease Control utilized data on 5,400 US children collected from the NHANES III, a nationally representative cross-sectional survey. Pulmonary function studies were performed in children 8–16 years of age. Logistic and linear

regression analyses of serum cotinine levels were stratified into tertiles and pulmonary function tests adjusted for age, height, ethnicity, SES, parental history of allergy or asthma, family size, maternal prenatal smoking and cotinine levels. Decrements in lung function were noted with high cotinine compared with low cotinine levels, with a mean change of -1.8% (95% CI -3.2--0.4%) in FEV_1, and a mean change of -5.9% (95% CI, -8.2--3.4%) in MMEF. Lower levels of lung function were also associated with a history of prenatal exposure to maternal smoking. A limitation of this study is the relatively short half-life of cotinine (3-4 days) making this an accurate evaluation of recent exposure but not long-term exposure. It is assumed that lifetime exposure is likely to be more accurately expressed by this in the youngest age groups. The study is strengthened by the large sample size, the representative nature of the population, use of biomarkers, adjusting for covariates and evaluation of potential confounders.

Li et al., 2000. Lung function was measured spirometrically on 5,263 children, ages 7-19 yrs, who participated in the University of Southern California Children's Health Study. Health, demographic and ETS exposure data were collected at enrollment. Forced vital capacity (FVC), forced expiratory volume (FEV) and maximum mid-expiratory flow (MMEF) were measured. ETS exposure was associated with deficits in lung flows and increases in lung volumes. These effects were also seen to be influenced by *in utero* exposure, children's gender and asthma status. *In utero* exposure to maternal smoking generally had a larger effect on lung function. A significant effect of exclusively postnatal ETS exposure was only observed in girls with asthma as a 4% deficit in MMEF. Current ETS exposure was found in this study to be detrimental to lung function although the measured effects were small and often not statistically significant after adjustment for *in utero* exposure. However these data were a cross-sectional sampling of a longitudinal study and there was no adjustment made for changes in parental smoking behavior nor for ETS exposure outside the home. Either situation would be expected to alter estimates of ETS effects, likely diluting the sensitivity of the study.

Bek et al., 1999. These investigators conducted a cross-sectional study in Turkey to evaluate the effect of ETS on lung function studies in 360 children 9-13 years. Information was obtained via a questionnaire and spirometry. Paternal smoking was associated with a 7% (p=0.02) reduction in $FEV_{25-75,}$ a 6% (p=0.03) reduction in peak expiratory flow, and 7% (p=0.008) and 9% (p=0.009) reductions in V_{max50} and $V_{max\ 75}$, respectively (flow rates after 50 or 75% of the vital capacity is expired). The description of methods is limited and it appears that confounding variables were not adequately considered which limits the usefulness of this study.

Bono et al., 1998. The effects of ETS on lung growth were determined by the rate of increase in measurements of FEV_1 and FVC taken in two consecutive years and related to urinary cotinine levels in this longitudinal study of 333 school children, ages 14-16. After controlling for changes in age, height, weight and smoke exposure between measurements, ETS exposure, as measured by urinary cotinine levels, was associated with a reduction in rate of increase of 0.66% for FEV_1 (p=0.05), and of 0.57% in FVC (p=0.082). Due to the narrowness of the developmental window during which these measurements were made, it is not known whether these small decrements in lung function growth are permanent and/or whether they become more pronounced with longer-term exposure. Nevertheless, the data indicate that ETS has at least a transient deleterious affect on lung function development.

Bearer et al., 1997. Persistent pulmonary hypertension of the newborn (PPHN) is a clinical disorder associated with remodeling of the pulmonary vasculature and elevated risk of perinatal death. It is characterized by abnormal vascular structure, growth and reactivity. The association between maternal and fetal nicotine exposure (cotinine levels) and PPHN was the topic of this study. Cotinine was assayed in cord blood or the earliest sample of newborn blood. PPHN was indicated by the lability of oxygenation and/or disparity of pre- and postductal oxygen saturation as assessed by pulse oximetry and confirmed by two-dimensional echocardiography. Thirty-one PPHN case infants were compared with 39 controls. Mothers were matched for ethnicity and there were no significant differences between groups for age, education, parity or gravidity. In the PPHN group, Apgar scores at 1 and 5 minutes were significantly lower ($p<0.0001$) and detectable cotinine was higher (5.2 ng/ml) than in the comparison group (2.0 ng/ml). Among those reporting passive smoke exposure only, cotinine was detected in 50% of the PPHN infants versus 18% of the comparison group, with a significantly higher median value for the PPHN group (3.5 ng/ml vs. 1.65 ng/ml). Logistic regression analysis was performed to correct for baseline differences in the groups and for potential selection bias, and resulted in an unadjusted OR of 4.68 (95% CI 1.68-12.76) for the association of passive smoke exposure and PPHN. The OR for PPHN reportedly increased to 6.10 after adjustment for ethnicity but no confidence interval was provided.

6.1.2. Studies on Lung Development in Animals

Recent studies of lung development in animals have concentrated on the effects of maternal ETS exposure during pregnancy on subsequent development in the fetus and neonate. In a study by Nelson *et al.* (1999a), histological changes were observed in the lungs of neonatal rats born to mothers exposed to sidestream smoke during pregnancy. Increasing changes in the mesenchyme and incidence of apoptosis in neonatal lungs were seen with increasing exposure of the dam to sidestream smoke (1-4 cigarettes/day for 1 week), especially when the exposure occurred during the third versus first or second week of gestation.

ETS has been implicated in the development of reactive airway disease. As described in section 6.5.1.4, a study by Rumold *et al.* (2001) used a murine model to test whether exposure to side stream smoke (SS; a surrogate for ETS) can induce allergic sensitization to inhaled ovalbumin (OVA). In this study, both total serum and OVA-specific IgE levels were significantly elevated in mice exposed to OVA/SS compared to OVA alone ($p<0.01$). Similarly IgG1 levels were significantly elevated in this group ($p<0.01$). The production of specific allergic antibodies to inhaled allergens is characteristic of the sensitization phase of reactive airway disease. These experiments indicate that ETS has the capacity to alter lung homeostasis and augment allergic sensitization to otherwise innocuous allergens.

In addition to allergic sensitization, ETS exposure may also render lungs more susceptible to subsequent injury by ozone. Yu *et al.* (2002) collected bronchoalveolar lavage (BAL) fluid and lungs from adult B6C3F1 mice exposed to aged and diluted sidestream smoke (ADSS), filtered air, ozone or ADSS followed by ozone. Exposure to ADSS (112 ppm CO, 29.5 mg/m^3 total suspended particulate) was for 6 hrs/day on three consecutive days. Cell proliferation in the lungs, as measured by bromodeoxyuridine (BrdU) incorporation, was used as an indicator of cell injury and death. BrdU incorporation was significantly elevated by ozone exposure compared to filtered air or ADSS ($p < 0.05$), and was further significantly elevated after exposure to the

combination of ADSS and ozone compared to ozone alone ($p < 0.05$). Similarly, in the BAL fluid, neutrophils were increased by ozone compared to air or ADSS ($p < 0.05$), with neutrophils, macrophages and protein significantly more abundant after ADSS and ozone combined than after ozone alone ($p < 0.05$). This indicated that prior smoke exposure exacerbated the cellular damage caused by ozone exposure.

6.1.3. Summary of ETS Effects on Lung Growth and Development

Childhood exposure to ETS was found to be associated with small decrements in various spirometric measures of lung function in pre-adolescents and adolescents in the range of 0.5-7%. One study demonstrated decreased diffusing capacity in passive smokers (Rizzi *et al.*, 2004). In addition, in at least one study, childhood ETS exposure was associated with respiratory symptoms and lung function in adults (Svanes *et al.,* 2004). From most of these studies it is not possible to determine the contribution of prenatal exposure to the observed effects. However, there are a few exceptions. Li *et al.* (2000) observed an independent effect of postnatal ETS exposure, but found that prenatal passive smoke exposure had a more pronounced effect on lung function than did postnatal ETS. In addition, Li *et al.* observed that *in utero* exposure combined with asthma resulted in significantly larger deficits than in children without asthma. Rizzi *et al.* (2004) found that *in utero* exposure resulted in larger lung function decrements than did postnatal exposure alone. Svanes *et al*. (2004) found that paternal smoking, but not maternal smoking was more strongly associated with lung function decrements in men but not in women. Thus postnatal ETS exposure appears to have possibly influenced men's adult lung health in this study, separate from *in utero* exposure. In three studies (Mannino *et al.*, 2001; Bono *et al.*, 1998; Bearer *et al.*, 1997), ETS exposure was documented by measurements of cotinine, an indicator of recent nicotine exposure, and an association was found between the adverse effects and elevated cotinine; thus, these studies implicate postnatal ETS exposure as causing decreased lung function growth. It is evident that childhood ETS exposure is at least transiently detrimental to lung development, and if the effects seen in Svanes *et al*. (2004) are repeated in other studies, the effects may indeed be permanent.

Studies of the effects of ambient air pollution are consistent with the adverse effects reported for ETS exposure. In an eight-year prospective study of 1,759 children recruited at 10 years of age in southern California, deficits in the growth of FEV_1 were significantly associated with exposures to components of ambient air pollution, specifically NO_2 ($p = 0.005$), acid vapor ($p = 0.004$), $PM_{2.5}$ ($p = 0.04$) and elemental carbon ($p = 0.007$) (Gauderman *et al*., 2004). Thus the plausibility of an adverse effect of ETS exposure on lung development is borne out by studies of the effects of air pollution on the same endpoints. In addition, these lung function changes can be considered permanent as the growth in lung function is essentially complete in an 18 year old.

6.2. Acute Health Effects in Children

6.2.1. Asthma Exacerbation

6.2.1.1. Previous Findings on Asthma in Children

A previous review by U.S. EPA (1992e) 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 who already have the disease." The 1997 Cal/EPA report, which reviewed additional studies, affirmed the causal connection between ETS exposure and childhood asthma exacerbation.

6.2.1.2. New Epidemiological Findings in Children

Fourteen more recent cross-sectional and cohort studies are described below and summarized in Table 6.20. Recent publications continue to confirm the adverse impact of ETS exposure on childhood asthma status.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Gilliland *et al.* 2003 US	Absenteeism among fourth-graders related to respiratory illness. n = 1,932	Parental smoking vs. child ± asthma None + asthma 1 + no asthma 1 + asthma ≥ 2 + no asthma ≥ 2 + asthma	Absenteeism due to respiratory illness 1.45 (1.15-1.83) 1.05 (0.79-1.39) 2.35 (1.49-3.71) 1.44 (1.04-2.00) 4.45 (2.80-7.07)	ETS increases absences due to respiratory illness as does asthma. ETS from ≥ 2 smokers exacerbates absentee risk 3-fold in asthmatic children.
Mannino *et al* 2002a NHANES III US	Population-based study cross-sectional: serum cotinine and asthma severity 4-6 yrs n = 523	Serum cotinine Highest vs. lowest tertile	Moderate to severe asthma 2.7 (1.1-6.8) FEV1 -8.1% (-14.7--3.5%) FVC -5.6% (-10.6--0.6%) FEV1/FVC -3.0% (-6.5-0.5%)	Highest cotinine levels associated with moderate to severe asthma; also with severe asthma but CI included no effect.
Crombie *et al* 2001 UK	Retrospective cohort study: salivary cotinine vs. health service contacts among asthmatic kids. 2-12 yrs. n = 438	Salivary cotinine. ≤ 2 ng/ml 2.1– 4.5 “ > 4.5 “	Health service contacts 1.0 (ref) (IRR[1]) 0.95 (0.82-1.11) 1.15 (0.98-1.34)	Measured ETS exposure for period following 12 months of tracked health service contacts.
Ehrlich *et al* 2001 S Africa	Cross-sectional study: urinary cotinine in 2nd grade asthmatics and bronchial hyper-responsiveness (BHR) n = 249	Urinary cotinine ng/mg 33.8-74.2 74.3- 137.7 “ > 137.7 “	BHR PR[2] (referent) 0.86 (0.61-1.20) 0.94 (0.68-1.30) 0.81 (0.57-1.15)	BHR not associated w/ETS. But parents of symptomatic children may decrease smoking.

[1] IRR incident rate ratio [2] PR prevalence ratio BHR bronchial hyperresponsiveness; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Venners *et al* 2001 China	Cross-sectional study: paternal smoking and pulmonary function in asthmatic kids 8-15 yrs, n = 529	Paternal < 30 cig/day ≥ 30 " < 30 cig/day ≥ 30 "	FEV_1 Girls -18 ml (p=0.75) -24 ml (p=0.73) FEV_1 Boys -38 ml (p=0.40) -72 (p=0.24)	Compared to nonsmoking fathers, statistically non-significant decrease in FEV_1 with increased paternal smoking. Dose-dependent trend suggested.
Melen *et al* 2001 Sweden	Cohort study: 2 yr follow-up of severe asthma attacks 1-4 yrs. n = 181	Parent reported Severe asthma ETS synergism w/dust mite allergen	Severe asthma 3.0 (0.74-12.2) 18 (3-101)	ETS associated with risk of severe asthma. ETS synergistic w/ dust mite allergen OR 18 (3-101).
Willers *et al* 2000 Sweden	Cross-sectional study: asthma symptoms vs. cotinine 8-11 yrs. n = 87	Plasma cotinine Asthma + wheeze +dyspnea previous asthma Urinary cotinine Asthma + wheeze +dyspnea previous asthma	median cotinine 0.50 µg/l plasma 0.80 µg/l plasma 0.60 µg/l plasma 0.60 µg/g creatinine 1.60 µg/g " 0.70 µg/g "	Current asthma with wheeze and dyspnea associated with highest cotinine in urine and plasma but significance unknown as study lacked statistical comparisons.
Schwartz *et al.* 2000 Finland	Cohort study: followed ETS and PEF in asthmatic kids for 3 mo 7-12 yrs n = 74	Parent diary Any vs. none Daily PEF l/min Evening PEF Mean decrement PEF Bronchodilator use Cough Phlegm production.	PEF decrement Any vs. no ETS -42 (-10 to –74) -41 (-8 to –74) ETS previous day 9.2 (-2.9 to 21) 10.3 (1.3 to 84) 12.4 (2.4 to 63) 7.8 (1.4 to 42)	ETS associated with decreased peak expiratory flow (PEF) both morning and evening. Also exposure-response trend for days of ETS and PEF (p=0.01)

FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Li *et al* 2000 US	Cross-sectional study: pulmonary function among asthmatic kids 7-19 yrs n = 749	Parent reported Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal Past ETS only Current ETS *In utero* *In utero* +postnatal	FEV_1 (ml) Boys -2.7 (-8.1-3.0) -0.4 (-5.5-4.9) -6.8 (-13.8-0.7) -7.2 (-11.4--2.8) FEV_1/FVC Boys -0.6 (-3.8-2.8) -1.7 (-4.6-1.4) -5.0 (-9.2--0.6) -2.8 (-5.4--0.1) MMEF Boys -2.8 (-14.2-10.0) -2.9 (-13.3-8.6) -14.0 (-27.3-1.7) -11.0 (-19.5--1.6) FEV_1 (ml) Girls 2.7 (-2.1-7.8) 3.3 (-1.5-8.3) 1.3 (-5.7-8.9) 0.2 (-3.4-4.0) FEV_1/FVC Girls 2.4 (-0.8-5.7) 0.9 (-2.2-4.1) -6.8 (-11.2--2.3) -2.6 (-4.9--0.1) MMEF Girls 10.3 (-0.9-22.7) 10.2 (-0.9-22.5) -17.1 (-30--2.6) -3.5 (-11.3-5.0)	*In utero* exposure in boys strongly associated with decreased pulmonary function (FEV_1) especially if combined with postnatal ETS compared to no parental ETS. Postnatal effect not evident for girls or other function measures.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Table 6.20 Studies of Asthma Exacerbation in Children

Reference Country	Study description	ETS exposure measure	Findings, measurement or OR (95% CI)	Comments
Oddoze *et al* 1999 France	Cross-sectional study: urinary cotinine vs. BHR in asthmatic kids hospitalized w/wheeze. 4-14 yrs. n = 90	Urinary cotinine	Cotinine inversely associated with amount of carbachol that doubled airway resistance	Same group as Dubus study with similar results but no effect estimates. p = 0.03
Dubus *et al* 1998 France	Cross-sectional study: urinary cotinine in asthmatic kids and BHR 5-13 yrs. n = 46	Urinary cotinine undetectable elevated	Carbachol to double airway resistance 161 µg 108 µg	ETS exposure increased BHR, as less carbachol was needed to double airway resistance. p = 0.04
Abulhosn *et al* 1997 US	Cohort study: follow-up for 4 wks after hospitalization for asthma 2-13 yrs n = 22	Parent reported Symptomatic Days Nights ß-agonist use/wk	ETS vs. none (days) 3.3 vs. 1.4 (p<0.05) 2.3 vs. 1.4 (p>0.05) 3 vs. –12 (p<0.001)	During 4 wk recovery, ETS-exposed had more symptomatic days and no decrease in ß-agonist use vs. decrease of 12 x/wk w/no ETS.
Meijer *et al* 1996 US	Cohort study: followed PEF amplitude and ETS after withdrawal of inhaled corticosteroids. 9.3 yrs n = 55	Parent report	Circadian PEF amplitude increase ß = 11.2 (p=0.001)	ETS increased variation in PEF (amplitude) suggesting effects on airway diameter.
Macarthur *et al.*, 1996 Canada	Cohort study: followed ETS vs. rehospitalization of asthmatic kids. 1-13 yrs n = 68	Parental smoking assessed from hospital records	Rehospitalization OR 1.4 (0.9-2.4)	ETS increased risk of re-hospitalization but accuracy of exposure assessment questionable.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity; MMEF maximum mid-expiratory flow; PEF peak expiratory flow.

Gilliland et al., (2003) evaluated the relationship between ETS exposure, asthma status and illness-related absenteeism in the Southern California Children's Health Study, a cohort of 1,932 fourth-grade children in 12 California communities. Data on sociodemographics, indoor exposures and medical histories were obtained from parents or guardians via questionnaires at study entry. Attendance data were collected from the schools, and parents were contacted by telephone to determine the reason for the absence. Illness-related absences were categorized into respiratory or gastrointestinal. To estimate the risk of absenteeism associated with ETS exposure, incident absence rates were stratified and adjusted for sociodemographic variables including community, ethnicity, age, gender, parental education, health insurance, family income, BMI, and number of hours of outdoor activity.

Any ETS exposure was found to significantly increase the incidence of missed school days, including non-illness-related (RR 1.29, 95% CI 1.02-1.63), illness-related (RR 1.33, 95% CI 1.13-1.57), and respiratory-illness-related (RR 1.27, 95% CI 1.04-1.56) absences. Among illness-related and especially respiratory-illness-related absences, there was evidence of dose-response relationships associated with increasing numbers of smokers in the household. Children with asthma or wheeze were particularly sensitive to ETS. The risk of absenteeism for respiratory-related illness among asthmatic children not exposed to ETS was 1.45 (95% CI 1.15-1.83) compared to 4.45 (95% CI 2.80-7.07) with exposure to two or more smokers (see Table 6.21). A similar trend was observed among children with wheeze. Exposure to ETS was also associated with an enhanced risk of absence due to gastrointestinal illness (RR 1.43-95% CI 1.12-1.82) that increased as the number of household smokers increased.

These data indicate that ETS exposure has a significant deleterious effect on children's health as measured by school absenteeism. Since even non-illness-related absences were higher among ETS-exposed children, it may be expected that ETS exposure may negatively affect scholastic performance and academic achievement in addition to its adverse health effects.

Table 6.21 ETS exposure and School Absenteeism (Gilliland et al., 2003)

	#Children	Non-illness related	Illness-related	Respiratory-illness-related
ETS/asthma		RR (95% CI)	RR (95% CI)	RR (95% CI)
No/No	1,264	ref	ref	ref
No/Yes	217	0.82 (0.58-1.16)	1.30 (1.06-1.59)	1.48 (1.17-1.81)
Yes/No	303	1.23 (0.96-1.59)	1.25 (1.04-1.50)	1.14 (0.91-1.44)
Yes/Yes	48	1.21 (0.69-2.14)	2.19 (1.59-3.01)	2.55 (1.78-3.65)
#Smokers/asthma				
0/No	1,294	ref	ref	ref
0/Yes	226	0.91 (0.66-1.26)	1.27 (1.04-1.55)	1.45 (1.15-1.83)
1/No	209	1.40 (1.05-1.87)	1.18 (0.95-1.47)	1.05 (0.79-1.39)
1/Yes	30	1.26 (0.63-2.53)	2.02 (1.35-3.00)	2.35 (1.49-3.71)
≥ 2/No	98	1.31 (0.90-1.92)	1.46 (1.12-1.89)	1.44 (1.04-2.00)
≥ 2/Yes	17	1.51 (0.64-3.59)	3.29 (2.16-5.03)	4.45 (2.80-7.07)
ETS/Wheeze				
No/No	968	ref	ref	ref
No/Yes	467	1.28 (1.01-1.61)	1.26 (1.08-1.47)	1.45 (1.20-1.75)
Yes/No	218	1.27 (0.94-1.73)	1.14 (0.92-1.42)	0.93 (0.69-1.25)
Yes/Yes	124	1.59 (1.11-2.26)	1.90 (1.50-2.39)	2.29 (1.75-3.00)
#Smokers/Wheeze				
0/No	992	ref	ref	ref
0/Yes	480	1.32 (1.05-1.66)	1.25 (1.07-1.47)	1.43 (1.18-1.73)
1/No	159	1.46 (1.04-2.05)	1.08 (0.93-1.41)	0.89 (0.62-1.27)
1/Yes	75	1.71 (1.11-2.62)	1.81 (1.36-2.41)	2.13 (1.53-2.97)
≥ 2/No	61	1.49 (0.93-2.39)	1.43 (1.03-2.00)	1.20 (0.76-1.88)
≥ 2/Yes	51	1.49 (0.88-2.50)	2.21 (1.62-3.02)	2.97 (2.09-4.23)

Mannino et al., 2002a. Using the population-based NHANES III data, Mannino and colleagues examined the impact of ETS exposure, as measured by serum cotinine, on asthma severity, which was classified based on frequency of respiratory symptoms and illnesses. Compared to the lowest serum cotinine tertile, the highest cotinine tertile was associated with a greater risk of moderate or severe asthma (OR 2.7; 95% CI 1.1-6.8). The risk of severe asthma was also elevated, but the confidence interval was wide and included no difference (OR 1.9; 95% CI 0.6-5.7). The highest cotinine tertile was also related to decreased pulmonary function, including a lower mean FEV_1 (-8.1%; 95% CI -14.7%--3.5%), FVC (-5.6%; 95% CI -10.6%--0.6%), and FEV_1/FVC ratio (-3.0%; 95% CI –6.5%-0.5%).

Crombie et al. (2001) evaluated the relationship between current salivary cotinine and health service contacts for asthma during the previous year. These investigators recruited 438 children aged 2-12 with asthma and one or more smoking parents from general practices in the U.K. Health contacts were determined by review of medical records and computerized pharmacy records. Compared to the lowest cotinine group, the highest cotinine group was associated with an increased risk of health care utilization for asthma expressed as the incident rate ratio (IRR 1.19; 95% CI 1.05-1.37). After controlling for asthma severity and sociodemographic covariates, the risk estimate was slightly lower (IRR 1.15; 95% CI 0.98-1.34). A major limitation of this study is the nature of the exposure-outcome relationship. Because ETS

exposure was ascertained for a period following the health care utilization, the causal pathway may not be clearly delineated. For example, the parent of a child with frequent asthma-related utilization may reduce their smoking, which would attenuate the risk estimate.

Ehrlich et al., 2001. In a population-based cross-sectional study from South Africa, researchers recruited a sample of 249 second-grade students with asthma to undergo bronchoprovocation testing with histamine. There was no statistical relationship between urinary cotinine-creatinine ratio and the risk of bronchial hyper-responsiveness. Similarly, there was no association between self-reported current maternal or paternal smoking and bronchial hyper-responsiveness, with prevalence ratios (PR) of 0.8 (95% CI 0.5-1.1) and 1.0 (95% CI 0.8-1.3), respectively. There was also no relation between cotinine-creatinine ratio and asthma symptom score ($p=0.40$). Current maternal smoking was associated with lower mean FEV_1 (mean decrement – 232 ml; 95% CI –461--2). This relationship was not observed for current paternal smoking (mean FEV_1 increment 112 ml; 95% CI -78-302). Overall, the study results support a negative impact of ETS exposure on pulmonary function, but not on bronchial hyper-responsiveness or asthma severity. As the authors point out, parents with symptomatic children may be more likely to quit smoking or not smoke around the child, which would attenuate the observed risk.

Venners et al., 2001. In a study from rural China, researchers using a cross-sectional design examined impact of paternal smoking on pulmonary function among 529 children with asthma. Because maternal smoking was rare, this study was able to independently evaluate the impact of paternal smoking. Exposure to paternal smoking was associated with decreased FEV_1 in both boys and girls, although the results were not statistically significant (Table 6.20). Inspection of the results suggests an exposure-response relationship. These results, based on a rural Chinese population, should be generalized to the California population with caution.

Melen et al. (2001) evaluated a cohort of 181 Swedish children with asthma two years after they were enrolled in an earlier case-control study. These children were initially recruited from pediatric allergy clinics in Stockholm for evaluation of asthma. Many had been hospitalized or seen in an emergency department for asthma. At follow-up, asthma severity was classified using structured interview data from parents, based on current asthma symptoms and level of inhaled corticosteroid use. Severe asthma was defined as daily regular corticosteroid use and activity restriction for more than 6 days/month (12 children met this definition at follow-up). Parental smoking was associated with a greater risk of severe asthma at 2-year follow-up (OR 3.0; 95% CI 0.74-12.2). Because the proportion of children with severe asthma was low, the confidence intervals are wide. In addition, the authors observed a synergistic interaction between high levels of dust mite allergen in the home and ETS exposure at baseline on asthma prevalence (OR for both factors 18.0; 95% CI 3.0-101).

Willers et al. (2000) recruited 85 of 137 children with asthmatic symptoms who were identified by a population-based survey. They evaluated the relationship between ETS exposure (plasma and urine cotinine levels) and asthma symptoms. Compared to children who indicated previous (but not current) asthma symptoms, subjects with current wheeze had similar plasma cotinine levels (median 0.50 µg/l vs. 0.60 µg/l). The results for urine cotinine-creatinine ratios were also similar (0.60 µg/g creatinine vs. 0.70 µg/g). Children with current wheeze and dyspnea had higher plasma and urinary cotinine levels (median 0.80 µg/l and 1.6 µg/g creatinine, respectively). In particular, children with current wheeze and dyspnea appear to have higher

urine cotinine-creatinine ratios than children with wheeze alone. Although no statistical comparisons are presented, these results were deemed "not statistically significant" by the authors. The lack of detailed statistical comparisons among the groups limits interpretation of this study.

Schwartz et al., 2000. Researchers recruited 74 asthmatic children, using a survey sent to primary school children in 8 schools in Kuopio, Finland. Participants were instructed to record daily respiratory symptoms, medication use, and ETS exposure in the home every day for a 3-month period. In addition, children measured their peak expiratory flow each morning and evening. As assessed by the diaries, any ETS exposure during the 3-month period was associated with a lower peak expiratory flow in the morning (mean decrement 42 L/min; 95% CI 10-74) and evening (41 L/min; 95% CI 8-74). This mixed effects regression analysis controlled for socioeconomic factors, height, asthma medications, and repeated measurements among subjects. There was also evidence of an exposure-response relationship between number of ETS exposure days and peak expiratory flow (p for trend = 0.01). When 1-day lagged ETS values were examined, the relationship between ETS and decreased peak expiratory flow was less strong (mean decrement 9.2 L/min; 95% CI 2.9-21). 1-day lagged ETS exposure was strongly related to a greater risk of subsequent bronchodilator use (OR 10.3; 95% CI 1.3-84), cough (OR 12.4; 95% CI 2.4-63), and phlegm production (OR 7.8; 95% CI 1.4-42). This study clearly supports an association between ETS exposure and exacerbation of asthma.

Li et al., 2000. A cross-sectional analysis, using children recruited for the University of Southern California Children's Health Study, examined the relationship between ETS exposure (past and current) and pulmonary function among 749 children aged 7-19 years with current asthma. Compared to boys without any parent-reported ETS exposure, a history of *in utero* tobacco exposure (i.e., maternal smoking) was most strongly associated with decreased FEV_1, FEV_1/FVC ratio, and maximal mid-expiratory flow (MMEF) (Table 6.20). Both past and current ETS exposures were related to lower pulmonary function values, but the confidence intervals were wide and included no effect. Boys exposed to two or more current smokers had lower FEV_1 (-2.9 ml; 95% CI –9.0-3.7), FEV_1/FVC ratio (-3.6 ml; 95% CI –7.2-0.1), and MMEF (-5.2 ml; 95% CI –18-9.5). The combination of *in utero* tobacco exposure and any postnatal ETS exposure was associated with statistically significant decreases in FEV_1 (-7.2 ml; 95% CI –11.4--2.8), FEV_1/FVC (-2.8 ml; 95% CI -5.4--0.1), and MMEF (-11.0 ml; 95% CI –19.5-–1.6). In girls, *in utero* tobacco exposure alone was associated with decreased FEV_1/FVC and MMEF, but not FEV_1. The combination of *in utero* tobacco exposure and subsequent ETS exposure was associated with a statistically significant decrease in FEV_1/FVC (-2.6; 95% CI -4.9--0.1) and an apparent, but not statistically significant, decrease in MMEF (-3.5 ml; 95% CI -11.3-5.0). Exposure to two or more smokers was associated with a decrease in FEV_1/FVC (-2.7 ml; 95% CI -6.0-0.6) and MMEF (-4.2 ml; 95% CI -14-7.2), but not to FEV_1 (2.7 ml; 95% CI -2.3-7.8). Taken together, these data support the subacute or chronic negative effects of ETS exposure on pulmonary function among children with asthma.

Oddoze et al., 1999. Another study from the same French investigators examined pulmonary function among 90 children recruited from a pediatric asthma clinic or who were recently hospitalized for wheezing. Although no effect estimates were presented, the authors noted a strong positive association between urinary cotinine and the degree of bronchial hyper-

responsiveness as measured by the response to carbachol (p=0.03). They reported no relationship between urinary cotinine and FEV_1 (no specific results presented).

Dubus et al. (1998) recruited 46 children (ages 5-13 years) with asthma who were referred to a pulmonary function laboratory. Based on urinary cotinine levels, they divided children into ETS-exposed (elevated urine cotinine) vs. unexposed (no detectable cotinine). The ETS-exposed children had greater bronchial hyper-responsiveness, as indicated by a lower dose of inhaled carbachol that doubled specific airway resistance (mean 108 µg vs. 161 µg). In contrast to the study by Ehrlich and colleagues (Ehrlich *et al.*, 2001), these results are consistent with an adverse effect of ETS exposure on bronchial hyper-responsiveness. While there was no assessment of a child's smoking history, it seems unlikely that this would have influenced the association observed in this study, since not many children younger than 10 or 12 smoke.

Abulhosn et al. (1997) followed a cohort of 22 children for 4 weeks following hospitalization for asthma. Based on parent responses, children were classified as living in homes with any smokers (exposed) vs. none (unexposed). After hospital discharge, ETS-exposed children had more symptomatic days from asthma than unexposed children (mean ± SEM 3.3 ± 3.7 symptomatic days vs. 1.4 ± 2.1 days, $p < 0.05$). Children with ETS exposure also had more symptomatic nights (mean 2.3 ± 3.4 vs. 1.4 ± 1.9), although the p value was greater ($p > 0.05$). After hospitalization, ETS-exposed children had no significant change in weekly bronchodilator use (mean increase 3.0 doses/week), whereas unexposed children had a reduction in weekly use (mean reduction 12 doses/week, $p < 0.001$). This study indicates that among children with a severe asthma exacerbation that requires hospitalization, ETS exposure is associated with delayed recovery.

Meijer et al. (1996) studied a cohort of 55 asthmatic children with allergy to house dust mite during and after withdrawal of inhaled corticosteroid therapy. The authors hypothesized that exogenous stimuli in the home, such as ETS, could increase circadian swings in airway diameter. To measure this phenomenon, they examined circadian peak expiratory flow (PEF) amplitude, which is the highest daily PEF minus the lowest PEF, expressed as a percentage of the day's mean value. Compared to unexposed children, ETS exposure was associated with a greater mean PEF amplitude after discontinuation of inhaled corticosteroids (29.7 vs. 19.4, $p < 0.05$). In multivariate analysis controlling for age, pet exposure, dust mite exposure, and degree of bronchial hyper-responsiveness, ETS exposure was associated with an increase in PEF amplitude ($ß = 11.2$; $p = 0.001$). These results suggest that ETS exposure can increase variability in bronchial airway diameter throughout the day.

Macarthur et al. (1996) recruited 68 children in Canada who had been hospitalized twice for asthma and followed them for repeat hospitalization. Predictor data, including parental smoking, were abstracted from the inpatient medical record. Compared to unexposed children, ETS exposure was associated with a greater risk of re-hospitalization (OR 1.4; 95% CI 0.9-2.4). Reflecting the small sample size, the confidence intervals were wide and included no effect. A serious limitation is assessment of ETS exposure based on medical record review, which may not accurately reflect exposure status in all cases. The small sample size and lack of statistical control for confounding variables also limit the conclusions that can be drawn from this study.

6.2.1.3. Summary – Asthma Exacerbation in Children

Taken together, the recent evidence supports the original 1997 Cal/EPA report's conclusion that ETS is a causal factor for asthma exacerbation among children. The cross-sectional studies are all limited by the possibility of selection effects, such as smoking reduction by parents who have children with more severe asthma. This bias, which is unavoidable in cross-sectional studies, would attenuate any observed risk estimate. The longitudinal studies, which are less prone to this bias, are most consistent with an adverse effect of ETS on childhood asthma status, and consistently show elevated risk of symptoms, more and prolonged medication use, and increased school absenteeism. In addition, as shown in a recent meta-analysis by Vork *et al.* (2002), hidden environmental differences between studies may distort risk estimates. Specifically, higher ETS-related asthma risks were reported in areas with lower ambient air pollution. It was suggested that in polluted areas, individuals who are genetically more susceptible to asthma may be more affected by the ambient air pollution than by ETS, thus masking the effects of ETS exposure. If nondifferential, failure to account for the effects of ambient air pollution could bias risk estimates towards unity.

6.2.2. Respiratory Infections (children)

6.2.2.1. Background

Prior to the 1997 Cal/EPA report, the role of ETS in respiratory infections in young children was extensively reviewed by the NRC (1986a), Surgeon General (U.S. DHHS, 1986b) and U.S. EPA (1992b). For this reason a separate *de novo* analysis of the primary literature was not conducted at that time. Based on those reviews, the Cal/EPA report asserted the following.

> "It has been clearly established in nearly two dozen reports reviewed by the National Research Council (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."

6.2.2.2. New Epidemiological Findings

The more recent studies summarized in Table 6.22 and the paragraphs below continue to support an elevated risk for lower respiratory infection (LRI) and reconfirm the observations of greater susceptibility at younger ages. Higher risks are observed for atopic children and children whose mothers smoked during pregnancy as well as after delivery.

Table 6.22 Respiratory Illness in Children Exposed to ETS

Reference Country	Study description	Exposure To smoke	Outcome and RR (95% CI)	Comments
Meta-analyses				
Li *et al.* 1999 Australia	Meta-analysis of 13 studies of ETS and lower respiratory tract infections (LRI). From 3 Chinese studies -	Pre/postnatal Hospitalization LRI 0-2 yrs old LRI 0-6 yrs old LRI 3-6 yrs old Postnatal only	LRI* 1.93 (1.66-2.25) 1.71 (1.33-2.20) 1.57 (1.28-1.91) 1.25 (0.88-1.78) 2.13 (1.52-3.00)	Hospitalization for respiratory illness nearly double by ETS in infancy and early childhood. ETS associated with LRI mainly in younger kids. Postnatal-only data from Chinese studies where mothers didn't smoke.
Strachan and Cook 1997 US	Meta-analysis of 38 studies of lower respiratory infection in first 3 yrs of life.	Parental smoking Either Maternal Other	Pooled ORs 1.57 (1.42-1.74) 1.72 (1.55-1.91) 1.29 (1.16-1.44)	Infection risk highest for maternal smoking. Risks also elevated if father or other household members smoked.
Original studies				
Gilliland *et al.* 2003	Absenteeism among fourth-graders related to respiratory illness. n = 1,932	Household Any ETS Maternal only Paternal only Both 1 smokers ≥ 2 smokers	Respiratory-illness-related absences 1.27 (1.04-1.56) 1.44 (1.06-1.94) 0.93 (0.64-1.35) 1.80 (1.31-2.46) 1.17 (0.92-1.49) 1.75 (1.33-2.30)	Children exposed to ETS had more illness-related and non-illness-related school absences than non-exposed children. Dose-dependence for both illness-related and respiratory-illness-related absences.
Lam *et al.* 2001 China	Health service usage among population-based cohort during first 18 mo. n = 8327	Mother *In utero* *In utero* Postnatal	Dr consults 1.26 (1.14-1.39) Hospitalizations 1.18 (1.05-1.31) 1.26 (1.00-1.25)	Mothers exposed to ETS during pregnancy and/or after. No maternal active smoking.
Gurkan *et al.* 2000 Turkey	Association of ETS with serum cotinine and bronchiolitis in infants, 2-18 mo. n = 28	Parental smoking Cotinine Both parents Mother only	Bronchiolitis 10.8 vs. 3.8 ng/ml in controls $p<0.05$ $p<0.05$	Infants with bronchiolitis had significantly higher serum cotinine ($p<0.0001$) and greater odds that one or both parents smoked.

Table 6.22 Respiratory Illness in Children Exposed to ETS

Reference Country	Study description	Exposure To smoke	Outcome and RR (95% CI)	Comments
Hajnal *et al.* 1999 Switzerland	Cross-sectional study of 6-14 yr olds and association of ETS and respiratory symptoms. n = 4470	Maternal smoking (current) Cough Respiratory infection Shortness of breath Any ETS at home Cough Respiratory infection Shortness of breath	Symptoms in last 12 months 1.36 (1.14-1.61) 1.25 (1.06-1.48) 1.71 (1.18-2.48) 1.15 (0.99-1.33) 1.19 (1.03-1.37) 1.50 (1.08-2.07)	Respiratory symptoms in preceding 12 months related to ETS, especially from maternal smoking. Risks higher if mother smoked in pregnancy.
Gergen *et al.* 1998 US	Cross-sectional from NHANES III of 2 mo-5 yr olds for bronchitis or wheezing during the previous 12 months. n = 7680	**2-24 mo** 1-19 cig/day ≥ 20 “ 1-19 cig/day ≥ 20 “ **3-5 yr** 1-19 cig/day ≥ 20 “ 1-19 cig/day ≥ 20 “	bronchitis 1.3 (0.8-1.9) 2.5 (1.6-4.1) wheezing 1.7 (1.2-2.5) 2.7 (1.7-4.2) bronchitis 1.2 (0.7-2.1) 1.3 (0.6-2.9) wheezing 1.2 (0.8-1.8) 1.2 (0.6-2.4)	Symptoms of respiratory illness (cough or wheezing) increased by ETS, especially at higher doses. Younger infants more susceptible than older.
Peters *et al.* 1998 Hong Kong	Healthcare usage by 8 -13 yr-olds for 3 month period for respiratory symptoms n = 10,402	Household 1 smoker ≥ 2 smokers 1 smoker ≥ 2 smokers	Any symptom 1.15 (1.01-1.31) 1.38 (1.14-1.67) 13.1% cost incr. 24.7% “	More frequent doctor consultations if one or both parents smoke especially for cough and phlegm. P for trend <0.001 for any symptoms resulting in doctor visits.

Table 6.22 Respiratory Illness in Children Exposed to ETS

Reference Country	Study description	Exposure To smoke	Outcome and RR (95% CI)	Comments
Margolis *et al.* 1997 US	Cohort study of ETS parental smoking and urinary cotinine in infants ≤ 12 months of age. n = 325	Parent report ≤ 10 cig/day > 10 " urine cotinine ≤ 120 ng/mg > 120 "	Acute LRI 1.5 (1.1-2.0) 2.2 (1.3-3.8) 1.3 (0.8-2.1) 1.4 (0.9-2.1)	ETS by parental report increased respiratory illness but urinary cotinine only weakly associated.
Jedrychowski & Flak 1997 Poland	Cross-sectional of 9-yr olds. ETS and respiratory infections. n = 1129 Pre- and postnatal. Atopy + postnatal-only	Postnatal ≤ 9 cig/day ≥ 10 " Pre + postnatal ≤ 9 cig/day ≥ 10 " Atopy + 0 Atopy ≤ 9 Atopy ≥ 10	Diagnosed RI* 1.32 (0.83-2.10) 1.74 (1.06-2.87) 2.32 (1.13-4.76) 2.36 (1.32-4.17) 2.86 (1.61-5.10) 3.39 (1.93-5.93) 3.31 (1.71-6.42)	Doctor-diagnosed respiratory infection (RI; laryngitis, tracheitis, bronchitis) risk significant at high ETS, especially if mother smoked in pregnancy or if child has atopy.
Nafstad *et al.* 1996 Norway	Prospective study: effects of breastfeeding and maternal ETS on LRI in 1-yr olds. n = 3238	Maternal breastfed 0-6 mo breastfed >6 mo breastfed 0-6mo breastfed >6 mo	Any LRI* 2.2 (1.6-3.1) 1.1 (0.7-1.6) Severe infection 4.6 (2.5-8.3) 1.1 (0.5-2.7)	LRI; bronchitis, pneumonia, bronchiolitis risk increased by ETS but effect ameliorated by prolonged breastfeeding.

RI respiratory infection; LRI lower respiratory tract infection

* LRI lower respiratory tract infection; RI respiratory infection

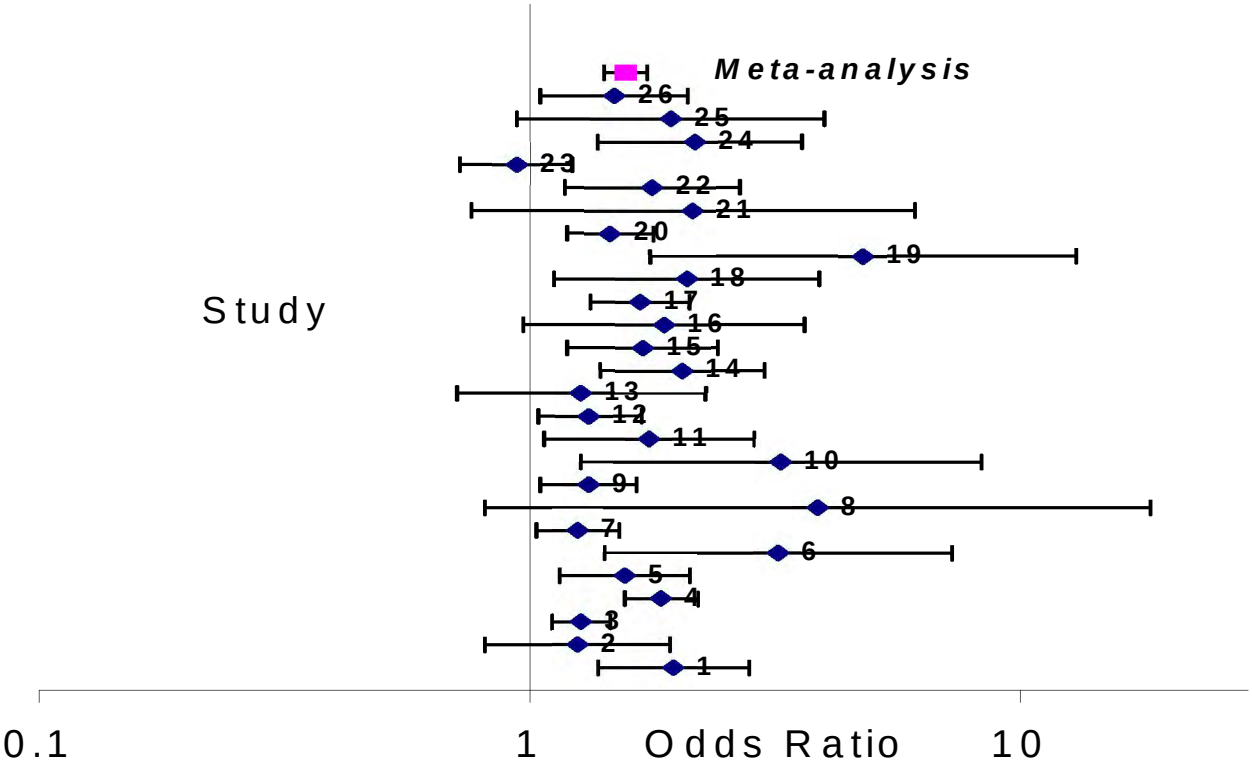
6.2.2.2.1. Meta-analyses

Li et al., 1999. The association between ETS exposure and lower respiratory tract infections (LRI; pneumonia, bronchitis, bronchiolitis) in childhood was also examined in a meta-analysis of thirteen studies, comprising 3 cohort, 2 case-control and 8 cross-sectional studies. The authors' criteria for inclusion in this meta-analysis included primary studies that provided information on individual level ETS exposure and serious lower respiratory tract infections or hospitalization for respiratory illness in infancy or early childhood. From seven studies it was possible to calculate an overall risk of hospitalization for respiratory illness associated with ETS exposure, resulting in an OR of 1.93 (95% CI 1.66-2.25). When the data were categorized by age, the ORs for LRI from ETS exposure were 1.71 (95% CI 1.33-2.20) for 0-2 yr olds, 1.57 (95% CI 1.28-1.91) for 0-6 yr olds, and 1.25 (95% CI 0.88-1.78) for 3-6 yr olds. While there was evidence of increased risk at all ages, after tests for heterogeneity of risk association across studies, only the risk for the 0-6 yr old group achieved statistical significance. The decrease in risk in older children is consistent with other studies. Adjustment for confounding was not uniform across studies. Sensitivity analysis of those studies adjusting for confounding resulted in a slight increase in the OR, from 1.93 to 2.05. Only three studies allowed differentiation of the effects of pre- versus postnatal smoke exposure. From these three studies, an OR of 2.13 (95% CI 1.52-3.00) was calculated for LRI from postnatal ETS. To address possible publication bias, the authors searched for unpublished studies. Two studies were found, neither of which had sufficient data to be included in the meta-analysis but both showed a positive association between ETS and LRI. This analysis thus provides strong evidence for an association between ETS exposure and early childhood infections of the lower respiratory tract.

Strachan and Cook (1997) conducted a meta-analysis of 38 studies examining various measures of lower respiratory illness in children exposed to ETS. Studies that looked at ETS exposure and acute lower respiratory illness (LRI) in the first three years of life were included in the meta-analysis. Inclusion required that adequate information be given so that odds ratios could be determined. The studies included represent community and hospital studies as well as all study designs (case-control, cross-sectional, and longitudinal). Odds ratios were pooled using a "random effects" model that made allowances for heterogeneity of effect between studies. Ten of the studies looked at "wheeze" as the outcome measure. The other studies looked at various combinations of acute bronchiolitis, acute bronchitis, pneumonia, and upper and lower respiratory infection.

Pooled odds ratios were 1.57 (95% CI; 1.42-1.74) for LRI with smoking by either parent, 1.72 (95% CI; 1.55-1.91) for maternal smoking, and 1.29 (95% CI; 1.16-1.44) for smoking by other household members where the mother did not smoke. All but one study that compared either parent smoking with neither parent smoking showed an increased risk to children of smokers and the ninety-fifth percentile confidence intervals for the vast majority of outcome measures did not include one (Fig 6.2). While not directly evaluated in a quantitative fashion, the authors report that the associations with parental smoking were robust to adjustment for possible confounders and that most studies showed evidence of an exposure-response relationship where data were adequate to investigate this. The pooled ORs for smoking by either parent and for smoking by other household members are statistically significant and support an association of postnatal ETS with respiratory illness that is independent of maternal prenatal smoking.

Figure 6.2 Effects of Either vs. Neither Parent Smoking on Respiratory Illness; Odds Ratios and 95% CI (Data from Strachan and Cook, 1997)



Study Descriptions and References

Community studies: "Lower Respiratory Illness".

1 Leeder *et al.*, 1976
2 Gardner *et al.*, 1984
3 Pedreira *et al.*, 1985
4 Ferris *et al.*, 1985
5 Fergusson & Horwood, 1985
6 McConnochie & Roghmann, 1986
7 Chen *et al.*, 1988
8 Hayes *et al.*, 1989
9 Forastiere *et al.*, 1992
10 Hakansson & Carlsson, 1992
11 Richards *et al.*, 1996

Community studies: "Wheezing Illness".

12 Fergusson & Horwood, 1985
13 Chen *et al.*, 1988
14 Burr *et al.*, 1989
15 Lucas *et al.*, 1990
16 Halken *et al.*, 1991

Community study: "Upper and Lower Respiratory Illness".

17 Ogston *et al.*, 1987

Hospital admission studies: "Lower Respiratory Illness".

18 Ekwo *et al.*, 1983
19 Hall *et al.*, 1984
20 Taylor & Wadsworth, 1987
21 Reese *et al.*, 1992
22 Jin & Rossignol, 1993
23 Victora *et al.*,1994
24 Rylander *et al.*, 1995

Hospital admission studies: "Lower and Upper Respiratory Illness".

25 Ogston *et al.*, 1985
26 Chen, 1994

6.2.2.2.2. New Epidemiological Studies

Gilliland et al., 2003. As described in section 6.1.1.2, this study examined the effects of ETS exposure on illness-related absenteeism in a cohort of 1,932 fourth-grade children in 12 California communities. Data on sociodemographics, indoor exposures and medical histories were obtained from parents or guardians via questionnaires at study entry. Attendance data were collected from the schools, and parents were contacted by telephone to determine the reason for the absence. Illness-related absences were categorized into respiratory or gastrointestinal. To estimate the risk of absenteeism associated with ETS exposure, incident absence rates were stratified and adjusted for sociodemographic variables including community, ethnicity, age, gender, parental education, health insurance, family income, BMI, and number of hours of outdoor activity.

Any ETS exposure was found to significantly increase the incidence of missed school days, including non-illness-related (RR 1.29, 95% CI 1.02-1.63), illness-related (RR 1.33, 95% CI 1.13-1.57), and respiratory-illness-related (RR 1.27, 95% CI 1.04-1.56) absences. Among illness-related and especially respiratory-illness-related absences, there was evidence of dose-response relationships associated with increasing numbers of smokers in the household.

Lam et al. (2001) also examined the general effects of ETS on healthcare utilization in a large prospective, population-based cohort study in China. Some 8,327 parent-infant pairs were followed for the first 18 months after birth. Health services usage was quantified as a broad measure of illness. The population was ideal for evaluating the effects of smoking by household members other than the mother since there was only a 4.6% maternal smoking rate. After adjusting for maternal education and employment, age, birth order, birth weight, delivery method and breastfeeding, ETS exposure *in utero* was associated with more outpatient consultations (OR 1.26; 95% CI 1.14-1.39) and hospitalizations (OR 1.18; 95% CI 1.05-1.31) in infants of nonsmoking mothers. Postnatal exposure to ETS was associated with increased hospitalization risk (OR 1.26; 95% CI 1.00-1.25) but not with outpatient consultation usage.

Gurkan et al., 2000. In a Turkish case-control study the association between viral bronchiolitis and ETS exposure as measured by serum cotinine was examined. The study group comprised 28 infants, 2-18 months old, admitted to an emergency room with acute syncytial viral bronchiolitis, and 30 age-matched controls admitted with non-respiratory diseases. At admission, cotinine levels were determined and data collected on health, demographics and family smoking history. Infants with bronchiolitis had significantly elevated cotinine levels compared to controls (10.8 vs. 3.9 nag/ml; $p < 0.0001$) both upon admission and during the post-bronchiolitis stage ($p < 0.0001$). Compared to controls, children with bronchiolitis were significantly more likely to have one or both parents who smoked ($p < 0.05$) and, where only one parent smoked, it was more often the mother ($p<0.05$). No significant differences were found between the two groups for the social, educational, and housing measures, nor for breastfeeding; and no multivariate analysis incorporating these factors was reported. The contribution of prenatal smoking was not assessed as this study focused on recent nicotine exposure as reflected in serum cotinine, levels of which correlated well with reported parental smoking. This study found a significant association between measures of current ETS exposure and increased incidence of syncytial viral bronchiolitis.

Hajnal et al., 1999. This investigation was part of a larger cross-sectional Swiss study of the effects of air pollution on childhood allergies and respiratory infections. Data were collected by questionnaire from the parents of 4,470 children, ages 6-14 yrs, on demographics, smoking habits, history of respiratory and allergic diseases, parental education, living situation and family size. Logistic regression analyses were used to calculate ORs for respiratory symptoms adjusted for age, sex, parental education, nationality, number of siblings, family history of atopy and asthma, heating and cooking fuels, pets, farming as the family profession, and study area. Children exposed to ETS at home had a statistically significantly elevated risk of respiratory infections (OR 1.19) during the preceding 12 months which increased if the source of ETS was the mother (OR 1.25), and even more if she smoked prenatally as well (OR 1.42) (Table 6.23). Similarly, attacks of shortness of breath after exercise, and repeated cough and bronchitis during the previous 12 months were increased by ETS exposure, especially where the mother smoked prenatally and continued to smoke currently ($p<0.05$). A dose response was observed with increasing numbers of cigarettes smoked per day for respiratory infections, repeated cough, and wheezing after exercise. Paternal current smoking was less strongly associated with these symptoms.

Table 6.23 Respiratory Symptoms with ETS Exposure; Odds Ratios (from Hajnal *et al.*, 1999)

Symptoms	Any exposure at home OR (95% CI)	Maternal current OR (95% CI)	Maternal current and prenatal OR (95% CI)	Paternal current OR (95% CI)
Repeated cough /12 mo	1.15 (0.99-1.33)	1.36 (1.14-1.61)	1.55 (1.24-1.93)	0.94 (0.78-1.14)
Respiratory infection /12 mo	1.19 (1.03-1.37)	1.25 (1.06-1.48)	1.42 (1.14-1.76)	1.13 (0.94-1.36)
Bronchitis /12 mo	1.18 (0.97-1.44)	1.25 (0.99-1.56)	1.33 (1.01-1.75)	1.12 (0.86-1.44)
Shortness of breath /exercise	1.50 (1.08-2.07)	1.71 (1.18-2.48)	1.73 (1.10-2.77)	1.18 (0.77-1.83)

The strengths of this study include extensive control for various risk factors and confounders, and the apparent ability to discriminate prenatal and postnatal maternal smoking. No airborne measures of ETS exposure or biomonitoring were included. The data support an association of ETS exposure with increased respiratory infection and impaired lung function.

Gergen et al., 1998. The Third National Health and Nutrition Examination Survey (NHANES III) was the basis for this cross-sectional analysis of the contribution of ETS exposure to respiratory illness in 7,680 children, 2 months to 5 years of age. Data on demographics, education, health history, breastfeeding and smoking habits were derived from home interviews and physical examinations.

Logistic regression analysis, adjusted for age, sex, race, birth weight, day care, history of allergy, breastfeeding, education, and household size showed that occurrence of bronchitis or three or more episodes of wheezing in the previous 12 months was associated with ETS exposure, especially at higher exposure levels. Stratification by age revealed that the youngest children (2 mo – 2 yrs) were more susceptible than were the 3-5 year olds (Table 6.24). Calculations of attributable risk from these data indicate that among children exposed to ETS from ≥ 20

cigarettes per day, 55-60% of the cases of chronic bronchitis and episodes of wheezing (3 or more per year) were attributable to ETS exposure.

Maternal smoking during pregnancy was seen to increase chronic bronchitis and episodes of wheezing, again especially in the younger children. While this study did not allow separation of pre- from postnatal exposures, the ORs for bronchitis and wheezing associated with ETS from ≥ 20 cigarettes per day were generally higher than those associated with *in utero* exposure. This suggests that, at the very least, postnatal ETS exacerbates deteriorations in respiratory health resulting from exposure *in utero*.

Table 6.24 Age-Dependent Respiratory Symptoms with ETS; Odds Ratios

Condition # cigarettes/day	Total OR (95% CI)	2 mo-2 yrs OR (95% CI)	3-5 yrs OR (95% CI)
Bronchitis 0	1	1	1
1-19	1.2 (0.8-1.7)	1.3 (0.8-1.9)	1.2 (0.7-2.1)
≥ 20	1.8 (1.1-3.0)	2.5 (1.6-4.1)	1.3 (0.6-2.9)
Wheezing 0	1	1	1
1-19	1.4 (1.1-1.9)	1.7 (1.2-2.5)	1.2 (0.8-1.8)
≥ 20	1.9 (1.2-3.1)	2.7 (1.7-4.2)	1.2 (0.6-2.4)
In utero exposure			
Bronchitis	1.5 (1.1-2.0)	2.2 (1.6-3.0)	1.0 (0.6-1.8)
Wheezing	1.8 (1.4-2.4)	2.1 (1.5-2.9)	1.3 (0.8-2.0)

(Data from Gergen *et al.*, 1998)

Peters et al., 1998. One way of quantifying the health and societal impacts of ETS exposure is to compare the utilization of healthcare services and the attendant costs for children from smoking versus nonsmoking households. The frequency of doctor consultations in Hong Kong for cough, phlegm, or wheeze over a three-month period among 10,402 children ages 8-13 years was assessed by questionnaires completed by both the children and their parents. Data were collected on respiratory symptoms, doctor visits, family smoking habits, socioeconomic status, age, area of residence and educational level. In the analyses, adjustment was made for potential confounding by age, sex, district of residence, father's education, and type of housing.

Physician consultations for all symptoms were significantly more frequent among children from households with one or more smokers (Table 6.25). There was also a significant dose response trend for the cough, phlegm, and any-symptom categories related to the number of household smokers. This trend was also reflected in the estimated costs associated with the provision of healthcare. The expected healthcare costs for children from households where only one person smoked were 13.1% higher, while if two or more people smoked the costs were 24.7% higher than in nonsmoking households.

Table 6.25 Doctor Consultations for Respiratory Symptoms by Number of Smokers

Household smokers	Cough OR (95% CI)	Phlegm OR (95% CI)	Wheeze OR (95% CI)	Any symptom OR (95% CI)
None	1	1	1	1
One	1.15 (1.01-1.32)	1.26 (1.02-1.54)	1.04 (0.76-1.41)	1.15 (1.01-1.31)
Two or more	1.33 (1.08-1.64)	1.33 (0.97-1.83)	1.57 (1.02-2.43)	1.38 (1.14-1.67)
Trend by # smokers	$p < 0.01$	$p < 0.05$	NS	$p < 0.001$

(Data from Peters *et al.*, 1998)

Margolis et al. (1997) examined the association between the incidence of acute lower respiratory illness (LRI) and two measures of passive smoke exposure in a community-based cohort study comprising 325 infants. Data on smoking habits, demographics, environment, health history and LRI symptoms were collected during home visits at 3 weeks, and 1, 6, and 12 months of age and by telephone. Urine was collected from the infants for cotinine analysis. The relationship between ETS and LRI was examined with Poisson regression models adjusted for such factors as education, birth weight, breastfeeding, gender, history of allergy or respiratory disease, maternal age, and daycare attendance.

By both measures of ETS, increased risk of LRI was associated with increasing exposure. Although the trend was similar, a statistically significant association with LRI was observed with parents' reported smoking but not with urinary cotinine. This is similar to Rylander *et al.* (1995). The strong association between reported ETS and LRI versus the weak association with urinary cotinine is likely related to individual differences in nicotine metabolism, and suggests that other smoke components in addition to nicotine or its metabolites are responsible for the effects of ETS on respiratory disease. This is consistent with a direct versus systemic action of smoke components on the lungs.

Table 6.26 Incidence and Risk of Lower Respiratory Tract Infection with ETS

Exposure	Incidence (95% CI) (episodes/child-yr)	RR (95% CI)
None	0.6 (0.30-1.2)	- - -
≤ 10 cigarettes/day	0.89 (0.42-1.9)	1.5 (1.1-2.0)
> 10 "	1.3 (0.54-3.2)	2.2 (1.3-3.8)
Cotinine (ng/mg)		
0	0.64 (0.37-1.1)	- - -
≤ 120	0.82 (0.41-1.6)	1.3 (0.8-2.1)
> 120	0.88 (1.46-1.7)	1.4 (0.9-2.1)

(Data from Margolis *et al.*, 1997)

Prenatal exposure data were not available for all cases but where available, the correlation between prenatal smoking with measures of ETS exposure and urinary cotinine reportedly was weak. This information was thus excluded from the analysis precluding determination of the contribution of prenatal exposure. Nevertheless, the data suggest that postnatal exposure to ETS from more than 10 cigarettes per day doubles the risk and incidence of LRI.

Jedrychowski and Flak, 1997. The effects of pre- and postnatal smoke exposure on respiratory infection were assessed in a cross-sectional study of 1,129 9-year old school children in Poland.

The occurrence of doctor-diagnosed upper (tonsillitis) and lower (laryngitis, tracheolitis, bronchitis) respiratory infections (RI) during the previous 12 months was the subject of this analysis. Data regarding the mothers' smoking habits both during and after pregnancy, educational level and child's history of diagnosed allergy were collected by interview and the latter were adjusted for in the multivariate analyses.

Postnatal-only exposure to ETS was associated with increased risk of RI (OR 1.32) that was statistically significant at higher exposure levels (OR 1.74) (Table 6.27). Combined pre- and postnatal smoking more than doubled the risk of RI relative to no exposure. In the absence of prenatal exposure, there was a significant risk of RI associated with atopy (reported doctor diagnosis of allergy; OR 2.86) that was exacerbated by postnatal exposure to ETS (OR 3.39).

Table 6.27 Respiratory Infections with Atopy, Pre- and Postnatal ETS; Odds Ratios

Smoke exposure	OR (95% CI)
Postnatal only ≤ 9 cigarettes/day	1.32 (0.83-2.10)
Postnatal only ≥ 10 "	1.74 (1.06-2.87)
Pre- & Postnatal < 9 "	2.32 (1.13-4.76)
Pre- & Postnatal ≥ 10 "	2.36 (1.32-4.17)
Atopy + none	2.86 (1.61-5.10)
Atopy + postnatal only ≤ 9 cig/day	3.39 (1.93-5.93)
Atopy + postnatal only ≥ 10 "	3.31 (1.71-6.42)

(Data from Jedrychowski and Flak, 1997)

This study found a strong association between postnatal ETS exposure and RI, especially at higher smoke levels, in combination with prenatal smoking and in the presence of underlying atopy. The estimation of exposure was, however, retrospective over a ten-year period and so may be subject to some recall bias. An evaluation of this smoking habit status questionnaire by the authors (utilizing plasma cotinine at delivery) suggests that the observed risk is underestimated by the exposure misclassification error.

Nafstad et al., 1996. Based on a birth cohort in Norway, this prospective study examined the effects of breastfeeding and maternal smoking on the incidence of reported doctor-diagnosed lower respiratory tract infections (LRI; i.e. bronchitis, pneumonia, bronchiolitis) during the first year of life in 3,238 children. Data collected at birth, and at 6 and 12 months of age included parental smoking habits, duration of breastfeeding, gender, birth weight, maternal age and education, family income, family structure and health history. Logistic regression analysis adjusted for these factors showed that in children breastfed for 0-6 months, ETS exposure from the mother carried a risk for all LRI of 2.2 (95% CI 1.6-3.1), and for infection requiring hospitalization, an OR of 4.6 (95% CI 2.5-8.3) compared to no smoking with breastfeeding for >6 months. The effect of ETS was ameliorated by prolonged breastfeeding, dropping the OR for all infections to 1.1 (95% CI 0.7-1.6), and for severe infections also to 1.1 (95% CI 0.5-2.7). It is not clear if and what other factors may have distinguished the long-term breastfeeding mother-infant pairs from those breastfeeding for less time. However it is evident that in the latter group, ETS exposure was associated with a doubling of the risk of any LRI, and a more than 4-fold increase in severe LRI requiring hospitalization.

6.2.2.3. Summary – Lower Respiratory Illness in Children

The studies reviewed provide additional strong evidence supporting the 1997 conclusion that ETS exposure is causally related to lower respiratory tract infections in children. All eleven of the studies reviewed above found increased risk of respiratory illness in children associated with smoke exposure as measured by incidence of symptoms, diagnosed disease or health services utilization. While the risk of illness was highest for children of mothers who smoked during pregnancy, from five studies in which it was possible to distinguish the effects of postnatal ETS exposure from maternal prenatal smoking, the OR for symptoms of respiratory disease ranged from 1.26 to 2.13 for postnatal ETS exposure. The effects of ETS were exacerbated if the child was atopic (OR 3.31 vs. 1.74; Jedrychowski and Flak, 1997) but ameliorated somewhat in one study by breastfeeding (OR 1.1 vs. 4.6; Nafstad *et al.*, 1996). As seen previously, younger children were more at risk than older children. This is thought to reflect not only maturation of the pulmonary and immune systems, but also less time spent in the presence of a household smoker as the child matures. Maternal smoking was generally the most important source of ETS and the risk of illness increased with more intense smoking and/or additional household smokers.

6.2.3. Otitis Media in Children)

6.2.3.1. Background/Definitions

The following pathophysiological background information is reiterated from the earlier Cal/EPA report:

> "Otitis media is the most commonly diagnosed problem in outpatient pediatrics in the United States today (Greer *et al.*, 1993). In the context of this discussion, it is useful to consider the anatomy 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 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 (Hackshaw *et al.*, 1997). 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.

6.2.3.2. Summary of Previous Findings

In its 1997 report, Cal/EPA reviewed a total of 22 reports examining a possible link between ETS exposure and otitis media (OM). Twelve of these studies had previously been reviewed by the Surgeon General's Office, and an additional 10 were added as part of Cal/EPA's review process. Ten of the 12 original studies showed significant positive associations between ETS exposure and OM, and 5 of 10 studies reviewed for the first time by Cal/EPA showed significant positive associations. Of this total of 25 studies, few were without potential methodological shortcomings. The three most convincing studies were summarized as follows:

> "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 (Iversen., 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." (Cal/EPA, 1997)

6.2.3.3. New Epidemiological Findings

Seven studies not previously reviewed by the Surgeon General's Office (U.S. DHHS, 1986b), NRC (1986b), US EPA (1992f) or Cal/EPA (1997) are summarized in Table 6.28 and in the following paragraphs.

Table 6.28 Studies of Middle Ear Effusion (MEE) or Otitis Media (OM) vs. ETS

Reference Country	Study Description	Exposure to smoke	Findings and OR (95% CI)	Comments
Ilicali *et al* 2001 Turkey	Case-control: OM in 3-8 yr olds vs. urinary cotinine n = 114, Ctrl = 40	Parental	Cotinine elevated in 74% cases, 55% controls. OM OR 2.29 (1.08-4.85) ($p<0.05$)	Cotinine elevated in more cases than ctrls. Age and sex but no other covariates used.
Rylander & Megevand 2000 Sweden	Cross-sectional 4-5 yr n = 304 OM, allergy, resp illness	ETS at home	1-19 cig, OR 1.04 > 20 cig, OR 1.18. CIs for both include 1.00	Control for allergies may have decreased OR for OM w/ETS
Gryczynska *et al* 1999 Poland	Unclear – purports to test ETS and OM among preschoolers	Parental	Results uninterpretable	Limited due to scant methodology and questionable analysis
Lister & Jorm 1998 Australia	Cross-sectional of kids 0-4 yr n = 4281 Respiratory illness	Parental	No significant association of smoking with OM	Limited due to no specific interview question on OM
Paradise *et al* 1997 US	Prospective cohort 2 mo to 2 yr. ETS and MEE n = 2253	ETS (home) Days MEE 1st yr.	# household smokers: 0: 18.4; 1: 22.8; 2: 25; ≥ 3: 24.8. Linear trend *p = <0.001*	Middle ear effusion (MEE). Controlled for SES, breastfeeding
Stenstrom *et al* 1993 Canada	Case-control of RAOM in kids < 5 yr old. n = 85	ETS in and outside the home.	ETS at home vs. RAOM OR 2.68 (1.27-5.65)	Recurrent acute otitis media (RAOM) increased with total adult smoking.
Owen *et al* 1993 US	Prospective cohort, birth to 1 or 2 yrs. Effects of ETS on OME. n = 534	ETS from parents	Significantly greater number of days of OME during 2nd year with increasing number of cigarettes smoked	Otitis media with effusion (OME). ETS measured as packs/day from interview.

* MEE middle ear infusion; OM otitis media; OME otitis media with effusion; RAOM recurrent acute otitis media

Ilicali et al., 2001. In the only study employing biomarkers of ETS exposure, Ilicali *et al.* recruited 114 children (aged 3-8 yrs.) who had been referred to an otolaryngology clinic for tympanostomy for chronic OM. Forty controls with a similar age- and sex-distribution were recruited from among children referred to orthopedic clinic. ETS exposure was ascertained from children's urinary cotinine levels, with a pre-determined cutoff for "exposed" individuals. Aside from matching criteria, no other covariates were considered. As judged by biomarkers, ETS exposure was highly prevalent in both groups (74% in the case group and 55% in the control group). Nevertheless, the odds ratio for ETS exposure and OM was elevated at 2.29 (95% CI 1.08-4.85). A potential weakness of this study is its limited attention to covariates.

Rylander and Megevand, 2000. In another cross-sectional study, 304 preschool children (aged 4-5 yrs) were randomly recruited as they were enrolled in mandatory health screening. Sixty-five percent of parents contacted (204 of 340 initial sample) agreed to be interviewed. Primary variables included smoking habits at home of parents and other family members, parental report of frequency of ear infections, and frequency of colds and bronchitis during the previous year. Covariates included physician-diagnosed allergy, and maternal age. Day care attendance, molds

in home, and pets in home were also examined as risk factors for respiratory disease. Odds ratios for ETS exposure (smoking in home) and OM were 1.04 for 1-19 cigarettes, and 1.18 for > 20 cigarettes per day, but both confidence intervals included 1.00. A potential weakness of this study is possible "over-control." Specifically, if ETS exposure is causally associated with atopy, and if atopy is associated with OM ($p<0.01$ in this study), then controlling for children's allergies would artificially deflate the odds ratios for ETS and OM.

Gryczynska et al., 1999. In an apparent cross-sectional study, Gryczynska and colleagues examined "interview questionnaires" [presumably of the parents] of 440 preschool (age >3 yrs., but upper limit not defined in paper) and 560 school-aged children (up to age 13). The study purports to show a relationship between ETS exposure and recurrent upper respiratory tract infection, including OM, among preschool children. However, as the study methodology was presented in only two sentences and the categorical analysis of data questionable, the study is essentially uninterpretable.

Lister and Jorm (1998) in a cross-sectional study, analyzed data obtained as part of Australian Bureau of Statistics National Health Survey during the period 1989-1990. 4,281 children aged 0-4 years were included. Paternal and maternal smoking, as well as total cigarettes smoked per day, were ascertained by interview. No specific questions were asked about OM; parents needed to volunteer the diagnosis as a "long-term condition." Covariates included gender, socioeconomic status, family size, and home language. No significant relationship between ETS exposure (i.e. parental smoking) and OM was found. Major limitations of the study included the lack of specific questions regarding OM, lack of specific questions regarding smoking in the home environment, the relatively limited treatment of potential confounders, and lack of biomarkers of ETS exposure.

Paradise et al., 1997. In a cohort study, Paradise *et al.* prospectively followed children less than or equal to 2 months of age who presented to participating hospital-based clinics or private pediatric practices. Of 3,663 children enrolled, 2,253 were successfully followed up until 2 yrs. of age with monthly screening for middle ear effusion (MEE), with or without acute otitis media, using pneumatic otoscopy. ETS exposure was ascertained by parental interview, and was indexed to the number of smokers in the household. Covariates included gender, race, birth weight, maternal age, maternal education, socioeconomic status, breast- vs. bottle-feeding, number of other children in household, and day care in the first year of life. The authors noted a significant trend toward more days with MEE during the first year of life as a function of reported number of smokers in the household (p value linear trend test = < .001; Table 6.28). There was no significant association noted during the second year of life. Strengths of this study included cohort size and prospective screening for MEE. Weaknesses included use of a historical index of ETS exposure (reported number of smokers in a household) without biomarkers, lack of specific questions about smoking in the home environment and lack of identification of family history of allergy or otitis media.

Stenstrom et al. (1993) recruited 85 children under age five years who were referred to a pediatric otorhinolaryngology clinic for recurrent acute otitis media (RAOM; defined as >4 episodes in 12-months) for this case-control study. An equal number of age- and gender-matched controls (free of OM for the previous 12 months) were recruited from a pediatric ophthalmology clinic. Exposure status was ascertained by parental questionnaire, and included

both the total number of cigarettes-per-day smoked by all caregivers/family members, as well as a specific history of smoking by any adult in the home. Potential confounders included family history of OM, documented atopy, prematurity, breast- vs. bottle-feeding, daycare attendance, and socioeconomic status. The authors observed a significantly elevated odds ratio for RAOM and ETS exposure (home exposure; OR 2.68; 95% CI 1.27-5.65), with a positive exposure-response gradient (total adult smoking). The strength of this study was its rigorous definition of RAOM and inclusion of potential exposures outside the home; its weakness was the use of an historical exposure index, without biomarkers.

Owen et al., 1993. For this cohort study, 698 healthy term infants were recruited from English-speaking homes at three hospital nurseries in Galveston, TX between 1984 and 1989. The children were followed prospectively from birth to 1 yr. of age (n = 534) and birth to 2 yrs. of age (n = 435). Children were screened prospectively at 2-4 week intervals for otitis media with effusion (OME) using tympanometry, supplemented with acoustic reflectometry in a subset of visits. ETS exposure was ascertained by parental interview, and was taken as a continuous variable proportional to the total number of packs smoked per day by all adults in the household. Potential confounders controlled in the study included sex, ethnicity, breast vs. bottle feeding, hours-per-week in group child care, and presence or absence of tympanostomy tubes. Family history of allergy and otitis media were not addressed. During the second year of life (and particularly between the ages of 12 and 18 months), there was a significantly greater number of days with OME as a function of reported total number of packs-per-day smoked by household members. A strength of this study was the prospective nature of otitis media screening. A weakness was the use of total packs-per-day of adult smoking rather than either a more specific history of in-home smoking, or use of a smoke exposure biomarker. Potential ETS exposure outside of the home was also not documented.

6.2.3.4. Biological Plausibility

In its 1997 report, Cal/EPA highlighted at least four potential mechanisms whereby ETS exposure might predispose children to the development of middle ear disease. Eustachian tube dysfunction (ETD) plays a central role in each of these mechanisms. Newer pathophysiological data pertaining to these mechanisms are reviewed here. In addition, two new studies, one involving an animal model of secretory OM and the other an *in vitro* study of mucus hypersecretion, are included in separate categories:

1) Decreased mucociliary clearance: No new data encountered

2) Decreased Eustachian tube patency due to adenoidal hyperplasia: No new data encountered

3) Decreased patency due to ETS-induced mucosal swelling

   Vinke et al. (1999) examined nasal biopsy material obtained from the inferior turbinates of children referred for tonsillectomy-adenoidectomy. In general, children underwent surgery because of recurrent upper respiratory tract infections, sleep apnea, or recurrent otitis media. From an initial group of 54 children screened for allergies using an in vitro test (radioimmunoassay), 10 non-atopic ETS-exposed children aged 1.4-10 years were

identified, along with a like number of gender- and age-matched controls. Using immunohistochemical staining techniques, the authors found a significantly greater density of IgE-positive eosinophils (consistent with allergic inflammation) but not mast cells (indicative of allergic sensitization) in the mucosae of ETS-exposed children. They interpreted this to show a link between parentally reported ETS exposure and allergic-like inflammation in the nasal mucosa, in the absence of true allergic sensitization.

Zavras et al. (1997) conducted a cross-sectional study of 54 children age 7-12 years recruited from a pediatric dentistry clinic at a major university. Parents completed a questionnaire (including information on children's allergies and/or asthma and ETS exposure at home) and children underwent acoustic rhinometry (to determine nasal volume and minimum nasal cross-sectional area). Roughly half of the children were ETS-exposed at home per parental report, and this subgroup had significantly lower nasal volumes, correcting for age, gender, race, obesity, and allergies. Although minimum cross-sectional area was lower among ETS-exposed children, it was not significantly so. The authors interpreted their findings to indicate that ETS exposure is associated with nasal mucosal swelling, along with possible inflammation, although the latter endpoint was not directly assessed.

4) Decreased patency and impaired mucociliary clearance secondary to increased frequency of viral upper respiratory tract infections (URI's): No new data encountered

5) Animal model of secretory OM

Coggins et al. (1997) exposed male Sprague-Dawley rats to aged and diluted sidestream tobacco smoke (STS), 6 hrs/day for 5 days. Three groups of 20 animals each were exposed to: 1) high-level STS; 2) low-level STS; and 3) control conditions. Ten of 20 rats in each group were pre-treated with cold air per external auditory canal to induce middle ear effusions, and rates of clearance, rather than induction of ear pathology, were observed in these groups. Animals were examined daily for secretory otitis media (SOM), and at the conclusion of the experiment the animals were sacrificed and their middle ears and Eustachian tubes examined histologically. Other than on the first day of exposure (when there were more incident cases of SOM in the low-exposure group than either control or high-exposure group), the rates of new-onset SOM (and rates of clearance of cold-air induced SOM) were not significantly different among the three treatment groups. Histological staining revealed no difference in the relative number of goblet cells between the three groups, nor were inflammatory cells observed. A potential limitation in interpreting this study is the fact that the rat nasal cavity much more efficiently clears water-soluble air pollutants before they can reach the pharynx (and Eustachian tube opening) than does the human nasal cavity.

6) Cell culture model of mucus hypersecretion

Borchers et al. (1999) exposed human lung carcinoma cells *in vitro* to acrolein, an irritant found in ETS. The cells produced significantly elevated levels of messenger RNA coding for two different mucins, MUC5AC and MUC5B. Mucins are an essential component of airway mucus, and the authors make the point that increased mucin

> production by airway epithelial cells translates clinically into mucus hypersecretion, as seen in various pathological respiratory tract conditions including asthma.

6.2.3.5. Summary and Conclusions – Otitis Media.

Of the additional seven studies reviewed here, four (all cohort or case-control studies) found a significant positive association between ETS exposure and OM. The two cohort studies (Owen *et al.*, 1993; Paradise *et al.*, 1997) both employed regular prospective screening for otitis media, using pneumatic otoscopy and/or tympanometry. (This design feature is important in eliminating the factor of "diagnostic bias" as a potential study limitation.) One of the two case-control studies utilized urinary cotinine as a marker of exposure (Ilicali, 2001). (Use of biomarkers is important in addressing the issue of potential exposure misclassification.) None of the newly reviewed studies used both prospective screening for OM *and* biomarkers, as was the case in the study by Etzel *et al.* (1992) which was reviewed in our 1997 document. Of the three remaining studies, one (Gryczynska *et al.*, 1999) was of unknown study design, and was generally uninterpretable. The remaining two "negative" studies were both cross-sectional. A major limitation of one of these studies is that it required that parents volunteer a diagnosis otitis media under the general rubric of "recent or chronic respiratory illnesses" (Lister and Jorm, 1998); the other was marred by possible overcontrol (for allergy status) (Rylander and Megevand, 2000). There is, in the literature reviewed, inadequate information to draw any conclusion regarding potentially susceptible subpopulations such as children with atopy or allergy.

In 1997, Cal/EPA concluded:

> "Overall, the epidemiological 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 two 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."

The current literature review provides no compelling evidence for modifying the above conclusions regarding the association of otitis media with effusion with ETS exposure in young children. Thus, the 1997 conclusion is still appropriate and consistent with the additional newer data.

6.2.3.6. Attributable Risk Considerations

In its 1997 report, Cal/EPA estimated that some 134,251 pediatric outpatient visits for middle ear disease (95% CI: 78,615-188,676) could be attributed to ETS exposure in the home. Given the interval decrease in estimated adult smoking rates in California, as well as the intervening change in population, the following re-calculation is offered:

1) According to the California Department of Health Services Tobacco Control Section an estimated 11.4% of California children under the age of 18 years were exposed to ETS in the home in 1999 (Gilpin *et al.*, 2001). This compares with an earlier estimate of 33% of children under 3 years (Tariq *et al.*, 2000), used in Cal/EPA's 1997 calculations.

2) Using data from Etzel *et al.* (1992) indicating that ETS-exposed children under age 3 years experience an average of 38% (95% confidence interval, 21-56%) excess incidence of OM (Relative risk – 1; R-1), we applied California's estimated ETS exposure prevalence (p) of 11.4 % to obtain an ETS-attributable otitis media fraction (a) of 4.1% (95% confidence interval, 2.5-6.4%).

$$a = p (R-1) / (p(R-1) +1)$$ (Lilienfeld and Lilienfeld, 1980b)

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% of all office visits for children under age 5 years). OM was cited as the principal diagnosis for 102 office visits per 100 children (under two years of age) per year in 1990; and for 48 office visits per 100 children aged 2-5 years (Schappert, 1992).

4) In 2000, California had a population of 1,459,066 children under age three years. Of these children, 483,143 were under age one year, 486,587 were 1-2 years, and 489,336 were in their third year of life (U.S. Census Bureau).

5) Assuming that ETS-related otitis media with effusion 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 with effusion) and the NAMCS data (pertaining to all OM-related office visits-- both initial, follow-up, acute and chronic). This calculation of attributable risk may represent 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. It may represent an over-estimation if a higher percentage of non-ETS related episodes result in acute otitis media which may be more likely to result in physician visits.

Combining the above data, one obtains an estimate of 50,184 office visits per year among California children under age three years for ETS-attributable otitis media episodes:

Table 6.29 ETS-attributable Office Visits for Otitis Media

	Population at risk x	**Age-specific Otitis Media visit rate =**	**OM-Related Office visits x**	**ETS-attributable fraction =**	**ETS-attributable visits/year**
Age ≤ 2 yr	969,730 x	102/100 =	989,125		
Age 2-3 yr	489,336 x	48/100 =	234,881		
Total			1,224,006 x	0.041 =	50,184

According to this and earlier estimates, some 84,000 pediatric physician office visits per year for otitis media may have been avoided by virtue of changes in smoking behavior on the part of California adults since the calculation in the 1997 document (based on smoking data from Wiley, 1991).

6.3. Chronic Health Effects (Children)

6.3.1. Chronic Respiratory Symptoms (children)

The previous review (Cal EPA, 1997) identified several studies addressing the occurrence of chronic respiratory symptoms in children, and concluded that these:

> "… 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.

Although several new studies of acute effects were discussed earlier (Section 6.1.2), no new studies addressing the chronic endpoints discussed in this section of the previous review were identified, so this conclusion is unmodified.

6.3.2. Asthma Induction in Children

Numerous studies have evaluated the impact of ETS exposure on childhood asthma induction (Chilmonczyk *et al.*, 1993). The 1997 Cal/EPA report included a meta-analysis of 37 studies conducted between 1975 and 1995 that evaluated ETS exposure as a risk factor for induction of childhood asthma. The pooled RR for asthma was 1.44 (95% CI 1.27-1.64). These data supported a causal association between ETS and new onset of childhood asthma cases (Cal EPA, 1997). Recent studies, including an updated meta-analysis by OEHHA (submitted for publication and abstract included below), continue to support a causal role of ETS in childhood asthma induction. The studies are presented below and in Tables 6.30 – 6.32. They are separated by study type: cross-sectional, case-control, and prospective cohort.

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Gilliland *et al* 2001 US	Cross-sectional study 4-12th graders n = 5,762	Parental smoking Postnatal only *In utero* only Both 1 smoker ≥ 2 smokers	Diagnosed asthma 1.1 (0.9-1.4) 1.8 (1.1-2.9) 1.4 (0.9-2.3) 0.9 (0.6-1.3) 1.7 (1.1-2.5)	Asthma increased by *in utero* exposure and increasing numbers of smokers postnatally but postnatal effect included unity.
Mannino *et al* 2001 NHANES III US	Cross-sectional study Cotinine and asthma in 1,533 4-6 yr; 2,225 7-11 yr; 1,642 12-16 yr	Serum cotinine Highest tertile	Asthma OR Ever 2.3 (1.1-5.1) Current 5.3 (2.2-12.7) Wheeze 3.8 (1.7-8.3)	ETS associated with asthma onset in 4-6 yr olds. Less clear risk in older kids.
Lanphear *et al* 2001 NHANES III	Cross-sectional study Asthma onset <6 yrs, n = 8257	Parental smoking Home – pre- and postnatal	Asthma OR for pre- and postnatal ETS 1.7 (1.2-2.5)	No relation between only pre- or only post-natal ETS and asthma
Kivity *et al* 2001 Israel	Cross-sectional study Prevalence 8-17 yr n = 1243	Town - parent Arab: father Jewish: father Jewish: mother	Asthma; ETS vs. none 11.4% vs. 6.6% p<0.05 19% vs. 11% “ 20% vs. 12% “	Parental smoking significantly increased asthma prevalence.
Al-Dawood 2001 Saudi Arabia	Cross-sectional study Boys 6-15 yrs n = 1,482	Parental smoking Mother Father	Asthma 1.32 p < 0.01 1.52 p < 0.01	Asthmatic children more likely to have smoking mothers (7.8% vs. 3.8%), fathers (53.9% vs. 30%)
Gupta *et al* 2001 India	Cross-sectional study 6-12th graders n = 9,090	Child report Home or none	Asthma symptoms 1.8 (1.3-2.4)	Child self-reported symptoms increased with parental smoking
Lam *et al* 1999 Hong Kong	Population-based Cross-sectional study 7-13 yrs n = 3,964	Home Any ETS 1 smoker 2 smokers ≥ 3 smokers	Asthma 0.92 (0.71-1.19) 0.93 (CI not given) 0.97 “ 0.74 “	ETS and asthma not significantly correlated but cough, phlegm production, and recent physician visits for wheeze were elevated.
Wang *et al* 1999 Taiwan	Cross-sectional study Prevalence 11-16 yr n = 165,173	Parental smoking	Asthma OR 1.08 (1.05-1.12)	Large, well-controlled population-based study

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Hajnal *et al* 1999 Switzerland	Population-based cross-sectional study 6-7 yr, 9-11 yr, 13-14 yr n = 4,470	Parental smoking Mother Others Any Mother Others Any Mother Others Any	Asthma 1.16 (0.89-1.55) 1.20 (0.87-1.65) 1.20 (0.94-1.54) Wheeze - past 12 mo 1.36 (1.03-1.60) 1.12 (0.81-1.55) 1.27 (0.99-1.63) Short breath after exercise – past 12 mo 1.71 (1.18-2.48) 1.18 (0.77-1.83) 1.50 (1.08-2.07)	Multicenter study. Wheeze and attacks of shortness of breath after exercise more strongly associated with ETS (esp. maternal) than asthma.
Ronmark *et al* 1999 Sweden	Cross-sectional study Ever asthma, atopy 7-8 yr n = 2454	Maternal smoking Atopic asthma Nonatopic asthma	1.29 (0.95-1.74) 1.17 (0.68-2.01) 1.67 (1.04-2.68)	ETS increased risk of asthma; ameliorated by breast-feeding. In families without history of asthma, and breast-fed < 3 months, OR for maternal smoking 1.95 (95% CI 1.18-3.24)
Shamssain & Shamsian 1999 UK	Population-based Cross-sectional study 6-7 yr n = 3000	Family ETS Father Mother	Ever asthma 1.10 (0.84-1.44) 1.39 (1.12-1.74)	Maternal ETS assoc. with asthma. Ever wheezing associated with maternal: 1.46 (1.19-1.79) and paternal:1.38 (1.11-1.72)
Gergen *et al.*1998 NHANES III	Cross-sectional study Asthma 2 mo-5 yr n = 7,680	Household 1-19 cig/day ≥ 20 “	Ever asthma 1.1 (0.8 -1.6) 2.1 (1.4 -3.2)	Physician-diagnosed asthma significantly elevated at higher exposures.
Lister & Jorm 1998 Australia	Cross-sectional study 0-4 yrs n = 4,281	Parental smoking Mother Father	Asthma 1.52 (1.19-1.94) 0.77 (0.60-0.98)	Maternal but not paternal smoking associated with asthma.

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Lam *et al* 1998 Hong Kong	Population-based Cross-sectional study 12-15 yrs n = 6,304	Self report home 1 smoker 2 smokers ≥ 3 smokers Father Mother	Physician diagnosed asthma 0.89 (0.69-1.12) 0.89 (0.6-1.32) 1.49 (0.81-2.71) 0.92 (0.72-1.17) 1.32 (0.71-2.45)	Self reported physician-diagnosed asthma. Highest exposure also associated with recent use of asthma medicine OR 2.86-95% CI 1.09 - 7.49
Kendirli *et al* 1998 Turkey	Population-based cross-sectional study 6-14 yr n = 2,334	Household parent reported	Physician diagnosed asthma 1.41 (1.16-1.72)	Domestic ETS exposure was also associated with rhinoconjunctivitis and wheezing.
Maier *et al* 1997 US	Cross-sectional study Onset 5-9 yr n = 925	Parental smoking Home: any ETS Occasional ETS	Asthma 1.6 (0.9-2.7) Wheeze 1.8 (1.0-3.2) Asthma 2.5 (1.5-4.3) Wheeze 1.8 (1.0-3.2)	Diagnosed asthma and wheeze increased with increased ETS
Hu *et al* 1997a US	Cross-sectional study 5th graders n = 705	Parental smoking Past week *In utero*	Diagnosed asthma 0.8 (0.5-1.5) 1.9 (1.1-3.5)	No association of ETS in past week with asthma. Result biased by short assessment period and maternal reporting bias.
Farber *et al* 1997 US	Cross-sectional study over 3 yrs 5-17 yr n=3,174	Parental smoking 1984-5 1987-8 1992-4	Asthma 1.35 (1.01-1.81) 1.51 (1.17-1.96) 1.39 (1.11-1.72)	Consistent association of asthma with maternal smoking over 10 yrs.
Selcuk *et al* 1997 Turkey	Cross-sectional study 7-12 yr n = 5,412	Home	Lifetime asthma 1.35 (1.12-1.62) Current asthma 1.28 (0.94-1.75)	Lifetime asthma more strongly associated with ETS than current asthma.
Cunningham *et al* 1996 US, Canada	Cross-sectional study School-based Effects of home current or previous ETS on respiratory symptoms	Maternal report Home current Home previous	Diagnosed asthma 1.08 Wheeze w/ cold 1.65 Wheeze no cold 1.15 Persistent wheeze 1.42 Diagnosed asthma 1.03 Wheeze w/ cold 1.24 Wheeze no cold 1.0 Persistent wheeze 1.03	No statistical association between current or previous ETS and "active asthma". However prenatal exposure raised risk of active asthma OR 2.7 (1.13-6.45). Statistically significant associations were found for several wheezing outcomes.

Table 6.30 ETS and New-onset Childhood Asthma – Cross-sectional Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Chen *et al* 1996 Canada	Cross-sectional study 6-17 yrs n = 892	Parental smoking. allergic children non-allergic 1-19 cig/day ≥ 20	Diagnosed asthma 1.04 (0.49-2.21) 2.47 (0.74-7.86) 3.96 (1.01-15.42) 4.58 (1.34-15.68)	Statistically non-significant effect when stratified by allergy status but significant effect by exposure level.
Peters *et al* 1996 Hong Kong	Cross-sectional study 8-12 yrs n = 3,521	Parental smoking 1 smoker ≥ 2 smokers	Asthma symptoms 0.91 (0.69-1.19) 1.55 (1.08-2.23)	Exposure-response seen for asthma symptoms especially with wheeze.
Beckett *et al* 1996 US	Cross-sectional study < 18 yr n = 9,276	Parental smoking Maternal	Diagnosed asthma 1.53 (1.31-1.80)	Race/ethnicity differences in asthma susceptibility
Stoddard & Miller 1995 US	Cross-sectional study < 18 yrs n = 7,578	Parental smoking Mother Father	Asthma last 12 mo 1.36 (1.14-1.62) 0.83 (0.67-1.02)	Risk from maternal smoke greatest for young kids; decreases with age. Maternal smoking (0-2 yr) OR 1.9 (95% 1.23-2.94).

Gilliland et al., 2001. A cross-sectional analysis of 5,762 children who participated in the Children's Health Study in Southern California evaluated the impact of *in utero* and postnatal ETS exposure on the risk of asthma. Current parent-reported smoking in the home, in the absence of previous *in utero* exposure, was not associated with the risk of reported physician-diagnosed asthma (OR 1.1; 95% CI 0.9-1.4). In contrast, exposure to maternal smoking *in utero* was related to a greater risk of asthma (OR 1.8; 95% CI 1.1-2.9). There was no evidence of effect modification by sex or family history of asthma or atopy. "Active asthma," which was defined as physician-diagnosed asthma with asthma-related symptoms or illnesses during the past 12 months, was also examined. There was no apparent relation between postnatal ETS exposure and the risk of active asthma (OR 1.1; 95% CI 0.8-1.4). However, there was evidence of an exposure-response relationship between number of current smokers and the likelihood of current asthma: 1 smoker (OR 0.9; 95% CI 0.6-1.3) and 2 or more smokers (OR 1.7; 95% CI 1.1-2.5) (p for trend = 0.073). There was also a suggestion that combined maternal and paternal current smoking was associated with active asthma (OR 1.4; 95% CI 0.9-2.3).

Mannino et al., 2001. Another cross-sectional study, using data from 13,944 non-smoking children who participated in NHANES III, evaluated the relationship between serum cotinine level and asthma. Among children 4-6 years old, the highest cotinine tertile was associated with a greater risk of ever and current asthma (OR 2.3; 95% CI 1.1-5.1 and OR 5.3; 95% CI 2.2-12.7, respectively). The highest cotinine tertile was also related to a greater risk of frequent wheezing (OR 3.8; 95% CI 1.7-8.3) and wheezing apart from colds during the past year (OR 4.8; 95% CI 2.4-9.9). Among older children, the impact of ETS exposure on the risk of asthma was less clear.

Lanphear et al., 2001. In a related report using an overlapping sample, other investigators evaluated child NHANES III participants who were younger than 6 years old. This analysis also used parent-reported household smoking, rather than a biomarker of ETS exposure. Parent-reported household smoking during both the prenatal and postnatal periods was associated with a greater risk of ever receiving a physician-diagnosis of asthma (OR 1.7; 95% CI 1.2-2.5). There was no relation between prenatal only or postnatal only exposure and asthma. Because serum cotinine is a more accurate measure of recent ETS exposure, the results reported by Mannino and colleagues (Mannino *et al.*, 2001) may provide better risk estimates.

Kivity et al., 2001. A study from Israel evaluated the prevalence of asthma among 585 children who resided in a Jewish town and 658 children who lived in a neighboring Arab town. In both towns, paternal smoking was associated with the risk of asthma. In the Arab town, the prevalence of asthma was higher among children whose fathers smoked (11.4% vs. 6.6%, $p < 0.05$). Smoking was rare among Arab mothers (2%). In the Jewish town, the prevalence of asthma was also higher among children with smoking fathers (19% vs. 11%) or mothers (20% vs. 12%) ($p < 0.05$).

Al-Dawood, 2001. This population-based cross-sectional study from Saudi Arabia evaluated 1482 boys aged 6-15 years. Based on parent survey responses, asthma was defined as reported ever wheezing, attacks of shortness of breath with wheezing, and normal breathing between attacks. Compared to non-asthmatic children, children with asthma were more likely to have smoking mothers (7.8% vs. 3.8%) and fathers (53.9% vs. 30%, $p < 0.05$ in both cases). In multivariate analysis controlling for respiratory symptoms, parental asthma status, eczema, and

pets in the home, maternal and paternal smoking were also associated with asthma (OR 1.32 and 1.52, $p<0.01$ in both cases).

Gupta et al. (2001) conducted a cross-sectional study focused on 9090 children in grades 6-12 in Chandigarh, India. Based on their written survey responses, children were classified as ETS exposed or unexposed at home (smoking parents or other family members). Asthma was defined as self-reported asthma plus recent wheezing or chest tightness. ETS exposure was associated with a greater risk of asthma, controlling for age and sex (OR 1.8; 95% CI 1.3-2.4).

Lam et al. (1999) examined a population-based sample of 3964 younger schoolchildren aged 7-13 years. Nearly half of the children (47%) indicated a smoking adult at home. There was no statistical association between passive smoking and the risk of self-reported physician-diagnosed asthma (OR 0.92; 95% CI 0.71-1.19). There was also no apparent exposure-response relationship between number of household smokers and the risk of asthma. ETS exposure was, however, associated with a greater risk of other respiratory complaints, such as cough, phlegm production, and recent physician visits for wheeze.

Wang et al., 1999. A population-based cross-sectional study from Taiwan surveyed 165,173 children and their parents. Asthma was defined based on children's responses to a video interview developed by the International Study of Asthma and Allergies in Childhood (ISAAC), which depicts children with wheezing and other respiratory symptoms. ETS exposure at home was associated with a greater risk of asthma OR 1.08 (95% CI 1.05; 1.12). The analysis controlled for area of residence, demographic factors, personal smoking, and other covariates.

Hajnal et al., 1999. A population-based study from Switzerland evaluated 4470 children aged 6-14 years who resided in 10 different communities that represented varying levels of urbanization, climate, and air pollution. Any household ETS exposure was associated with a greater risk of parent-reported childhood asthma (OR 1.20; 95% CI 0.94-1.54). The confidence interval, however, did not exclude no relationship. When the authors examined maternal and paternal smoking separately, paternal smoking was not associated with any respiratory symptom. In contrast, maternal smoking was related to poorer respiratory health, including a greater risk of symptoms that suggest asthma during the past 12 months: attacks of shortness of breath after exercise (OR 1.71; 95% CI 1.18-2.48) and wheezing (OR 1.36; 95% CI 1.03-1.80). There was a suggestion that children whose mothers smoked were more likely to suffer from recent wheezing after exercise (OR 1.32; 95% CI 0.96-1.81). High level ETS exposure, as defined as 20 or more cigarettes per day, was associated with a greater risk of exertional wheezing (OR 1.71; 95% CI 0.91-3.22). Taken together, these findings suggest that household ETS exposure is related to asthma and related respiratory symptoms.

Ronmark et al., 1999. Researchers from Sweden evaluated the impact of ETS exposure on childhood asthma in a sample of 2,454 children aged 7-8 years. Asthma was defined based on a combination of respiratory symptoms and parent-reported physician diagnosed asthma. In a multivariate analysis controlling for gender, family history of asthma, home dampness, pets at home, geographic location, and breast-feeding history, current maternal smoking was associated with a greater risk of ever having asthma (OR 1.29; 95% CI 0.95-1.74). In families without a family history of asthma and who breastfed less than 3 months, the 95% CI for maternal smoking excluded no effect (OR 1.95; 95% CI 1.18-3.24). While exposure to ETS increased the risk of

asthma, this was ameliorated by breastfeeding for greater than 3 months. Further analysis evaluated the impact of ETS exposure on atopic asthma, which was defined as asthma plus one or more positive skin tests to common aeroallergens. The effect estimate for ETS was greater for non-atopic (OR 1.67; 95% CI 1.04-2.68) than atopic asthma (OR 1.17; 95% CI 0.68-2.01).

Shamssain and Shamsian, 1999. This cross-sectional survey of parents of 6-7 year olds from northeast England found that maternal smoking was associated with a higher risk of ever having asthma (OR 1.39; 95% CI 1.12-1.74). There was no statistical impact of paternal smoking on asthma history (OR 1.10; 95% CI 0.84-1.44). Both maternal and paternal smoking were related to a greater risk of ever wheezing (OR 1.46; 95% CI 1.19-1.79 and OR 1.38; 95% CI 1.11-1.72, respectively).

Gergen et al., 1998. Other investigators studied a similar sample of children aged 2 months to 5 years who participated in NHANES III. In this report, intensity of household smoking was evaluated in more detail, with categories for no smoking in the home, 1-19 cigarettes smoked per day, and 20 or more cigarettes smoked per day. Compared to the unexposed group, the risk of parent-reported physician-diagnosed asthma was greater in the highest exposure group (OR 2.1; 95% CI 1.4-3.2). This elevated risk was similar in the younger (2 months-2 years) and older (3-5 years) age strata.

Lister and Jorm, 1998. In a population-based sample of Australian children aged 0-4 years, Lister and colleagues examined ETS exposure as a risk factor for asthma. Maternal smoking, but not paternal smoking, was associated with a greater risk of childhood asthma (OR 1.52; 95% CI 1.19-1.94 and OR 0.77; 95% CI 0.60-0.98, respectively). When the outcome variable was redefined as asthma or wheezing, the results were very similar.

Lam et al., 1998. A school-based cross-sectional study from Hong Kong examined the relation between self-reported household ETS exposure and the risk of self-reported physician diagnosed asthma among 6304 students aged 12-15 years. Residence with three or more smokers was associated with a greater risk of current asthma, although the confidence interval does not exclude no relationship (OR for living with 3 smokers vs. none 1.49; 95% CI 0.81-2.71). The highest level domestic ETS exposure group had a higher risk of recent asthma medication use during the past two days (OR 2.86; 95% CI 1.09-7.49). The risk estimates for asthma were higher for maternal than paternal smoking (OR 1.32; 95% CI 0.71-2.45 and OR 0.92; 95% CI 0.72-1.17).

Kendirli et al., 1998. Another population-based cross-sectional study from Adana, Turkey, examined 2650 children aged 6 to 14 years. As in the other study from Turkey, household smoking was related to a greater risk of parent-reported physician-diagnosed asthma (OR 1.41; 95% CI 1.16-1.72). Domestic ETS exposure was also associated with rhinoconjunctivitis and wheezing.

Maier et al., 1997. This cross-sectional study evaluated 925 children aged 5-9 years who were recruited from schools in Seattle, Washington. Parental report of smokers in the home was associated with a greater risk of reported physician-diagnosed asthma (OR 1.6; 95% CI 0.9-2.7) and current wheezing in their children (OR 1.8; 95% CI 1.0-3.2), after controlling for sociodemographic covariates. When ETS exposure was defined as occasional or more smoking

in the home, the impact of ETS was greater on physician-diagnosed asthma and current wheezing (OR 2.5; 95% CI 1.5-4.3 and OR 1.8; 95% CI 1.0-3.2). Additional analysis, which controlled for other indoor environmental exposures such as fireplace use, stove use, or dampness, did not reduce the calculated risk estimates.

Hu et al., 1997a. A cross-sectional survey focused on predominately African-American fifth grade children in Chicago. Smoking during pregnancy was related to a higher risk of asthma (OR 1.9; 95% CI 1.1-3.5). Maternal smoking during the past week was not associated with ever having a physician diagnosis of asthma (OR 0.8; 95% CI 0.5-1.5). However, the evaluation of smoking during the past week, as opposed to a longer or average time period, could have biased this result (but not the pregnancy related findings). If mothers with actively wheezing children were less likely to recently smoke (or report smoking), the risk estimate would be biased toward the null. In fact, mothers of children who had wheezing during the past 12 months were less likely to report recent smoking.

Farber et al., 1997. Investigators recruited a population-based sample of 3174 children aged 5-17 years who resided in a semi-rural, biracial community (African-American and white). Maternal smoking was associated with a greater risk of parent-reported childhood asthma during three successive cross-sectional surveys of the population: 1984-5 (OR 1.35; 95% CI 1.01-1.81), 1987-8 (OR 1.51; 95% CI 1.17-1.96), and 1992-4 (OR 1.39; 95% CI 1.11-1.72). The consistency of findings over a ten-year period supports the link between ETS exposure and childhood asthma.

Selcuk et al., 1997. A cross-sectional population-based study from Edirne, Turkey evaluated 5,412 children aged 7 to 12 years. Passive smoking in the household was associated with a greater lifetime history of parent-reported childhood asthma (OR 1.35; 95% CI 1.12-1.62) and current asthma (1.28; 95% CI 0.94-1.75).

Cunningham et al., 1996. This school-based cross-sectional study of 11,534 children living in the U.S. or Canada evaluated the relationship between maternal reports of smoking in the home and respiratory status. "Active diagnosed asthma" was defined as reported diagnosis of asthma plus respiratory symptoms or asthma medication use during the past year. There was no statistical association between any current (OR 1.08) or previous home ETS exposure (OR 1.03) and the risk of active asthma. In contrast, exposure to maternal smoking during pregnancy was associated with a greater risk of active diagnosed asthma (OR 2.7; 95% CI 1.13-6.45). Current and previous home ETS exposures were both associated with a greater risk of several wheezing outcomes, including wheezing with colds [OR 1.65 (95% CI 1.45-1.88) and OR 1.24 (95% CI 1.05-1.45), respectively]. Current ETS exposure was also related to a higher likelihood of persistent wheeze (OR 1.42), dyspnea with wheeze (OR 1.35), wheeze with exercise (OR 1.24), medication for wheeze (OR 1.23), and emergency department visit for wheeze (OR 1.63) ($p<0.05$ in all cases). For all wheezing outcomes, there was evidence of an exposure-response relationship for number of cigarettes smoked per day in the home.

Chen et al., 1996. A population-based cross-sectional study from Saskatchewan, Canada, evaluated 892 children aged 6-17 years. Asthma was defined as parental report that the child had ever been diagnosed with asthma by a physician. The analysis was stratified by childhood allergy status, which included reported allergy to food, inhaled allergens, skin allergy, or other

allergy. Among children with any reported allergy, there was no apparent relation between parent or other household member smoking and the risk of ever having asthma (OR 1.04; 95% CI 0.49-2.21). In the non-allergic stratum, smoking in the household was associated with a greater risk of asthma (OR 2.47; 95% CI 0.74-7.86), although the confidence interval was wide and did not exclude no effect. In the allergic group, there was also evidence of an exposure response relation. Compared to households with no smokers, households with 1 smoker (OR 3.42; 95% CI 0.95-12.33) or >2 smokers (OR 5.77; 95% CI 1.59-21) were associated with a greater risk of asthma; the latter category reached statistical significance. When total daily household cigarette consumption was examined, there was also a progressive increase in the risk of asthma: 1-19 cigarettes/day (OR 3.96; 95% CI 1.01-15.42) and >20 cigarettes/day (OR 4.58; 95% CI 1.34-15.68).

Peters et al., 1996. A study from Hong Kong recruited 3,521 children younger than 18 years old from two districts with good and poor air quality. As part of the study, they surveyed parents about smoking in the home and childhood asthma. ETS exposure was defined as number of different categories of exposure, defined as mother, father, siblings, lodgers, and the like. In the 1991 survey, which took place after an outdoor air pollution intervention, having two or more ETS exposure categories was associated with a greater risk of "wheezing or asthmatic symptoms" (OR 1.55; 95% CI 1.08-2.23). The impact of ETS exposure categories on asthma alone was less strong (OR 1.22; 95% CI 0.78-1.92). In the 1989-90 pre-intervention survey, there was no clear relation between ETS exposure and either health outcome.

Beckett et al., 1996. A population-based cross-sectional study from Connecticut recruited mothers of children less than 18 years of age. Maternal smoking was associated with a greater risk of having an asthmatic child in the family, defined as mother-reported physician-diagnosed asthma (OR 1.53; 95% CI 1.31-1.80). In further analysis, the authors examined the impact of ETS by race-ethnicity. Among white and black families, ETS exposure was associated with a greater risk of asthma (OR 1.36; 95% CI 1.05-1.76 and OR 1.75; 95% CI 1.12-2.75, respectively). In the Hispanic stratum, comprised mostly of persons from Puerto Rico, there was no apparent relation between ETS exposure and asthma (OR 1.02; 95% CI 0.53-1.96).

Stoddard and Miller, 1995. Using data from the population-based U.S. National Medical Expenditure Survey (1987), Stoddard and colleague evaluated the impact of parental smoking on current respiratory status. Asthma was defined as parent-reported "asthma or wheezing" during the past 12 months. Maternal smoking was associated with a greater risk of asthma or wheeze (OR 1.36; 95% CI 1.14-1.62). Paternal smoking was not related to asthma/wheeze (OR 0.83; 95% CI 0.67-1.02). The risk estimate for maternal smoking was greatest for younger children: OR 1.90 (95% CI 1.23-2.94) for 0-2 yrs, OR 1.53 (95% CI 0.99-2.37) for 3-5 years; OR 1.35 (95% CI 1.01-1.81) for 6-12 years; and OR 1.07 (95% CI 0.76-1.49) for 13-17 years.

Table 6.31 ETS and New-onset Childhood Asthma – Case-control Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Jones *et al* 1999 U.K.	Case-control study Asthma, ctrl n=100 4-16 yr	Parental smoking Mother Father	Diagnosed asthma 1.17 (p = NS) 0.85 (p = NS)	No significant ETS association found.
Infante-Rivard *et al.*1999 Canada	Case-control study 9-11 yr n = 404	Maternal smoking >0-20 cig/d > 20 "	Persistent asthma 1.22 (0.79-1.88) 3.84 (1.68-8.76)	Persistent not transient asthma associated with maternal smoking
Agabiti *et al* 1999 Italy	Population-based case-control study 6-7 yr n = 18,737 13-14 yr n = 21,068	Parental smoking Any smoking Mother only Father only Both Any smoking Mother only Father only Both	Current asthma 6-7 yr 1.34 (1.11-1.62) 1.46 (1.13-1.87) 1.26 (1.01-1.58) 1.35 (1.09-1.69) 13-14 yr 1.17 (0.99-1.39) 1.23 (0.98-1.53) 1.04 (0.86-1.27) 1.29 (1.06-1.56)	Current asthma defined as history of asthma plus wheeze in last 12 mo. Any ETS increased risk in young children. Effects less pronounced in adolescents.
Yang *et al* 1998 Taiwan	Population- based case-control study. 6-12 yr n = 330	Household	Physician-diagnosed asthma 0.83 (0.54-1.27)	Cases were parent-reported physician-diagnosed asthma; Controls had no asthma, atopy, wheeze, etc.
Ehrlich *et al* 1996 So. Africa	Case-control study Asthma n=368 Ctrls n=294 7-8 yrs	Cot/creatinine 30.6-63.5 63.6-130.1 > 130.1	Asthma or wheeze 1.21 (0.76-1.93) 1.66 (1.04-2.66) 1.61 (1.01-2.58)	Asthma risk increased with cotinine and #smokers: OR 1.15 per smoker (1.01-1.30)
Strachan & Carey 1995 UK	Case-control study Asthma n=486 Ctrls n=475	Parental smoking Mother 1-10 > 10 cig/d Father 1-10 > 10 cig/d	Severe asthma 1.13 (0.73-1.74) 1.49 (0.80-2.77) 0.97 (0.64-1.47) 0.62 (0.32-1.18)	No evidence of effect of paternal smoking. Maternal effect but CI includes unity.
Lindfors *et al* 1995 Sweden	Case-control study 193 Asthma 318 Ctrls 1-4 yrs	Parental smoking during 1st 2 yrs + skin test -skin test	Diagnosed asthma 2.1 (1.0-4.2) 1.6 (1.1-2.3)	More asthma with ETS esp. if skin test to cat or dog allergen is positive.

Table 6.31 ETS and New-onset Childhood Asthma – Case-control Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Azizi *et al* 1995 Malaysia	Case-control study Asthma n=158 Ctrls n=201 1 mo-5 yr	Parental smoking Shared bedroom with smoker	First acute asthma 1.91 (1.13-3.21)	ETS effects but study can't distinguish induction vs. exacerbation

Jones et al., 1999. Researchers recruited 100 cases of asthma from a general practice asthma register in Plymouth, U.K. These children had received a clinical diagnosis of asthma and had received asthma treatment during the past year. Each case was matched by age and gender to a control child, who had no history of asthma or respiratory symptoms. Parent-reported maternal smoking (OR 1.17) and paternal smoking at home (OR 0.85) were not associated with the risk of asthma. Confidence intervals for smoking data were not reported in this study which looked primarily at house moves, indoor air, and heating methods.

Infante-Rivard et al. (1999) published a 6 year follow-up of their initial case-control study of incident asthma cases diagnosed by a pediatrician. The original study (Infante-Rivard, 1993), which linked maternal smoking with a greater risk of incident asthma among 3-4 year-olds, was included in the 1997 OEHHA meta-analysis (Cal/EPA, 1997). Based on 6-year follow-up, the investigators classified subjects as having transient asthma (no subsequent symptoms or asthma medication use) or persistent asthma (continued symptoms or medication use). Subjects were compared to their original matched controls. Maternal smoking was associated with a greater risk of persistent asthma (OR for mean daily cigarette consumption > 0 to < 20 was 1.22; 95% CI 0.79-1.88; for > 20 cigarettes per day OR was 3.84; 95% CI 1.68-8.76). There was no relation between maternal smoking and transient asthma (OR 0.81; 95% CI 0.37-1.76 for 20 cigarettes or less and OR 1.07; 95% CI 0.35-3.26 for >20). Building on the original case-control study, this study further implicates ETS exposure as a cause of persistent asthma.

Agabiti et al., 1999. The authors conducted a case-control analysis of data from a large cross-sectional survey among Italian schoolchildren of two ages: 6-7 years (n=18,737) and 13-14 years (n=21,068). Parents completed the survey for younger children; adolescents also completed the survey. Current asthma was defined as a history of asthma plus wheezing symptoms during the past 12 months. Among children aged 6-7 years, any current parental smoking was associated with a greater risk of current asthma (OR 1.34; 95% CI 1.11-1.62). Smoking by the mother only or the father only was also associated with a higher likelihood of current asthma (Table 6.31). Any current parental smoking was also associated with a greater risk of asthma among adolescents, although the confidence interval included no effect (OR 1.17; 95% CI 0.99-1.39).

Yang et al., 1998. Using participants in a cross-sectional survey conducted in a subtropical region of Taiwan, investigators identified cases of parent-reported physician-diagnosed asthma and compared them to controls with no asthma history, persistent wheeze, cough, phlegm, pneumonia, or bronchitis. Household smoking by any household member was not statistically associated with asthma (OR 0.83; 95% CI 0.54-1.27). According to the authors, many smokers in developing countries smoke lightly. Because smoking intensity was not assessed, the lack of association could be explained by low level ETS exposure.

Ehrlich et al., 1996. A population-based case-control study from South Africa recruited children who had parent-reported asthma or other respiratory symptoms such as wheezing (cases) and controls with "no or few asthma symptoms." Urine cotinine was used as a biomarker of ETS exposure. As cotinine-creatinine ratio increased, the risk of asthma progressively also increased (OR 1.21 for second vs. first quartile, OR 1.66 for third quartile, OR 1.61 for fourth quartile; Chi-square test for linear trend = 5.4 with p = 0.02). In bivariate analysis, current maternal smoking was related to a greater risk of asthma (OR 1.7; 95% CI 1.23-2.34). Risk estimates were similar for maternal ever smoking (OR 1.8; 95% CI 1.29-2.50) and maternal smoking

during the child's first year of life (OR 1.7; 95% CI 1.20-2.35). There also appeared to be exposure-response relationships for daily maternal cigarette consumption and number of household smokers. In multivariate analysis that included maternal smoking during pregnancy, current maternal smoking was less strongly associated with asthma (OR 1.33; 95% CI 0.85-2.00). Number of household smokers was related to a greater risk of asthma (OR 1.15 per smoker; 95% CI 1.01-1.30).

Strachan and Carey, 1995. A population-based case-control study from Sheffield, England identified 486 cases of severe asthma based on parental reports of >12 wheezing attacks or >1 speech-limiting attack of asthma during the past year. Controls (n = 475) with no history of asthma or wheezing were matched on age and school class. Low-level maternal smoking (1-10 cigarettes/day) was not related to the risk of severe asthma (OR 1.13; 95% CI 0.73-1.74). Higher level maternal smoking (>10 cigarettes/day) was associated with a greater risk of severe asthma, but the confidence interval was wide and did not exclude no impact (OR 1.49; 95% CI 0.80-2.77). Paternal smoking was not associated with the risk of severe asthma.

Lindfors et al., 1995. This case-control study from Sweden recruited cases of childhood asthma (age 1-4 years) from an allergy clinic. Because inclusion criteria required three or more episodes of asthma exacerbation, cases had moderate-to-severe asthma (most had recent hospitalization or emergency department visits for asthma). A random sample of controls was selected from the same catchment area, matched on age. The analysis was stratified by whether or not children had a positive skin test to dog or cat allergen. Among the skin test positive subjects, parent-reported smoking during the child's first two years of life was associated with a greater risk of asthma (OR 2.1; 95% CI 1.0-4.2). A similar relation was observed in the skin test negative stratum (OR 1.6; 95% CI 1.1-2.3).

Azizi et al., 1995. A study from Kuala Lumpur, Malaysia recruited 158 cases, defined as children with their first hospitalization for acute asthma, and 201 controls, who were hospitalized for non-respiratory causes. Controls were matched on age and day of admission. Sharing a bedroom with a smoker was associated with a greater risk of asthma hospitalization (OR 1.91; 95% CI 1.13-3.21). One difficulty in interpreting this study is that the case definition could capture children with new-onset asthma or exacerbation of pre-existing asthma. As a consequence, the separate effects of ETS on asthma induction and exacerbation cannot be clearly separated.

Table 6.32 ETS and New-onset Childhood Asthma - Cohort Studies

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Jaakkola *et al* 2001 Norway	Cohort study: 0-4yr n = 2,531	Parental smoking Smoke at birth	Bronchial obstruction OR 1.43 (1.07-1.90) asthma 1.10 (0.79;1.53)	More ETS effect on bronchial obstruction by age 2 than on asthma
Ponsonby *et al* 2000 Australia	Cohort study: 0-7 yrs n=863	Smoker in same room	Current asthma at 7 yr 1.52 (1.01-2.29)	Exposure-response suggested: 1.04/20 cig (0.99-1.10)
Tariq *et al* 2000, 1998 U.K.	Cohort study: 0-4 yrs n=1218	Maternal report at 1 yr of age 2 yr 4 yr	Asthma prevalence 2.5 (1.7-3.7) 2.2 (1.5-3.4) 1.2 (0.3-2.7)	ETS increased asthma but focus was on prevalence not incidence
Oddy *et al* 1999 Australia	Birth cohort study Followed to age 6 n = 2,187	Home ≥ 1 cig/day	Asthma 1.27 (1.04-1.55)	Physician-diagnosed asthma elevated after control for sex, age, breastfeeding, and childcare attendance.
Wennergren *et al* 1997 Sweden	Cohort study: dx 2 yr follow-up 10 yr n = 92	Parental smoking ETS infancy ETS age 10	Asthma persistence vs. not at 10 yr 82 vs. 59% p=0.05 54 vs. 52% p=NS	Exposure during infancy more critical than later.

Jaakkola et al., 2001. The Oslo birth cohort study followed children from birth through age 4 years. Of the 3,754 children enrolled at birth, 2,985 completed two-year follow-up and 2,531 were traced at 4 years. ETS exposure was defined as parent-reported smoking at the time of the child's birth. Two related health outcomes were examined: asthma at age 4 years, which was defined as parent reported physician-diagnosed asthma plus respiratory symptoms during the previous 12 months; and bronchial obstruction during the first two years of life, which was defined as two or more episodes of respiratory symptoms or one episode lasting more than one month. ETS exposure was associated with a greater risk of bronchial obstruction during the first two years of life (OR 1.43; 95% CI 1.07-1.90). The relation between ETS exposure and asthma at four years of age was less clear (OR 1.10; 95% CI 0.79-1.53).

The investigators further examined the joint effects of genetic predisposition to asthma, defined as parental asthma or hay fever, and ETS exposure. For both bronchial obstruction and asthma, the risks conferred by ETS and genetic predisposition were more than additive (i.e., synergistic). The risk of asthma associated with both genetic predisposition and ETS exposure (OR 2.68; 95% CI 1.70-4.22) was greater than that for genetic predisposition (parental atopy) or ETS exposure in the absence of parental atopy (OR 1.66; 95% CI 1.08-2.54 and OR 0.84; 95% CI 0.53-1.34).

Ponsonby et al., 2000. A cohort study from Australia evaluated 863 children at age 7 years who had previously participated in an infant cohort study. The investigators examined the relation between parent-reported ETS exposure during infancy and current asthma at age 7 years. The analysis was stratified according to whether household residents smoked ("smoker households") or did not smoke ("non-smoker households"). Compared to smoker households where no one ever smoked in the same room as the baby, infants whose mothers or others smoked in the same room as the baby had an increased risk of current asthma at age 7 years (RR 1.52; 95% CI 1.01-2.29). In non-smoker households, there was no relationship between any smoking in the baby's room and subsequent asthma (RR 0.65; 95% CI 0.38-1.13). There was a suggestion of an exposure-response response relationship between number of cigarettes smoked in the home during infancy (reported during the past 48 hours) and the risk of asthma at age 7 years (RR 1.04 per 20 cigarettes; 95% CI 0.99-1.10).

Tariq et al., 2000; Tariq et al., 1998. Investigators from the Isle of Wight (U.K.) followed a population-based birth cohort of 1,218 infants through age 4 years. Asthma was diagnosed based on clinical criteria. Parental smoking was updated at each age. Maternal smoking was associated with a greater risk of asthma at age 1 year (OR 2.5; 95% CI 1.7-3.7) and 2 years (OR 2.2; 95% CI 1.5-3.4). There was no statistical relationship at age 4 years (OR 1.2; 95% CI 0.3-2.7). Study limitations include a focus on asthma prevalence at each age, rather than on asthma incidence. In addition, no longitudinal analysis of postnatal ETS exposure on subsequent asthma risk was conducted.

Oddy et al., 1999. A birth cohort study of 2,187 children living in Western Australia evaluated the impact of breastfeeding on parent-reported physician-diagnosed asthma. In this study, smoking in the household, as defined by one or more cigarettes smoked inside the house per day, was associated with a greater risk of asthma (OR 1.27; 95% CI 1.04-1.55), controlling for sex, gestational age, breastfeeding, and childcare attendance.

Wennergren et al., 1997. A cohort study re-investigated children at 10 years of age who had been previously hospitalized for acute asthma before age 2 years. After 10 years, only 30% of children had symptomatic, persistent asthma. At 10-year follow-up, the proportion of children with persistent asthma who had previous ETS exposure during infancy was higher than that of symptom-free children (82% vs. 59%, p=0.05). At age 10 years, the proportion of children with current ETS exposure was similar among those with persistent asthma vs. no asthma (54% vs. 52%). These results suggest that early childhood ETS exposure had more influence on the risk of persistent asthma than continued exposure later in childhood. Alternatively, parents with symptomatic children may be more likely to quit smoking.

6.3.2.1. Asthma in Childhood: Meta-analyses and Conclusions

Based on considerable epidemiological evidence, the 1997 Cal/EPA report concluded that there is compelling evidence that ETS exposure causes new-onset childhood asthma. Supporting this conclusion, OEHHA conducted a meta-analysis of 37 studies that evaluated the impact of ETS exposure on childhood asthma induction. The 1997 OEHHA report elaborated as follows.

> "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 pre-natal exposures may cause persistent decrements in lung growth and development (Cunningham *et al.* 1994, 1995, Hanrahan *et al.* 1992). It is possible that pre-natal 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 nonsmoking adults (Leuenberger *et al.,* 1994), indicate that post-natal 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; (4) cigarette smoke causes airway inflammation in active smokers (Niewoehner, 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke. Taken as a whole, the epidemiologic evidence of causation is compelling."

OEHHA conducted an update of the meta-analysis found in the 1997 document to examine the association between exposure to ETS in the home and the development of childhood asthma. OEHHA surveyed 85 studies, covering over 460,000 children, and representing 29 countries.

For the purposes of meta-analysis, relative risk estimates were extracted according to preset exclusion/inclusion criteria, and represented various combinations of exposure and outcome definition, subgroup stratification, and levels of exposure. To make ORs more comparable between studies, exposure levels for measures of cigarettes smoked per day, number of household smokers and cotinine levels were normalized. A correction formula was applied to convert ORs to RRs among cross-sectional and cohort studies with greater than 10% asthma prevalence. The degree of inter-study heterogeneity and a pooled estimate of risk were derived from a random-effects model after evaluation of the data by both fixed- and random effects models.

Analyses based on 29 studies that controlled for the child's history of atopy and personal smoking, and in which all ages were combined gave a pooled OR for new-onset asthma of 1.32 (95% CI, 1.24-1.41). The test for heterogeneity gave Q = 30.63 (p = 0.334) and a between-study variance of 0.002. A subset of these studies, comprising 5 birth cohort studies, was used to examine the effects of exposure duration. Based on this analysis, the risk (RR) of asthma onset among children exposed to postnatal ETS for 5 years was 1.22 (95% CI 1.16-1.34), and 1.42 (95% CI 1.28-1.70) following 10 years of exposure. Of the 29 studies, 23 controlled for age and gender with an RR of 1.29 (95% CI 1.21-1.37). Additional control for race raised the RR to 1.35 (95% CI 1.21-1.50).

While preschool children appeared to be more at risk than older children (RR 1.44, 95% CI 1.04-1.99 vs. RR 1.26, 95% CI 1.19-1.32), it is notable that the risk for asthma onset was not limited to young children or those exposed during pregnancy. Older children exposed to ETS were also at significant risk for new onset asthma (see Table 6.33).

Table 6.33 Subgroup Analysis of Asthma Induction Risk after ETS Exposure

Study characteristic	N*	Pooled RR	95% CI
Case-control (CC)	7	1.36	1.15-1.61
Cross-sectional (XS)	14	1.28	1.18-1.39
Cohort (incident cases)	8	1.27	1.14-1.42
CC & XS prevalent cases	21	1.33	1.23-1.43
Hospital/clinic case source	7	1.45	1.14-1.85
Community case source	22	1.27	1.20-1.35
Included older children	24	1.26	1.19-1.32
Restricted to preschool	5	1.44	1.04-1.99
Control by age and sex	23	1.29	1.21-1.37
No control by age and sex	6	1.35	1.07-1.70
Control by race	17	1.35	1.21-1.50
No control by race	12	1.24	1.17-1.32

*N = number of studies included in pooled estimate

From subset analysis it was noted that estimates based on studies that identified asthma cases from hospital and clinical records were higher than those based on community- based surveys or interviews (RR 1.45, 95% CI 1.13-1.84 and 1.27, 95% CI 1.20-1.35, respectively). Disease

misclassification in community surveys may have contributed to lower risk estimates in some of the earlier studies (see Table 6.33).

The timing of ETS exposure (pre- vs. postnatal) was examined in the studies listed in Table 6.34. Six of the studies that combined pre- and postnatal exposures had elevated ORs, four of them significantly so. In the studies reporting postnatal compared to combined pre- and postnatal exposures, the risks were generally higher for the combined exposure. Postnatal-only exposure resulted in elevated asthma risk in seven of eight studies, and that risk was statistically significant in three of the studies.

Table 6.34 Effect of Timing of ETS Exposure on Risk of Asthma Induction

Study author	Age range	Exposure timing*	RR	95% CI
Azizi *et al.*, 1995[h]	1 mo-5.5 yr	Postnatal only	1.91	1.13-3.21
Mannino *et al.*, 2001[h]	4 – 6 yr	Pre-& postnatal	4.31	2.15-6.58
"	"	Postnatal only	3.20	1.34-5.68
Agabiti *et al.*, 1999[m]	6 – 7 yr	Pre-& postnatal	1.62	1.34-1.96
"	"	Postnatal only	1.12	0.93-1.35
Neuspiel *et al.*, 1989[m]	0 – 10 yr	Pre-& postnatal	1.56	1.30-1.87
"	"	Postnatal only	2.3	1.26-4.22
Hajnal *et al.*, 1999[m]	6 – 14 yr	Pre-& postnatal	1.31	0.92-1.85
Mannino *et al.*, 2001[h]	7 – 11 yr	Pre-& postnatal	0.63	0.22-1.58
"	"	Postnatal only	0.91	0.43-2.15
Azizi & Henry, 1991[h]	7 – 12 yr	Postnatal only	1.08	0.91-1.61
Gilliland *et al.*, 2001[h]	9 – 15 yr	Pre-& postnatal**	1.24	0.91-1.61
"	"	Postnatal only	1.24	0.91-1.54
Agabiti *et al.*, 1999[m]	13 - 14	Pre-& postnatal	1.22	1.02-1.47
"	"	Postnatal only	1.15	0.99-1.34

[h] household exposure; [m] maternal exposure; *exposure status based on current smoking; **exposure status based on ever-smoking.

From the pooled estimate, we concluded that the risk of developing asthma was likely in the range of 1.21 to 1.37. We also concluded that the meta-analysis suggested an assessment of causality and that the relationship between ETS exposure and asthma induction is causal. Several features of this study strengthen the evidence suggesting a causal association between ETS exposure and asthma in children. The analysis emphasized studies of recognized or diagnosed asthma rather than those that included wheeze alone, thereby limiting disease misclassification. In the studies selected for analysis, cases and controls were selected by the same criteria. To facilitate comparison, exposure level values were normalized from the entire range of smoking levels in the study population rather than from a subset of exposure levels. Pooled studies all controlled for confounding by the child's own smoking history and history of atopy. We also included an analysis for publication bias by the Begg and Mazumdar (1994) rank sum correlation procedure. No evidence of publication bias was found ($z = 1.58$, $p = 0.115$). It thus appears unlikely that unmodeled confounding and publication bias can explain the association between ETS and asthma reported in this study. Based on the risk estimate range

given above, an asthma prevalence of 9.4% and ETS exposure prevalence of 11.4% among the 9,250,000 children 0-17 years old, it is possible to calculate an attributable risk. Using a non-threshold model (Lilienfeld and Lilienfeld, 1980b), the authors estimate that the number of prevalent cases of asthma among children 0-17 years of age in California in 2001 that are attributable to ETS exposure is 31,000 (24,000-40,000).

The current review of 37 recent studies and OEHHA's more recent meta-analysis of 85 studies strongly support the original conclusion in the OEHHA 1997 document that ETS exposure is causally associated with new-onset asthma among children

6.3.2.2. Attributable Risk Calculation

As the OEHHA analysis continues to support a causal association of asthma onset and exacerbation and ETS exposure it is thus possible to estimate the number of cases of childhood asthma attributable to ETS exposure.

State and national surveys quantifying asthma in children generally include persons reporting being diagnosed with asthma by a physician at any time and reporting symptoms of asthma during the preceding 12 months. According to CDC's asthma surveillance report, in 1999 among children ≤ 14 yrs of age, the number of children with attacks or episodes was 3,113,000 (Mannino *et al*., 2002b). This estimate is limited to children ≤14 years of age and thus does not include cases among individuals 15-17 years of age. As reported in the meta-analysis by Vork *et al*. (2005), the risk of developing childhood asthma after exposure to ETS is 1.32.

For California, an exposure level of 11.4% represents the percentage of children 0-17 yrs old in households not protected from ETS (CDHS, 2001). This exposure level may be low as it does not include exposures occurring outside the home that become relatively more important among older children. An attributable fraction may be calculated:

a = 0.035 [0.114(1.32-1)/(0.114(1.32-1)+1].

The California Health Interview Survey reported an asthma symptom prevalence of 9.6% among children 0-17 years old in 2000 (CHIS, 2001). In 2000 there were 9,257,588 children 0-17 years of age. Active smoking prevalence was 1.8% among 12-13 year olds, 5.5% among 14-15 year olds and 16.2% among 16-17 year old children. This left 9,026,316 nonsmokers 0-17 years of age of whom 867,000 had asthma. Using the attributable fraction above of 0.035, the number of individuals with at least one ETS-attributable asthma episode in the previous 12 months was approximately 31,000. Since this represents the number of individuals affected but not the number of individual asthma episodes, this may significantly underestimate the actual number of ETS-related asthma events.

Similarly for the US, with an exposure rate of 21.9% (CDC, 1997), there were 202,300 individuals 0-14 years of age with ETS-related asthma episodes [0.219(1.32-1)/(0.219(1.32-1)+1) = 0.065; 0.065 x 3,113,000 = 202,300.

6.4. Acute Health Effects (Adults)

6.4.1. Asthma (exacerbation)

6.4.1.1. Previous Findings on Asthma Exacerbation in Adults

Because adults with asthma have chronic airway inflammation, they may be particularly susceptible to the effects of ETS exposure. As reviewed above, ETS exposure has been strongly linked with exacerbation of pre-existing asthma among children. Adults with asthma commonly report ETS exposure as a trigger for asthma exacerbation (Abramson *et al.*, 1995; Dales *et al.*, 1992). However, the impact of ETS exposure on adults with asthma has received less research than in children.

Based on the review of studies focusing on children or adults, the previous Cal/EPA report concluded that the evidence "…supports the existence of an association of chronic or repeated ETS exposure with severity of asthma measured by a variety of indices." Because most of these studies evaluated children, the Cal/EPA report tempered its conclusions about adults: "…there is suggestive evidence that ETS exposure may exacerbate adult asthma."

6.4.1.2. New Epidemiological Findings in Adults

More recent studies, shown in Table 6.40 and described below, substantiate the assertion of evidence that ETS exposure may exacerbate adult asthma.

Table 6.40 ETS and Adult Asthma Exacerbation

Reference Country	Study description	ETS exposure measure	Findings and OR (95% CI)	Comments
Eisner *et al.* 2002 US	Cross-sectional: Cotinine and pulmonary function asthmatics n = 440	NHANES Serum cot in nonsmoking asthmatics	FEV_1 in women -261 ml (-492 to -30) FVC, FEV_1/FVC also impaired	Elevated serum cotinine associated with pulmonary function deficits in women but not men. Asthmatics more affected than general pop.
Eisner *et al.* 2001 US	Prospective cohort 7 day; respiratory symptoms in adult asthmatics 18-50 yr n = 50	Nicotine badge 0-0.05 µg/m^3 > 0.05 " 0-0.05 µg/m^3 > 0.05 "	Resp. symptoms OR 1.9 (0.4-8.8) 6.8 (1.4-32.3) Bronchodilator use OR 2.2 (0.3-15) 8.1 (1.3-50)	Nicotine measured by personal badge associated with increased bronchodilator usage and respiratory symptoms. Linear exposure-response.
Tarlo *et al.* 2000 Canada	Nested case-control Exacerbation of asthma 13-55 yr.* n = 42	ETS past year Exacerbation Controls	Reported ETS exposure 39% 17% p<0.03	More cases (adults and adolescents) with exacerbation of asthma reported ETS exposure in previous 12 mo.
Kunzli *et al.* 2000 Switzerland	Cross-sectional: pulmonary function in asthmatic adults 18-60 yr n = 3534	Self report FEV_1 FVC $FEF_{25-75\%}$	% change -4.8 (-9.2-0) -1.7 (-5.5-2.1) -12.4 (-20.4--3.7)	ETS at work decreased pulmonary function in women more than men. Linear exposure-response trend for hrs per day and # years exposed.
Jindal *et al.* 1999 India	Cross-sectional: pulmonary function women w/asthma 20-40 yrs n = 50	Home, work questionnaire	ETS vs. none PD_{20} 1.7 vs. 6.1 p<0.01 No difference in FEV_1, FEV/FVC	ETS increased bronchial hyperresponsiveness (↓PD_{20}). ETS increased continuous bronchodilator use (39% vs. 26%; p<0.05)
Sippel *et al.* 1999 US	Prospective cohort health outcomes in asthmatics 15-55 n = 619	Self report ETS No ETS Hospital care	Asthma care events 28/100 person-yrs 10/100 " OR 2.34 (1.8-3.1)	ETS associated with worse health status and asthma-specific quality of life at baseline, and more hospital-based care during follow-up.
Eisner *et al*. 1998 US	Case-crossover Bartenders Resp. health n = 53	Self report and spirometry before/after smoking ban	Respiratory symptoms per 5-hr reduction in ETS 0.7 (0.5-0.9)	74% reported symptoms before ban, 32% after ban. FVC and FEV1 improved after ban.

FEF_{25-27} forced expiratory flow at 25-75% of vital capacity; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; PD_{20} histamine dose to give 20% decrease in FEV_1. *This study included adolescents with adults.

Eisner, 2002. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), Eisner examined the relationship between serum cotinine and pulmonary function among 440 non-smoking adults with asthma (corresponding to a population of 4.9 million asthmatics). There was no apparent impact of ETS exposure, as measured by serum

cotinine level, on pulmonary function among men. In the female stratum, higher levels of ETS exposure were associated with greater impairment of FEV_1, FVC, and FEV_1/FVC ratio. In particular, the highest cotinine tertile was related to a mean FEV_1 decrement of -261 ml (95% CI -492--30). The impact of ETS exposure appeared to be greater among adults with asthma compared to non-smoking members of the general population.

Eisner et al., 2001. To study the impact of ETS exposure on adults with asthma, Eisner and colleagues used data from an ongoing prospective cohort study of adults with asthma recruited from a random sample of allergy, pulmonary, and family practice physicians practicing in Northern California. Of the overall cohort, 50 subjects were recruited to wear a personal nicotine badge monitor for one week. At the conclusion of the monitoring period, respiratory symptoms and medication use were ascertained. Compared to subjects with no measurable nicotine levels for the past 7 days, lower level (0-0.05 $\mu g/m^3$) and higher level exposures (>0.05 $\mu g/m^3$) were associated with a greater risk of respiratory symptoms at follow-up (OR 1.9; 95% CI 0.4- 8.8 and OR 6.8; 95% CI 1.4- 32.3). Lower- and higher-level ETS exposures were also related to an increased risk of extra bronchodilator use after exposure (OR 2.2 and 8.1). For both outcomes, there was evidence of a linear exposure-response relationship (p value for trend 0.017 and 0.022 respectively).

Tarlo et al., 2000. A prospective cohort study from Canada followed children and adults with asthma for the development of acute exacerbation. The main goal was to evaluate the impact of viral upper respiratory infections on the risk of asthma exacerbation. In this study, subjects less than 13 years of age were considered children, while adolescents were included with adults. More than half of subjects were aged 13 years or older (58%), ranging up to age 55 years. Within the cohort, a nested case-control study was performed, with cases of acute asthma exacerbation compared to controls without exacerbation. Cases with asthma exacerbation were defined by increasing asthma symptoms refractory to usual medications for more than 48 hours or urgent health care utilization for asthma: hospitalization, emergency department visit, or urgent physician visit. Cases (with acute asthma exacerbation) were more likely to have indicated ETS exposure during the previous year (39%) than controls without exacerbation (17%) ($p<0.03$). Although the investigators ascertained exposures to colds, dust, and other factors during the week preceding the exacerbation, ETS exposure was not reported for this period.

Kunzli et al., 2000. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) focused on a random sample of adult never-smokers aged 18-60 years residing in Switzerland. A report from the SAPALDIA investigators found similar effects of self-reported ETS exposure on pulmonary function among 3534 never smoking adults with asthma. ETS exposure at work was related to average decrements in FEV_1 (-4.8%, 95% CI –9.2-0), FVC (-1.7%, 95% CI –5.5-2.1), and forced expiratory flows at mid-lung volumes ($FEF_{25\%-75\%}$ -12.4%, 95% CI –20.4- -3.7). The impact of ETS exposure on FEV_1 and $FEF_{25\%-75\%}$ was greater among women than men (-8.7% vs. 0.5% and -20.8% vs. -1.4%, respectively). There was evidence of linear exposure-response trend for daily exposure duration and years of exposure.

Jindal et al., 1999. In a cross-sectional study, Jindal and colleagues recruited 50 women with asthma from a university hospital chest clinic in India. ETS exposure at home and work was assessed by questionnaire. Compared with women who indicated no ETS exposure, subjects

indicating any ETS exposure had similar FEV_1 (78% predicted vs.79%) and FEV_1/FVC ratio (94% vs. 86%) (p = N.S. in both cases). The ETS-exposed women had greater bronchial hyperresponsiveness, as indicated by lower PD_{20}, the amount of histamine required to produce a 20% decrease in FEV_1 (median 1.70 vs. 6.1 units; $p<0.01$). ETS exposure was also associated with greater asthma medication use. The proportion that indicated "continuous" bronchodilator use was higher among exposed women (39% vs. 26%; $p<0.05$), although the precise definition of this term was not provided. Taken together with the European Community Respiratory Health Survey, ETS exposure is related to greater bronchial hyperresponsiveness among adults with asthma.

Sippel et al., 1999. A cohort study of 619 adult HMO members with asthma evaluated the association between ETS exposure and health outcomes. The prevalence of self-reported regular ETS exposure was 38% and a small proportion of subjects (11%) indicated current personal cigarette smoking. In cross-sectional analysis of baseline data, regular ETS exposure was associated with worse asthma-specific quality of life (QOL) and generic health status (physical functioning and general health domains). During longitudinal follow-up, ETS exposure was associated with a greater incidence of hospital-based episodes of asthma care (28 events vs. 10 events per 100 person-years). After controlling for socio-demographic covariates, ETS exposure was associated with a greater risk of hospital-based care (RR 2.34; 95% CI 1.8-3.1).

Eisner et al., 1998. Using a case-crossover design, the effects of California State Assembly Bill 13, which prohibited tobacco smoking in bars and taverns, on the respiratory health of bartenders was studied. Based on a random sample of all bars and taverns in San Francisco, the authors interviewed and performed spirometry on 53 bartenders before and after the smoking ban. After prohibition of smoking, self-reported workplace ETS exposure sharply declined from a median of 28 to 2 hours per week. Thirty-nine (74%) of the 53 bartenders reported at least one respiratory symptom at baseline (including cough, dyspnea, and wheezing), while only 17 (32%) were still symptomatic at follow-up. Of the 39 bartenders reporting baseline symptoms, 23 subjects (59%) no longer indicated any respiratory symptoms after prohibition of smoking ($p<0.001$). In particular, 70% of the 17 bartenders reporting baseline wheezing noted resolution after workplace smoking prohibition. In conditional logistic regression analysis, a 5-hour reduction of workplace ETS exposure was associated with a lower risk of respiratory symptoms at follow-up (OR 0.7; 95% CI 0.5-0.9), after controlling for upper respiratory infections and reduced personal cigarette smoking. After prohibition of workplace smoking, improvement in mean FVC (0.189 L; 95% CI 0.082-0.296) and mean FEV_1 (0.039; 95% CI -0.030- 0.107) was observed. Complete cessation of workplace ETS exposure was associated with an even greater pulmonary function improvement.

6.4.1.3. Controlled Human Exposure Studies (adults)

The 1997 Cal/EPA report reviewed 10 controlled human exposure studies that focused on persons with asthma. Most of the studies indicated slight-to-moderate transient effects on pulmonary function. The report concluded that the "…controlled exposure studies do not clearly demonstrate a consistent effect of acute ETS exposure on asthmatics as a whole." There have been few subsequent controlled human exposure studies among adults with asthma.

Nowak et al., 1997a. In 17 adult subjects with mild asthma, experimental ETS exposure for 3 hours resulted in greater reduction in mean FEV_1 (5.6%) compared to a sham exposure group (3.0%) (p=0.013). As measured by methacholine challenge, there was a tendency toward greater responsiveness in the ETS exposure group, but the results were not statistically significant (p=0.18). Another study by the same investigators exposed 10 adults with mild asthma to ETS in an experimental chamber. Compared to the sham group, there was no "significant" difference in the change of FEV_1 (0.8% decrease vs. 1.4% increase).

Interpretation of controlled exposure studies is limited by small sample size, substantial inter-individual heterogeneity in response to ETS, and variable chamber exposure methodology. The recent evidence from chamber studies is consistent with the 1997 OEHHA report's conclusion that there may be a small effect of experimental ETS exposure on pulmonary function, but these findings have not been consistent. In addition, the response of people with mild asthma may be under-predictive of the response of those with moderate to severe asthma. For medical and ethical reasons controlled exposure studies are not performed in those with more severe disease.

6.4.1.4. Summary of Acute Effects in Adults

Examination of the Bradford Hill (Hill, 1971) criteria supports a causal association between ETS exposure and exacerbation of adult asthma. Several studies demonstrated an exposure-response relationship between ETS exposure and exacerbation of adult asthma (Eisner *et al*., 2001; Kunzli *et al*., 2000; Eisner, 2002). The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies, especially the longitudinal cohort studies. Biologic plausibility is supported by the fact that ETS includes potent respiratory irritants and immunotoxicants; and exposure has been linked to greater bronchial hyperresponsiveness (Janson *et al*. 2001; Jindal *et al.,* 1999). The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, ETS has been consistently linked with poorer asthma status. The relationship between ETS exposure and asthma has also been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. The studies reviewed also demonstrate coherence in the association between ETS exposure and exacerbation of adult asthma. ETS exposure has been associated with an adverse impact on a variety of asthma outcomes, including diverse endpoints such as respiratory symptoms, pulmonary function, and hospitalization for asthma. Taken together, the evidence is consistent with a causal effect of ETS on adult asthma exacerbation.

6.4.2. Sensory Irritation and Annoyance

In the 1997 Cal/EPA report, OEHHA staff reviewed data on "… acute and reversible irritative effects of ETS on the upper respiratory tract… [including] eye, throat, and nasal irritation, rhinorrhea, nasal congestion, hoarseness, and odor 'annoyance'." Reference was made to previous reviews of the subject in both the Surgeon General's and NRC reports (U.S. DHHS, 1986c; NRC, 1986c, as well as by Samet *et al.*, 1991). The 1997 Cal/EPA report concluded that "ETS exposure produces a variety of irritative symptoms involving the upper respiratory tract... In addition to irritation, odor annoyance may detract significantly from subjective well-being and productivity among building occupants."

The above conclusion was based upon review of both controlled human exposure (chamber) and field (epidemiological) studies of ETS exposure and upper airway/mucous membrane symptoms. Since the publication of the 1997 Cal/EPA report, additional chamber and epidemiological studies have been completed. Some of the epidemiological studies have a longitudinal component, with questionnaires and/or objective testing being administered to the same subjects before and after a smoking prohibition affecting potential ETS exposure. In this context, these studies assume the status of "natural experiments." In addition to chamber and field studies, OEHHA staff identified two “miscellaneous” health studies: one animal experiment involving ETS exposure and eye irritation, and one retrospective study of ETS exposure and the risk of laryngospasm among pediatric patients undergoing general anesthesia. Finally, an industrial hygiene survey of California buildings with designated smoking areas is reviewed. These studies are summarized below, organized by study type.

6.4.2.1. Definitions (from Cal/EPA, 1997)

> "… '*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.

6.4.2.2. Epidemiological Studies

Table 6.41 Occupational Exposure to ETS

Reference Country	Study Description	Exposure to smoke	Findings and OR (95% CI)	Comments
Mizoue *et al.* 2001 Japan	Cross-sectional study of ETS and non-specific building-related illness in 1,281 municipal workers	ETS hrs/day ≥ 4 vs. < 1	Adj OR Symptoms 2.7 (1.6- 4.8) Eye, nose, throat, skin symptoms increased with increasing exposure.	Symptoms persisted after adjustment for age, gender, stress, video use, and lifestyle
Jones *et al.* 2001 New Zealand	Surveyed restaurant workers about ETS- related symptoms. 435 interviews	ETS at work	59% exposed at work with >50% reporting throat or lung irritation.	75% of interviewees favored smoking restriction in bars.
Wieslander *et al.* 2000 Sweden	Survey of 80 airline crew on 40 smoking, 40 nonsmoking flights for respiratory symptoms, cabin air quality (CAQ)	In flight: Smoking Nonsmoking	Respirable particulates: 66 $\mu g/m^3$ 3 $\mu g/m^3$	On nonsmoking flights, CAQ improved, fewer respiratory symptoms Improved mucous membranes and tear film stability.
Eisner *et al.* 1998 US	Survey of bartenders' respiratory symptoms before and after ban of workplace smoking n = 53	Pre-ban ETS: 28 hr/wk. Post-ban: 2 hr/wk.	Sensory irritation (eye, nose, throat), reported by 41 bartenders, resolved for 32 (78%) after smoking ban ($p<0.001$).	Smoking ban associated with rapidly improved respiratory health as measured by FVC and FEV_1.
Raynal *et al.* 1995 US	Assessed respiratory symptoms in 375 workers that improved outside of work in smoke-permitted office. 22 Ctrls	ETS in office with open-plan smoking policy	Among nonsmokers, positive association between area nicotine and reported symptoms esp. eye, nose and throat irritation ($r=0.165$; $p<0.01$)	Non-smokers validated by salivary cotinine. Active smokers had fewer symptoms than nonsmokers for given area nicotine levels.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity

Mizoue et al. (2001) examined data from a 1998 cross-sectional survey of 1,281 municipal employees who worked in a variety of buildings in a Japanese city. The authors were interested in overtime work and ETS exposure as determinants of symptoms consistent with non-specific building-related illness or "sick building syndrome" (SBS). Potential confounders, which were adjusted for in a logistic regression model, included age, gender, hierarchical position, use of video display terminal > 4 hours/day, psychological stress at work, and lifestyle factors. Using

workers exposed to ETS for less than one hour/day as the reference group, the odds ratio for the SBS symptom constellation among nonsmokers exposed to ETS $\geq$ 4 hours/day was 2.7 (95% CI: 1.6, 4.8). For symptoms referable to the eyes, nose, throat, and skin, odds ratios increased with increasing hours of ETS exposure. These relationships persisted after adjustment for all covariates, including overtime, which was an independent predictor of SBS symptoms.

Jones et al. (2001) surveyed bar staff, waiters, and restaurant managers and owners in New Zealand to determine attitudes and beliefs regarding the health consequences of ETS exposure. A minor component of the questionnaire also dealt with ETS-related symptoms and annoyance. The investigators were able to complete 435 interviews at 364 of an originally targeted 472 locations. The self-reported ETS exposure prevalence among respondents was 59%. More than half of those exposed to ETS reported irritation from second hand smoke to their "throat or lungs," and three-quarters of interviewees indicated that they wanted some sort of smoking restriction in bars.

Wieslander et al. (2000) surveyed 80 commercial aircraft crew members on smoking-permitted and smoking-prohibited international flights of long (11-12 hour) duration. Interviews and physical examinations were conducted, including 39 performed in-flight and 41 post-flight. Half of the flights permitted smoking, and the other half occurred soon after a smoking ban. Endpoints included cabin air quality (CAQ - both measured and perceived), upper respiratory tract/mucous membrane symptoms, tear-film stability, nasal patency (by acoustic rhinometry), and biomarkers in nasal lavage fluid (eosinophilic cationic protein, myeloperoxidase, lysozyme, and albumin). Cabin air was found to be of low relative air humidity (2-10%) although carbon dioxide concentrations - a surrogate for the adequacy of ventilation relative to occupancy - were in an acceptable range. Total respirable particles were reduced dramatically by the smoking ban, with the mean falling from 66 to 3 $\mu g/m^3$. The perceived CAQ was improved, and symptoms - particularly ocular - were less prevalent on non-smoking flights. In terms of objective endpoints, tear-film stability increased after the smoking ban, and although there was a trend toward increased nasal patency, it was not consistent by study subgroup. The authors concluded that in-flight ETS exposure is associated with poor perceived air quality, as well as with symptomatic and [selected] objective indices of upper respiratory tract/mucous membrane irritation.

Eisner et al. (1998) obtained a random sample of bars and taverns and surveyed bartenders before and after a statewide prohibition on smoking in such establishments. Interviewers assessed lower respiratory tract symptoms, sensory irritation symptoms (eye, nose or throat irritation), ETS exposure, personal smoking, and recent upper respiratory tract infections. Spirometry was also performed. Fifty-three of 67 eligible bartenders were interviewed; all reported workplace ETS exposure at baseline. Respondents reported a reduction in median weekly workplace ETS exposure from 28 hours pre-to 2 hours post-intervention ($p<0.001$). One-quarter of bartenders were active smokers, a number that was unchanged post-intervention. Of the 41 (77%) respondents who initially reported sensory irritation symptoms, 32 (78%) reported resolution of symptoms post-intervention ($p<0.001$). The authors concluded that "…establishment of smoke-free bars and taverns was associated with a rapid improvement of respiratory health."

Raynal et al. (1995) studied 375 office employees in a large, open-plan smoking-permitted building and 26 individuals from a building in which no smoking was permitted. Participants

were administered a questionnaire regarding a variety of symptoms which improved outside of the work environment during the twelve months prior to survey. These included mucous membrane (eye, nose, throat) irritation, lethargy, flu-like illness, chest tightness and "difficulty breathing." A composite score ("Personal Symptom Index" or "PSI") was constructed for each individual, utilizing adjustment for demographic variables. Active smoking histories were taken, and both exhaled breath carbon monoxide (CO) and salivary cotinine levels measured for validation purposes. Workplace temperature, humidity and airflow were measured in 5 locations each, and vapor-phase nicotine levels in 23 different sub-areas of the main workplace.

The sample of potentially exposed workers was 70% female and 25% active smokers; the unexposed group was younger and more predominantly male, but comparable in their active smoking rate (19%). Eleven subjects self-reported as non-smokers but had salivary cotinine levels greater than 15 ng/mL; these respondents were analyzed separately from those whose smoking histories and biomarkers were concordant. Among validated non-smokers, there was a positive association between [area] environmental nicotine measurements and both reported symptoms ($r = 0.165$; $p<0.01$) and saliva cotinine levels ($r = 0.313$; $p<0.001$). Among the various symptoms reported, eye nose and throat irritation were most closely related to environmental nicotine levels. Active smokers reported fewer symptoms than did non-smokers for a given [area] nicotine measurement. No symptom correlations were found with variations in temperature, humidity, or airflow. The authors indicated that the small size of the control group may have obscured differences in composite scores (the "Building Symptom Index" or "BSI") between the main study and control groups. However, the relationship between symptoms and ETS exposure was based upon a cross-sectional comparison within the main workplace, and was not affected by sample size considerations.

6.4.2.3. Controlled Human Exposure Studies of Sensory Irritation

Investigators from the laboratory of Dr. Rebecca Bascom completed a total of four studies that were not referenced in the 1997 Cal/EPA report (Bascom *et al.*, 1995; 1996; Kesavanathan *et al.*, 1996; Willes *et al.*, 1998). These build upon the work described in the original two reports that were reviewed in the earlier Cal/EPA report (Ehrlich *et al.*, 1996 and Ng *et al.*, 1993), and address dose-response considerations, alternative measures of nasal patency (acoustic rhinometry rather than rhinomanometry), and alternative physiologic endpoints (nasal mucociliary clearance rather than nasal patency). In addition, three other controlled human exposure studies were identified which emphasized upper airway endpoints (Nowak *et al.,* 1997b; Walker *et al.*, 1997; Junker *et al.*, 2001). These investigations are summarized below.

Table 6.42 Controlled Human Exposure to ETS and Sensory Irritation

Reference Country	Study Description	Exposure to smoke	Findings and OR (95% CI)	Comments
Junker *et al.* 2001 Switzerland	3 studies: emissions by smoking machine; odor threshold; respiratory irritation in 24 women.	Sidestream (SS) at 4.4-431 μg/m^3 $PM_{2.25}$ in chamber	Eye, throat and nasal irritation elevated even at lowest SS levels corresponding to dilution vol of >3000 m^3/cigarette	Odor threshold much lower than typical ETS measured in field. Symptoms at levels much lower than previously reported.
Willes *et al.* 1998 US	Upper airway symptoms in 14 ETS-S and 9 ETS-NS.	Sidestream 15 ppm CO for 2 hr	Nasal symptoms and NAR rose significantly with exposure but no significant differences in mean response between ETS-S and ETS-NS.	ETS-related NAR increases greatest in ETS-S group. Exposure validated by urinary cotinine.
Nowak *et al.* 1997b Germany	Exposed 10 asthmatics to sidestream smoke. Evaluated nasal lavage (NL) and lower airway inflammation.	Sidestream 22 ppm CO for 3 hr on alternate days	Smoke exposure gave significant increase in eye, nose and throat irritation. NL not different before vs. after.	Based on NL, 3 hr ETS not significant stimulant of inflammation in upper airway.
Walker *et al.* 1997 US	Assessed behavior and respiratory symptoms after expo to 5 levels of ETS in 17 men.	90 min expo to 5 levels of ETS (0.25-3 ppm CO	Expo-related increases in eye irritation, odor annoyance, nose and throat irritation. Trend of increasing anxiety and anger with ETS.	Changes in symptoms, respiration and behavior: increasing with higher expo.
Bascom *et al.* 1996 Kesavanathan *et al.* 1996 US	Nasal mucociliary clearance (NMC) in 13 ETS-sensitive (ETS-S) and 16 non-sensitive (ETS-NS) adults.	Sidestream 1, 5, 15 ppm CO, for 2 hr	Symptoms increased with exposure. Nasal volume decreased in exposure-dep. manner for ETS-S Nasal airway resistance (NAR) different at 1, 5 ppm for ETS-S vs. -NS	Complex differences in responses to SS by ETS-S vs. ETS-NS. Subjective congestion correlated with NAR in ETS-S but with nasal volume in ETS-NS
Bascom *et al.* 1995 US	Nasal mucociliary clearance (NMC) in 6 ETS-sensitive (ETS-S) and 6 non-sensitive (ETS-NS) adults.	Sidestream for 60 min on 2 days (CO 15 ppm)	Nasal clearance of radiotracer slower in ETS-S after smoke exposure.	Small study and marked heterogeneity in NMC response to smoke.

ETS-NS: ETS-nonsensitive ; ETS-S : ETS-sensitive ; NAR : nasal airway resistance: NL: nasal lavage; SS: sidestream smoke

Junker et al. (2001) conducted three separate substudies relating to ETS. The first was an emissions study, in which they found that machine-smoked cigarettes yielded significantly more VOCs and CO, but lower particulate mass, than had previously been documented. The second was an "odor threshold" study using an olfactometer, in which 18 female non-allergic non-smoking subjects detected SS odor in an ascending series, method of limits paradigm. The mean odor threshold corresponded to fresh air dilution volume of > 19,000 m^3 per cigarette, over 100 times more than had previously been suggested for acceptable indoor air conditions. The third substudy was a whole-body ("chamber") study, in which 24 female subjects breathed SS over a

wide concentration range (4.4 – 431 μg/m^3 $PM_{2.25}$), the lowest of which corresponded to the level yielding odor detection in 95% of the threshold trials. Eye, throat and nasal irritation, arousal, and annoyance were significantly elevated at the lowest SS exposure level, corresponding to a fresh air dilution volume of > 3,000 m^3 per cigarette. The authors pointed out that odor threshold concentrations for SS are three and more orders of magnitude lower than typical ETS concentrations measured in field settings, and that symptoms appeared at one order of magnitude lower SS concentrations than previously reported. They concluded that acceptable air quality for nonsmokers in smoking-permitted buildings may only be achievable with complete physical separation of smokers and non-smokers.

Willes et al. (1998) studied 23 subjects, 14 ETS-S and 9 ETS-NS, with controlled exposures on two separate days to clean air or SS (15 ppm CO equivalent times two hours). Eight of fourteen ETS-S subjects (57%) were judged to be atopic by skin testing, and an even greater proportion of the ETS-NS subjects (78%) had evidence of allergies. In terms of upper airway endpoints, subjects rated symptoms and had nasal airway resistance (NAR) measured by posterior rhinomanometry both pre- and post-exposure. Nasal lavage (NL), on the other hand, was limited to post-exposure. Urinary cotinine levels were used to validate exposure. Following SS exposure nasal symptoms increased and NAR rose significantly. Although 7 of the 8 subjects with the greatest ETS-related increases in NAR were in the ETS-S group, the two groups did not differ significantly in their mean response to ETS challenge. Nasal lavage markers, on the other hand, including total cell counts, neutrophils, and albumin, were unaffected by ETS exposure.

Nowak et al. (1997b) exposed 10 mild asthmatics to sidestream smoke at 22 ppm CO-equivalents for 3 hours, with control (clean air) exposure on separate days. Although the emphasis of this study was the lower airway (see Section 6.1.1.5), nasal lavage (NL) fluid was also obtained 30 minutes before and 30 minutes after smoke exposure. NL fluid was analyzed for histamine, albumin, eosinophilic cationic protein, myeloperoxidase, hyaluronic acid, and tryptase. Sidestream smoke exposure resulted in significantly greater increases in self-reported eye, nose and throat irritation compared with clean air exposure ($p < 0.05$). NL mediators post-SS exposure were not significantly different from pre-challenge or post-sham values, however. The authors concluded that a 3-h ETS exposure was not a significant pro-inflammatory stimulus in the upper airway.

Walker et al. (1997) exposed 17 non-smoking, non-allergic white male subjects to clean air and five different experimentally generated ETS levels between 58 and 765 μg/m^3 total respirable particles (0.25-3 ppm CO over background). Sessions lasted 90 minutes with a 50-min "plateau" period. Endpoints included symptom reporting, respiratory behavior, eye blink rate, cognitive performance, and mood state. Subjective eye irritation, eye dryness, odor, annoyance, and lack of air quality acceptability all rose significantly at the lowest ETS level employed, and increased monotonically with concentration thereafter. Nose and throat irritation were significantly elevated at or above the second ETS exposure level (0.5 ppm CO over background). Respiratory changes consisted of decreased respiratory rate and increased tidal volume, with minute ventilation staying relatively constant. Ventilatory changes occurred at all ETS exposure levels, without evidence of a dose-response relationship. Significant increases in eye blink rate occurred at the highest exposure level only. There were no significant exposure-related changes in cognitive performance, but a trend toward increased anxiety and anger – and decreased curiosity – which was significant at the highest exposure level. The authors argued that even the

lowest ETS exposure level employed in this experiment was higher than real-life ETS exposures, and that 80% of individuals would be expected to find air containing ETS at 63 $\mu g/m^3$ total respirable particles unacceptable.

Bascom et al. (1996) and *Kesavanathan et al. (1996)* studied 13 ETS-S and 16 ETS-NS subjects exposed to "low-to-moderate" SS levels (1, 5, and 15 ppm CO times 2 hours). A high proportion of subjects in both groups (69% of ETS-S and 50% of ETS-NS) had skin test reactivity to one or more aeroallergens. Objective endpoints included both nasal airway resistance (NAR) measured by posterior rhinomanometry, and nasal cross-sectional area/volume by acoustic rhinometry (AR). In general, postexposure symptoms increased monotonically with exposure level, with eye irritation and odor reaching significance at a lower exposure level (1 ppm CO) than nasal congestion, rhinorrhea, or cough (15 ppm) (see Table 6.43). Differential responses by historical sensitivity status were evident for NAR at 1 and 5 ppm – but not at 15 ppm. The pattern of differences was complex, in that the ETS-NS group showed more objective nasal congestion at 1 ppm and the ETS-S group showed more congestion at 5 ppm. The pattern of differences for AR was even more complex, depending upon the portion of the tracing targeted (anterior, mid-, or posterior nasal cavity). In ETS-S subjects, nasal volume decreased in a dose-dependent manner. ETS-NS showed a qualitatively complex response pattern, with significant dimensional reductions in mid- and posterior nasal at 1 ppm CO but not at 5 ppm CO, and reductions in posterior nasal volume at 15 ppm CO. Kesavanathan *et al.* (1996) formally compared the endpoints of NAR and AR from this dataset in terms of coefficient of variation and correlation between symptoms and instrumental findings. In this latter regard, baseline subjective congestion correlated with NAR in ETS-S subjects, but with AR in ETS-NS subjects.

Bascom et al. (1995) studied nasal mucociliary clearance (NMC) in 12 healthy adults, half of whom had a history of ETS sensitivity and an objective, congestive response to a controlled challenge to ETS (ETS-S) and half non-sensitive (ETS-NS). Investigators exposed subjects to either air or sidestream tobacco smoke (SS) on 2 separate days, at least a week apart, in a climate-controlled chamber. Exposures lasted 60-min and the level of SS was regulated to a carbon monoxide concentration of 15 ppm. Roughly an hour after the exposure, 99 mTc-sulfur colloid aerosol was introduced nasally and serial counts were measured with a scintillation detector over the following hour. As a group, ETS-NS subjects showed more rapid clearance of the radiolabeled tracer than did ETS-S subjects. This group difference was based on half (3 of 6) ETS-S subjects, who showed marked inhibition of NMC. This subgroup did not differ significantly from the other ETS-S subjects with regard to age, gender, or allergy status. The authors acknowledged a marked heterogeneity in response of NMC to SS exposure, and the fact that multiple factors may govern the response. If present, slowed NMC could predispose individuals to respiratory tract infections.

Table 6.43 Symptomatic Responses to Sidestream Smoke - ETS Sensitive Subjects* Bascom *et al.*, 1996.

Symptom	1 ppm CO	5 ppm CO	15 ppm CO
Headache	0.2	0.5[a]	1.1[a]
Eye Irritation	0.9[c]	1.8[e]	3.3[e]
Nose Irritation	0.5[a]	0.3[c]	2.2[e]
Nasal Congestion	0.4	0.2	1.3[d]
Rhinorrhea	0.4[a]	0.1	1.3[b]
Sneezes	0	0.1	0.2
Odor Perception	1.2[e]	2.2[e]	3.5[e]
Chest Tightness	0	0.1	0.8
Cough	0.1	0.2	1.0[a]

Mean mid-exposure values of symptom response scores: [a]p<0.05, [b]p<0.01, [c]p<0.005, [d]p<0.001,[e]p<0.0001

6.4.2.4. Miscellaneous Health Studies

Avunduk et al. (1997) conducted an animal experiment to identify the subacute effects of tobacco smoke exposure on the conjunctiva. The authors exposed 12 male albino rats to mainstream cigarette smoke for 2 hours per day over a 60 day period; conjunctival histology was compared with a like group of control (air-exposed) animals. Total particulate levels were approximately 1200 $\mu g/m^3$. Both light and electron microscopy was employed. The authors found that in the exposed animals the conjunctivae were thinned and atrophied, and that microvillous projections and desmosomal connections were absent in comparison with the control conjunctivae. They concluded that the pathology appeared to be a non-specific irritant effect. Extrapolation of these results to humans exposed to ETS would require quantitative factoring for: 1) sidestream vs. mainstream smoke exposure; 2) lower-dose extrapolation; and 3) interspecies extrapolation.

Lakshmipathy et al. (1996) were interested in laryngeal irritability – as manifest by intraoperative laryngospasm – as a function of ETS exposure in children. To study this, they performed a retrospective analysis of 310 consecutive pediatric patients who underwent an outpatient elective ear, nose, and throat or urologic surgery using halothane general anesthesia in a hospital and ambulatory surgical center. Laryngospasm was identified by medical record review, and cases were excluded if there was a history of asthma, bronchopulmonary dysplasia, pneumonia, or viral upper respiratory symptoms within the two weeks prior to surgery. To determine ETS exposure status, patients' families were questioned within one week after surgery, and the number of smokers in each child's household was determined. A relative risk was then calculated (data treated as retrospective cohort). Ninety-six children were identified with household ETS exposure and 214 without; the two groups were comparable in terms of gender and mean age. Nine of the exposed (9.4%) and two of the unexposed (0.9%) children developed laryngospasm. The authors stated: "…the relative risk for developing laryngospasm was 10 times higher in the ETS-exposed patients compared with the non-ETS-exposed group (RR = 10.0; 95% CI 2.2- 45.6; $p < 0.001$)," and concluded that "…ETS exposure is a strong risk factor for laryngospasm in infants and children during general anesthesia." An alternative analysis of the data would treat the data as cross-sectional, and would examine an odds ratio (OR) instead of a relative risk. Using this statistical paradigm, the OR=10.97, with a similar statistical conclusion.

6.4.2.5. Industrial Hygiene Surveys

Liu et al. (2001) surveyed 111 municipal buildings in California with 118 designated smoking areas during the years 1991 to 1994, before the institution of no-smoking ordinances for public buildings in the state. In terms of physical separation, they found that 41% of designated smoking areas lacked separation from adjacent non-smoking areas, and only 31% were separated with walls that did not terminate in "false ceilings." In terms of ventilation, 72% of designated smoking areas had no separate exhaust fan, and only 25% had exhaust fans that led directly to the outside. Overall, less than half of designated smoking areas (38%) had exhaust ventilation that was not recycled into the main building system. Based upon indoor measurements of airborne nicotine and tracer gas (SF_6) studies, the authors concluded that the most effective reduction in cross-contamination required a combination of physical separation, exhaust to outside, and no air recirculation. These conclusions were largely rendered moot in California with the implementation of AB-13 in 1995.

6.4.2.6. Summary of Sensory Irritation and Annoyance, and Dose-response Considerations

A number of newer studies reinforce the role of ETS in the genesis of mucous membrane irritative symptoms ("sensory irritation"). These include cross-sectional surveys within or between smoking-permitted workplaces (Raynal *et al.*, 1995; Mizoue *et al.*, 2001; Jones *et al.*, 2001) and longitudinal studies of occupational cohorts before and after the institution of indoor smoking restrictions (Eisner *et al.*, 1998; Wieslander *et al.*, 2000). In addition to epidemiological surveys, a number of newer controlled human exposure studies were identified. In general, these studies have utilized lower provocative exposure levels than did earlier studies. For example, Bascom's group evaluated sidestream smoke effects at CO-equivalent exposures between 1 – 15 ppm (vs. an earlier provocative level of 45 ppm – Bascom *et al.*, 1991). To generalize from the studies reviewed here, on a dose-response basis, subjective complaints of odor, annoyance, and eye irritation appear at lower SS concentrations than do nose and throat irritation, rhinorrhea, and cough (with the former appearing as low as 1.0 ppm CO-equivalent). Objective nasal congestion among exposed subjects has been demonstrated at exposure levels as low as 1.0 ppm CO-equivalent (Bascom *et al.*, 1996). Exposures for as long as 3 hours to SS at 15-22 ppm CO-equivalent, however, did not produce an inflammatory response in nasal lavage fluid (Willes *et al.*, 1998; Nowak *et al.*, 1997b).

Walker and colleagues (1997) documented increases in eye blink rate with SS exposures indexed at 765 $\mu g/m^3$ total respirable particles (3 ppm CO over background), whereas Junker *et al.* (2001) observed no such changes at 431 $\mu g/m^3$. This compares with earlier work by Muramatsu *et al.* (1983), who documented both subjective eye irritation and increases in blink rate at SS exposure levels greater than 1.3 ppm CO. A problem that is immediately apparent is the lack of a universally accepted surrogate measure of ETS exposure. The majority of studies to date have included CO as a surrogate measure, either alone (Bascom *et al.*, 1995, 1996; Willes *et al.*, 1998) or in conjunction with respirable particulate matter (Nowak *et al.*, 1997b; Walker *et al.*, l997). One study analyzed here, however, utilized only PM as an exposure surrogate (Junker *et al.*, 2001). An integrated risk assessment utilizing data from all of these studies would require a conversion factor between the two metrics, which have widely varying ratios both within and between different studies.

Another dimension of a subset of the studies reviewed here (i.e., those conducted by Bascom and colleagues) is the identification of "historically ETS-sensitive" and "ETS-nonsensitive" subject subgroups prior to exposure. In their original 1991 study, Bascom *et al.* documented augmented reactivity to SS (objective nasal congestion) in the former group compared to the latter. This apparent differential sensitivity has been an inconstant feature of subsequent studies by this group. A potential confounding variable, however, is the fact that, from study-to-study, varying proportions of the two subgroups have documented allergies (i.e., skin test positivity to one or more common aeroallergens). Since allergic inflammation has been proposed as a neuromodulator, up-regulating both afferent and efferent portions of respiratory tract reflexes, studies stratifying on self-reported ETS sensitivity might profitably control for the presence of recognized allergic disease in research subjects (Shusterman *et al.*, 1998; Togias, 2000; Undem *et al.*, 2000).

A final note deals with ETS-related annoyance and the concept of "acceptable" air quality. As information disseminates to the general public regarding acute and chronic ETS-related health effects, attitudes (and risk perception) change. Cognitive biases regarding the health significance of odor sources appear to affect the likelihood of symptom reporting, both in field and in laboratory settings (Shusterman *et al.*, 1991; Dalton *et al.*, 1997). Thus, estimates of indoor air quality "acceptability" are specific to the experimental group employed, and may show trends over time, with lower ETS exposure levels likely to be tolerated by an informed (and concerned) public.

The overall conclusions of OEHHA staff regarding the sensory impact of ETS exposure remains unchanged from that offered in the 1997 document:

> "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 wellbeing 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."

6.5. Chronic Health Effects in Adolescents and Adults

6.5.1. Pulmonary Function Changes and Respiratory Symptoms

In its 1997 report, Cal/EPA reviewed a total of twenty studies examining the health endpoints of chronic chest symptoms, pulmonary function changes and frank chronic obstructive pulmonary disease (COPD) in adults exposed to ETS. Eleven of these studies had previously been reviewed by the Surgeon General's Office (U.S. DHHS, 1986d), NRC (1986d), or the U.S. EPA (1992g); an additional nine studies were reviewed by Cal/EPA staff. Based upon their review, Cal/EPA staff concluded:

> "…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."

6.5.1.1. Newer Epidemiological Data

This section reviews the epidemiological evidence bearing on the question of chronic exposure to ETS, lung function, and chronic respiratory symptoms in adults. In this update, the literature has been divided between studies describing adult chronic respiratory symptoms and/or pulmonary function changes as individual findings (reviewed here) and studies of adult-onset medical diagnoses of asthma and/or COPD (reviewed in Section 6.5.2). In the former category, we identified a total of five additional relevant studies, which are summarized below and in Table 6.50

Table 6.50 Respiratory Function Changes vs. ETS Exposure

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Kunzli *et al* 2000 Switzerland	Cross-sectional Spirometry vs. ETS n = 3534 nonsmokers	Home and work by questionnaire	Sig. decrement in FEV_1 & FEF_{25-75} in asthmatic women	ETS (hr/d and years) predicted pulmonary decrements. Possible recall bias.
Berglund *et al* 1999 US	Longitudinal cohort: Spirometry n = 1391 Chronic airway disease (AHSMOG)	Home and work by questionnaire	Years living with smoker predicted chronic obstructive pulmonary changes	Obstruction as ratio FEV_1/Vcmax < 65% or FEV_1 < 75% of predicted
Abbey *et al* 1998 US	Longitudinal cohort: Spirometry vs. air pollutants n = 1391 (AHSMOG)	Home and work ETS assessed by questionnaire	ETS not significantly associated with FEF or FEV_1/FVC. ↑PEF lability in males.	↑PEF lability from work ETS only seen in males.
Mannino *et al* 1997 US	Cross-sectional: respiratory disease exacerbation n = 43,732	Home, work: self report	Disease exacerbation 1.44 (1.07- 1.95)	Chronic bronchitis, sinusitis, emphysema worsened by ETS.
Jaakkola *et al* 1996 Canada	Longitudinal cohort: 15-40 yr old non-smokers. 8 yr follow-up for respiratory symptoms. n = 117	Home and work ETS assessed yearly by questionnaire	New onset dyspnea associated with ETS. Wheeze and cough elevated but not significantly.	Small sample size and no objective ETS measures
Lam *et al*., 2000 Hong Kong	Cross-sectional study of Hong Kong police officers; respiratory symptoms among never-smokers (4,468 men, 728 women)	Workplace ETS and home ETS assessed by questionnaire	Any respiratory symptoms OR 2.33; (95% CI 1.97-2.75), and physician consultation OR 1.3 (95% CI 1.05-1.61) in men exposed to ETS at work	Exposure-response trends for all symptoms and health care utilization ($p< 0.002$) for men.; less effect in women, but smaller sample size

AHSMOG Adventist Health Study of Smog; FEF_{25-27} forced expiratory flow at 25-75% of vital capacity; FEV_1 forced expiratory volume in one second; FVC forced vital capacity ; MMEF maximum mid-expiratory flow; PEF peak expiratory flow

Kunzli et al. (2000) focused on workplace ETS exposure in a cross-sectional sample of 17,300 Swiss adults age 18-60 years. The authors successfully recruited 9,651 for questionnaire survey and spirometry, of whom 3,534 yielded lifetime non-smoking histories. In this subgroup, ETS exposure histories were obtained over the one-year prior to sampling including number of smokers at home, presence or absence of smokers at work, and total hours of ETS exposure per day. Researchers also asked about degree of "disturbance" [annoyance] due to ETS exposure. Atopy was indexed by a semiquantitative blood test for total IgE (Phadiatop®). Other covariates included age, gender, and educational level. Of the 3,534 in the final sample, 61% were female (a fact that the authors attributed to the lower prevalence of active smoking in females), and 10% were asthmatics. Fifteen percent of females reported ETS exposure at work (compared to 22% of males), and 18% and 12% of females and males, respectively, reported ETS exposure at home. Restricting the analysis to individuals with no household ETS exposure, the authors found that workplace ETS exposure was associated with a significant decrement in FEV_1 and FEF_{25-75} in asthmatic women only. Semi-quantitative measures of ETS exposure (hours/day and total years exposed) predicted decrements in one or both of the above pulmonary function measures. The authors pointed out that an inherent weakness of the study is the potential for recall bias among individuals with asthma and/or female respondents (although females did not report significantly higher subjective annoyance than did males), as well as the lack of objective measures of ETS exposure.

Berglund et al. (1999) reported on a sub-cohort study from the AHSMOG study (see Abbey *et al*., 1998, described below). From 3,091 surviving and 1,870 eligible study participants, 1,510 were examined and 1,391 met criteria for adequacy of spirometry data, current non-smoking status, and lack of other (non-obstructive cardiopulmonary) health conditions. Spirometry was performed according to ATS guidelines; "obstruction" was defined as either a ratio of $FEV_1/VCmax < 65\%$ or $FEV_1 < 75\%$ of predicted. "Chronic airway disease" (CAD), including asthma, chronic bronchitis, and emphysema, was defined based upon both symptom data and reported physician diagnosis. Covariates accounted for in the analysis included age, gender, family history of CAD or hay fever, and childhood respiratory illnesses. In a multivariate logistic regression analysis, the authors found that obstructive pulmonary function changes, as defined above, were significantly more common as a function of ETS exposure, the latter being defined as years living with a smoker as an adult. Other ETS exposure indices, including years working with a smoker and years living with a smoker as a child, did not predict pulmonary obstructive changes.

Abbey et al. (1998) reported on a long-term cohort study of 6,338 non-smoking non-Hispanic white Seventh-day Adventists originally begun in 1977 (Adventist Health Study of Smog, or AHSMOG study). The focus of this study was ambient air pollutants, with self-reported ETS exposure at home or work being a covariate (along with age, years of smoking prior to 1977, workplace dust and/or exposure, years of education, body mass index, exercise habit, housing density, housing heating source, and % of time spent outdoors). Of surviving study participants, 1,914 met eligibility criteria for age (<80 years), residence (within 20 miles of an air monitoring station), and participation (having completed questionnaires in 1977, 1987, and 1992). Of these, 1,510 were willing and/or able to be examined in clinic in 1993, and 1,391 met criteria for adequacy of spirometry data, current non-smoking status, and lack of other (non-obstructive cardio-pulmonary) health conditions. ETS exposure was ascertained by questionnaire and spirometry was performed according to ATS guidelines. Participants were further instructed to

obtain pulmonary peak expiratory flow (PEF) measurements at home, four times per day for one week. Peak flow "lability" was defined as the difference between the highest and lowest values of PEF divided by the mean value for a given day. In a multivariate regression model, neither home nor workplace ETS exposure was associated with significant decrements in percent predicted FEV_1 or % FEV_1/FVC. Self-reported ETS exposure at work was significantly associated with increased PEF lability in male subjects only.

Mannino et al., 1997. In an analysis of 43,732 adults completing the Health Promotion and Disease Prevention supplement of the 1991 National Health Interview Survey, the cross-sectional association between self-reported ETS exposure at home or work and the risk of "chronic respiratory disease exacerbation" was examined. This study outcome was defined as activity limitation or a physician visit due to a chronic respiratory disease: asthma, chronic bronchitis, emphysema, or chronic sinusitis. Among never-smokers, ETS exposure was associated with an increased risk of chronic respiratory disease exacerbation (OR 1.44; 95% CI 1.07-1.95). Although the population-based sampling and careful control of confounding are study strengths, the relationship between ETS exposure and asthma alone cannot be clearly elucidated from the published study.

Jaakkola et al., 1996. In a cohort study of respiratory health in "young adults" (aged 15-40 at time of initial recruitment), Jaakkola *et al.* conducted an eight-year follow-up of a subset of 117 never-smoking participants. ETS exposure and respiratory symptoms were determined on year-by-year basis using the American Thoracic Society standardized questionnaire. Covariates for which adjustment was made in multivariate analysis included age, gender, atopy, and the presence of respiratory symptoms at baseline. ETS exposure was ascertained separately for the home and workplace, and a total exposure index was constructed. Overall, 62% of subjects reported regular exposure to ETS either at work or at home during the study period. A significant association was found between total ETS exposure index and new-onset dyspnea during study period (OR 2.37/10 cigarettes/day; 95% CI 1.25- 4.51). Central estimates of odds ratios for new-onset wheeze and cough (but not phlegm) were also elevated, but not significantly. The strengths of this study were its longitudinal design and use of a standardized questionnaire. The weaknesses include the lack of objective indices of ETS exposure, as well as the small sample size. A companion study of pulmonary function by Jaakkola *et al.* (1995) in the same cohort was reviewed in the 1997 Cal/EPA document, and failed to demonstrate significant pulmonary function decrements over the above follow-up period.

Lam *et al.* (2000) reported a significant association between ETS exposure at work and respiratory symptoms in a cross-sectional study of police officers in Hong Kong. The outcomes measured by questionnaire among never-smokers (4,468 men, 728 women) included sore or itchy throat, cough or phlegm, wheezing or whistling in the chest, blocked or running nose, and utilization of health services. ETS exposure was quantified by the number of nearby smokers and hours per day of exposure. Multiple logistic regression analyses were adjusted for age, marital status, education, police rank, type of police duties, time on the force, exposure to dusty environments in previous jobs, and ETS exposure at home. Men were more affected than women by workplace ETS. The ORs for various symptoms in men with over 16 cigarette-hours of ETS ranged from 1.43 to 4.89, while the risks associated with ETS exposure from six or more smokers ranged from 1.68 to 3.50; all statistically significant. The OR for any symptoms for

ETS exposure at work was 2.33 (95% CI 1.97-2.75) for men and 1.63 (95% CI 1.04-2.56) for women.

Among men with workplace ETS exposure, there were significant exposure-response trends for all symptoms and health care utilization ($p< 0.002$) based on numbers of smokers. The trends were similar but less pronounced ($p< 0.04$) for women exposed at work for morning cough, cough during the day or night, phlegm, blocked or running nose, and any symptoms. Exposure based on cigarette-hours per day again showed highly significant ($p < 0.001$) trends for men in all symptom categories, with a less pronounced effect in women. The risks associated with ETS exposure at home were generally elevated but significantly so only for ever wheezing in men, and for throat problems in women.

6.5.1.2. Summary of Epidemiological Data – Pulmonary Function and Symptoms.

Newer epidemiological data support a small but potentially biologically significant effect of ETS exposure on pulmonary symptoms and function in adults. Two of three pulmonary function studies (Berglund *et al.*, 1999 and Kunzli *et al.*, 2000) demonstrated significant changes in spirometric parameters (FEV_1 % of predicted, FEV_1/VC, and FEF_{25-75}) among all or subsets of ETS-exposed subjects compared to controls. The third study (Abbey *et al.*, 1998) did not replicate these findings, but did find more lability in ambulatory peak flow measurements among males with self-reported workplace ETS exposure. This latter finding is consistent with a longitudinal study of bartenders by Eisner *et al.* (1998), in which the prevalence of respiratory symptoms (wheeze, cough, and phlegm production) decreased - and pulmonary function parameters (FEV_1 and FVC) increased - following the institution of a smoking ban in bars and taverns. In a small cohort study of young adults, self-reported ETS exposure at work or home was significantly associated with the development of at least one chronic respiratory symptom (Jaakkola *et al.*, 1996). Finally, Lam *et al*. (2000) found significant elevation in respiratory symptoms in men exposed at work to ETS, and evidence of a dose-response gradient. Collectively, these data suggest that ETS exposure may play a role in the genesis of chronic respiratory symptoms and produce small, but measurable, decrements in pulmonary function.

6.5.1.3. Other Respiratory Effects

Blanc et al., 1999. In the Swedish component of the European Community Respiratory Health Survey, Blanc and colleagues examined the cross-sectional impact of self-reported workplace ETS exposure among 2,065 adults (20-44 years). Regular workplace ETS exposure was associated with a greater risk of respiratory-related work disability (prevalence ratio 1.8; 95% CI 1.1-3.1), defined as self-reported change in job or leaving work due to affected breathing. Moreover, workplace ETS exposure was related to a greater risk of work-associated symptomatic asthma, defined as self-reported asthma, airway hyper-responsiveness, and work-related chest tightness or wheezing (PR 1.7; 95% CI 0.9-3.3). Because this study focused on workplace factors, home and other sources of ETS exposure were not examined.

6.5.1.4. Animal Model of Allergic Sensitization.

Rumold et al. (2001) used a murine model to test whether exposure to side stream smoke (SS; a surrogate for ETS) can induce allergic sensitization to inhaled ovalbumin (OVA) in both high

(BALB/c) and low (C57BL/6) IgE-responsive mice. Adult mice (6-8 wks) were exposed on 10 consecutive days to either saline or nebulized 1% OVA for 20 min., SS from 5 cigarettes for 1 hr, or SS for 1 hr followed by OVA for 20 min. Twenty days later, the mice were re-exposed to 1% OVA for 20 min. Bronchoalveolar lavage (BAL) was performed 24 hours later for determination of cytokines in BAL fluid. IgE and IgG1 levels were measured in peripheral blood.

By day 18 following initiation of exposure (8 days following cessation), both total serum and OVA-specific IgE levels were significantly elevated in both high and low responders exposed to OVA/SS compared to OVA alone ($p<0.01$). Similarly IgG1 levels but not IgG2a were significantly elevated in this group ($p<0.01$). Cytokine induction (IL-5, GM-CSF, IL-2) was observed after OVA re-exposure in BAL fluid from mice exposed to SS/OVA but not in mice exposed to OVA alone. Mice exposed to SS/OVA but not OVA alone developed eosinophilia, had significantly less IFN-γ, and had increases in the Th2 cytokine IL-5. SS alone resulted in elevated GM-CSF and IL-2 upon re-exposure. The production of specific allergic antibodies to inhaled allergens is characteristic of the sensitization phase of reactive airway disease. These experiments indicate that ETS has the capacity to alter lung homeostasis and augment allergic sensitization to otherwise innocuous allergens.

6.5.1.5. Mechanisms of Airway Effects.

In its 1997 review, Cal/EPA staff outlined several potential mechanisms whereby ETS might produce obstructive airway disease (as in emphysema) and/or mucous hypersecretion (as in chronic bronchitis). These included "…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..." Newer data are available on two of these mechanisms.

Borchers et al., 1999. In an in vitro study, Borchers and colleagues exposed human lung carcinoma cells to acrolein, an irritant found in ETS. The cells produced significantly elevated levels of messenger RNA coding for two different mucins, MUC5AC and MUC5B. Mucins are an essential component of airway mucus, and the authors make the point that increased mucin production by airway epithelial cells translates clinically into mucus hypersecretion, as seen in chronic obstructive pulmonary disease.

von Ehrenstein et al., 2002. In humans, inhibition of anti-proteases has emerged as a credible mechanism for diminished lung function, at least in children. In a meeting abstract, Von Ehrenstein *et al.* reported on a survey of nearly 1,256 schoolchildren on whom parental questionnaire, spirometry, and plasma levels of α1-antitrypsin were obtained. Both parentally-reported ETS exposure and low α1-antitrypsin levels were associated with slightly decreased lung function parameters (% predicted FEV_1 and FVC). The combination of both risk factors was synergistic, producing significantly lower PFT values. This type of investigation - known as "molecular epidemiology" - will be useful in identifying susceptible subpopulations.

6.5.2. Asthma Induction in Adolescents and Adults

6.5.2.1. Asthma Induction in Adolescents and Adults – Recent Epidemiological Studies

Table 6.51 ETS and New-onset Asthma in Adolescents and Adults

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Svanes *et al*. 2004 Europe	Cross-sectional Childhood ETS and adult asthma. n=18,446	Parental ETS Maternal smoking Both parents	≥ 3 asthma symptoms 1.14 (1.02-1.26) 1.22 (1.07-1.39) p for trend 0.004	Elevated risk of asthma in adults exposed in childhood to maternal smoking.
Eagan *et al.* 2004 Norway	Cohort 11 yr Asthma follow-up n = 2,819	Self-report - Pre- and postnatal maternal smoking Maternal smoking All childhood ETS	Incident adult asthma OR 3.5 (1.8-6.8) Attributable fraction 16.9 % (4.8-27.4) 26.0 (0.03-45.2)	In utero or childhood ETS from mother and others increased risk of adult-onset asthma
Upton *et al*. 2004 U.K.	Cohort. Childhood ETS and Adult COPD n = 2,000	Maternal smoking	Current asthma 1.08 (0.73-1.61) Ever asthma 0.92 (0.66-1.28)	Unadjusted ORs calculated from data presented show no association with ETS
Jaakkola *et al.* 2003 Finland	Case-control Population-based 239 asthma 487 ctrl	Self report- Home Work Trend 10 cig/day Total Trend 10 cig/day	Previous 12 months 4.77 (1.29-17.7) 2.16 (1.26-3.72) 1.44 (1.03-2.01) 1.97 (1.19-3.25) 1.33 (1.02-1.75)	Clinically diagnosed new asthma more strongly associated with recent vs. lifetime ETS
Radon *et al*. 2002 Germany	Cross-sectional Asthma n = 1,843	Self report- Work >8 hr/d	Asthma symptoms 1.51 (0.99-2.32) 2.06 (1.07-3.97)	Elevated asthma risk with daily ETS exposure at work
Iribarren *et al.* 2001 US	Cross-sectional Asthma or hay-fever. n = 47,721	Self report - total ETS. Asthma, hayfever	Diagnosed 1.22 (1.11-1.34) 1.14 (1.06-1.24)	Risk of physician-diagnosed asthma or hayfever increased
Larsson *et al.* 2001 Sweden	Cross-sectional Asthma n = 8,008	Self report. ETS in childhood vs. none. Asthma family history	Diagnosed adult asthma 7.6 vs. 5.8% p=0.035 1.82 (1.28-2.58)	ETS in childhood or with family history of asthma increased risk
Janson *et al.* 2001 Europe	Cross-sectional Asthma 20-48 yr n = 7,882	Self report - Home Work	Current asthma 1.14 (0.68-1.90) 1.90 (1.25-2.88)	Home ETS defined as living w/smoker Work: regular smoking in work area
Thorn *et al.* 2001 Sweden	Case-control Asthma 20-50 yr 174 cs; 870 ctrl	Self report – home during or prior to asthma onset	Diagnosed onset Male: 4.8 (2.0-11.6) Female: 1.5 (0.8-3.1)	Increased risk only among neversmokers; not current or ex-
McDonnell *et al.* 1999 US	Cohort 15 yr Asthma follow-up. n = 3091	Self report work Men Women	Asthma N.S. 1.21 (1.04-1.39)	At 15 yr follow-up, only females had increased risk
Pilotto *et al.* 1999 Australia	Cross-sectional Adult asthma	Self report – home only	Asthma 1.09 (0.65-1.82)	Non-significant association with ETS at home.

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Kronqvist *et al.* 1999 Sweden	Cross-sectional Asthma and allergic rhinitis. n = 1,015	Self report - total ETS.	Respiratory symptoms: NS	No association found with ETS but no risk estimates given
Hu *et al.* 1997b US	Cohort 7th graders Asthma at 20-22 n = 2,041	Parental report Maternal ETS Paternal ETS	Diagnosed as adult 1.8 (1.1-3.0) 1.6 (1.1-2.4)	ETS at baseline raised risk of asthma in adulthood 7 yr later
Flodin *et al.* 1995 Sweden	Case-control Asthma ≥ 20 yr 79 cs; 304 ctrl	Self report – prior 3 yr Home Work	Diagnosed onset 0.9 (0.5-1.5) 1.5 (0.8-2.5)	Study doesn't support association of asthma with ETS
Greer *et al.* 1993 US	Cohort 10 yr Asthma follow-up n = 3917	Self report work	Asthma 1.5/10 yr (1.2-1.8)	Duration of working with smoker increased risk at 10 yr follow-up

The 1997 OEHHA report reviewed studies that evaluated the relationship between ETS exposure and chronic pulmonary disease among adults, including asthma. Based on this review, the report concluded that "…ETS exposure may make a significant contribution to chronic respiratory symptoms in adults." Although the report reviewed five studies that supported an association between ETS exposure and adult asthma (Dayal *et al.*, 1994; Greer *et al.*, 1993; Leuenberger *et al.*, 1994; Ng *et al.*, 1993; Robbins *et al.*, 1993), no specific conclusions were articulated about asthma *per se*.

Svanes et al. (2004) evaluated respiratory health of adults in relation to ETS exposure in childhood. This study is described in more detail in Section 6.1. Current asthma was defined as medication use or asthma attacks in the previous 12 months. The category of "3 or more asthma symptoms during the previous 12 months" was based on positive answers to questions about current asthma or asthma medication use, wheeze with or without shortness of breath, waking with wheeze or shortness of breath, and night cough. The relationship between parental smoking in childhood and adult asthma was evaluated using logistic regression models with adjustments for age, gender, body mass index, current smoking, current ETS exposure, occupation, and study center.

In adults, current asthma was not significantly associated with parental smoking. However, the broader category of 3 or more asthma symptoms in the previous 12 months was significantly associated with maternal smoking during pregnancy (OR 1.28; 95% CI 1.11-1.48) and during childhood (OR 1.14; 95%CI 1.02-1.26). If both parents smoked, the risk increased to 1.22 (95% CI 1.07-1.39) with a p for trend of 0.004.

Eagan et al., 2004 (abstract). A prospective cohort study was conducted in 1985 to 1997 in western Norway to evaluate the impact of childhood ETS exposure on the risk of adult-onset asthma. The cohort included 2819 adults of an original cohort of 3786 persons aged 15 to 70 years who were evaluated 11 years earlier (74% completed both baseline and follow-up). ETS exposure was ascertained by self-report. Incident adult asthma was defined as self-reported asthma at follow-up among persons who did not report asthma at baseline. The attributable

fraction was adjusted for the potential confounding effects of age, sex, educational attainment, atopy, active smoking, and occupational exposures. The adjusted attributable fraction due to maternal smoking, either in utero or in childhood, was 16.9% (95% CI 4.8-27.4%). The adjusted attributable fraction due to all childhood ETS, which included maternal smoking (pre- and post-natal) and other persons smoking, was 26.0% (95% CI 0.03-45.2%). The investigators evaluated ETS exposure from maternal smoking in more detail (Tomas Eagan, personal communication, 9/15/04). Postnatal maternal smoking (without prenatal smoking) was associated with a greater risk of adult-onset asthma (OR 1.8; 95% CI 0.7-4.5) after controlling for confounders, although the confidence interval did not exclude no association. Prenatal maternal smoking, without postnatal smoking, was not common and was not statistically related to incident adult asthma (OR 1.8; 95% CI 0.2-15.9). The combination of maternal smoking pre- and postnatally was strongly associated with the development of adult-onset asthma (OR 3.5; 95% CI 1.8-6.8). In sum, this prospective cohort study supports a link between childhood ETS exposure and the development of incident adult-onset asthma.

Upton et al. (2004) analyzed the effects of maternal and personal smoking on airflow limitation in 2,000 adult offspring of couples from an earlier population-based study of lung function. Whereas maternal smoking was inversely correlated with several measures of lung function (FEV_1, FVC and FEF_{25-75}), there was no significant association between asthma and maternal smoking based on our calculation of the relative risks (ORs) from the data presented. However, this study was designed to look at chronic obstructive pulmonary disease rather than asthma. The ORs are unadjusted and sources of ETS exposure other than maternal smoking were not included, making the lack of association difficult to interpret.

Jaakkola et al. (2003) examined the role of passive smoke exposure in the development of adult-onset asthma in a population-based case-control study of 239 asthma patients and 487 controls in Finland. The study population comprised clinically diagnosed new cases of asthma among 21-63-year-old adults between 1997 and 2000. Passive smoke exposure was assessed from self-administered questionnaires dealing with environmental factors in general (the Finnish Environment and Asthma Survey). Lifetime ETS exposure at home and at work, as well as ETS exposure during the preceding 12 months were determined. ETS exposure, in terms of the number of cigarettes per day and the duration of exposure, was determined for eight age periods (0-1, 1-6, 7-10, 11-15, 16-20, 21-30, 31-40, $\geq$ 40 years). Odds ratios were estimated by logistic regression analyses adjusted for gender, age, parental atopy or asthma, education (a proxy for SES), visible mold or mold odor, pets in the home, and occupational exposure to sensitizers, dusts or fumes (excluding ETS).

The incidence of adult-onset asthma was significantly associated with total ETS exposure (combined home and workplace) during the preceding 12 months (OR 1.97, 95% CI 1.19-3.25) with evidence of an exposure response: OR 1.33 per 10 cigarettes per day (95% CI 1.02-1.75). After controlling for exposure at home, any exposure to ETS in the workplace was also associated with an elevated risk of asthma (OR 2.16, 95% CI 1.26-3.72) and an exposure response OR of 1.44 per 10 cigarettes per day (95% CI 1.03-2.01). While there was significant risk associated with home exposure (OR 4.77, 95% CI 1.29-17.7), the confidence limits were wide, reflecting the small number of cases, and there was no evidence of exposure response. These estimates were somewhat lower after adjustment for cumulative lifetime exposure (Table 6.52).

Analyzed as cumulative lifetime exposure, the risk of asthma was elevated, especially from workplace and combined exposures but many of the confidence intervals included no effect. There was some suggestion of an exposure response in the cumulative home and combined exposures but these trends did not achieve statistical significance.

The strengths of this study include the use of a questionnaire dealing with environmental factors in general rather than one that was ETS-specific. This may have reduced reporting bias among cases. In addition, the use of only clinically diagnosed, new cases of asthma avoided potential bias associated with self-diagnosis and possible ETS-related behavioral changes among previously diagnosed asthmatics. Another strength was the assessment of both recent and cumulative lifetime ETS exposures. However, recall bias may have affected the latter estimate and may, in part, explain the lack of an association with cumulative lifetime exposure. It is therefore difficult to determine the relative importance of recent versus cumulative exposures in the association of ETS with asthma. With respect to ETS in the home, the number of individuals reporting home exposure was small, severely limiting the assessment of this important source of exposure. Thus, concentrating on total and workplace exposures to ETS during the preceding 12 months, this study found a significant association between ETS and the onset of asthma in adults. The authors estimated that 49.2% of the asthma incidence among individuals exposed to ETS from all sources during the preceding year was attributable to the ETS exposure. This translated into an ETS-attributable fraction of 8% for the whole working age population.

Table 6.52 Risk of Adult-onset Asthma in Relation to ETS Exposure in the Preceding 12 Months and Cumulative Lifetime Exposure (from Jaakkola *et al*., 2003)

ETS during preceding 12 months			
Exposure	**Cases/Ctrls**	**OR (95% CI)[a]**	**OR (95% CI)[b]**
Workplace - any	34/41	2.16 (1.26-3.72)	1.83 (1.05-3.21)
1-9 cig/day	15/19	2.06 (0.97-4.36)	1.85 (0.89-3.98)
≥ 10 cig/day	12/12	2.90 (1.14-7.34)	2.10 (0.81-5.47)
Home - any	7/8	4.77 (1.29-17.7)	3.83 (0.99-14.8)
1-9 cig/day	4/3	3.93 (0.80-19.4)	3.62 (0.71-18.6)
≥ 10 cig/day	2/5	0.75 (0.13-4.29)	0.56 (0.10-3.30)
Combined - any	38/41	1.97 (1.19-3.25)	1.66 (0.99-2.76)
1-9 cig/day	17/22	2.13 (1.05-4.30)	1.88 (0.92-3.86)
≥ 10 cig/day	14/17	2.14 (0.95-4.82)	1.56 (0.67-3.61)
Cumulative lifetime ETS exposure			
Exposure	**Cases/Ctrls**	**OR (95% CI)[c]**	**OR (95% CI)[d]**
Workplace - cig-yrs			
1-49	32/70	1.17 (0.71-1.93)	1.08 (0.65-1.80)
50-99	15/17	2.35 (1.07-5.14)	2.25 (1.03-4.93)
100-149	7/18	1.28 (0.49-3.31)	0.93 (0.34-2.57)
≥ 150	22/27	2.21 (1.15-4.27)	1.84 (0.93-3.64)
Home - cig-yrs			
1-49	24/66	0.95 (0.55-1.64)	0.99 (0.57-1.71)
50-99	13/38	0.78 (0.39-1.57)	0.81 (0.40-1.62)
100-149	12/21	1.05 (0.48-2.30)	1.09 (0.50-2.40)
≥ 150	50/69	1.37 (0.87-2.16)	1.40 (0.89-2.20)
Combined - cig-yrs			
1-49	26/91	0.80 (0.48-1.36)	0.79 (0.46-1.34)
50-99	22/44	1.30 (0.71-2.35)	1.28 (0.70-2.34)
100-149	19/25	2.01 (1.02-3.99)	1.76 (0.87-3.55)
≥ 150	68/96	1.84 (1.21-2.80)	1.71 (1.11-2.64)

All ORS adjusted as described in the text with additional adjustment:
[a] for ETS exposure in other setting (work or home)
[b] for cumulative ETS exposure.
[c] for cumulative ETS exposure in other setting.
[d] for ETS exposure in past 12 months.

Radon et al. (2002) presented a secondary analysis of the German data from the European Community Respiratory Health Survey, a population-based, cross-sectional survey, to determine the effects of ETS exposure on asthma and chronic bronchitis in young adults. Asthma was defined by the use of asthma medication, or in the past 12 months having had an asthma attack or being awakened by an attack of shortness of breath. Based on 1,842 respondents, and after adjustment for city, age, gender, active smoking, SES, and occupational exposure to dusts and fumes, multiple logistic regression analyses indicated an OR for asthma from any workplace ETS exposure of 1.51 (95% CI 0.66-2.32). An exposure-response trend was observed for increasing duration of daily exposure with a significant asthma risk associated with >8 hrs of exposure (OR 2.06, 95% CI 1.07-3.97).

Iribarren et al., 2001. In a previous report, the authors examined cross-sectional data from 47,721 adult never-smoking Northern California Kaiser Permanente members who underwent multiphasic health check-ups between 1979 and 1985. Using a written questionnaire, current ETS exposure was ascertained for several locations: home, other small spaces (e.g., office or car), and large indoor spaces (e.g., restaurant). In each location, the survey assessed average duration of exposure. In both men and women, any ETS exposure was associated with a greater risk of self-reported physician-diagnosed asthma or hay fever (OR 1.22; 95% CI 1.11-1.34 and OR 1.14; 95% CI 1.06-1.24, respectively), controlling for socioeconomic and demographic covariates. The risk estimates were similar for high level exposure ($\geq$ 40 hours/week) compared to no exposure. For weekly exposure duration, there was evidence of an exposure-response relationship among women but not men.

Larsson et al., 2001. A population-based study of 8,008 adult never smokers from Sweden examined the impact of childhood ETS exposure on current self-reported physician-diagnosed asthma during adulthood. Adult asthma was more common among subjects who indicated childhood ETS exposure (7.6%) compared to unexposed persons (5.8%) (p=0.035). Current self-reported "breathing difficulties from cigarette smoke" were also more common among subjects who indicated a history of childhood ETS exposure. In further analysis, the authors stratified by family history of asthma. Although there was no clear impact of ETS among subjects without a family history of asthma, ETS exposure was associated with a greater risk of asthma among those with a positive family history (OR 1.82; 95% CI 1.28-2.58). These results could be consistent with higher rates of smoking cessation by asthmatic parents, reducing exposure of their children with asthma.

Janson et al., 2001. The European Community Respiratory Health Survey investigators examined the respiratory health impacts of ETS exposure among 7,882 adult never smokers aged 20-48 years. Compared with no ETS exposure, <u>any</u> ETS exposure at home or work was not associated with a greater risk of self-reported current asthma (OR 1.15; 95% CI 0.84-1.58). When each source of exposure was examined individually, workplace exposure was related to a higher risk of asthma (OR 1.90; 95% CI 1.25-2.88). There was no apparent impact of home exposure (OR 1.14; 95% CI 0.68-1.90). These apparently discrepant results could be explained by the method of ETS exposure measurement. Home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. Because residence with a smoker may not always reflect domestic ETS exposure (Eisner *et al.*, 2001), use of this exposure measure could attenuate the effect estimate for home ETS exposure.

The investigators also found a similar pattern of results for several asthma-like symptoms, including wheeze, nocturnal chest tightness, and dyspnea (nocturnal or exertional). In these instances, workplace ETS exposure was related to a greater risk of respiratory symptoms, whereas home exposure had no apparent impact. An exposure-response relationship was noted for all respiratory symptoms, but not clearly for asthma. Furthermore, both home and workplace ETS exposures were associated with greater bronchial hyper-responsiveness (assessed by methacholine challenge). Because bronchial hyper-responsiveness is a cardinal feature of asthma, this result adds additional support to the observed link between ETS exposure and self-reported asthma.

Thorn et al., 2001. A Swedish population-based case-control study of adults 20-50 years old examined the impact of ETS exposure on the onset of asthma after age 16. The investigators ascertained home exposure only, during or previous to the year of asthma diagnosis (and at a randomly selected time for control subjects). In this study, ETS exposure was associated with a greater risk of adult-onset asthma (OR 2.4; 95% CI 1.4-4.1). This increased risk was observed only among never smokers and not among current or ex-smokers. When the results were stratified by sex, the association was stronger for males (OR 4.8; 95% CI 2.0-11.6) than females (OR 1.5; 95% CI 0.8-3.1).

Pilotto et al. (1999) conducted a cross-sectional study of the prevalence of self-reported asthma, bronchitis/emphysema, and wheezing in adults as a function of local industry, air quality and cigarette smoke exposure in Port Adelaide, Australia. The controls for this study derived from the 1995 National Health Survey and may not be representative of the exposures experienced by the subjects in Port Adelaide. Among nonsmokers with household ETS exposure (n = 1,123), no significant association with asthma was found (OR 1.09; 95% CI 0.65-1.82) after adjustment for age, gender, area of the city, and clustering within households. Although the authors report a higher overall smoking prevalence in Port Adelaide than in the national survey, suggesting possibly higher passive smoke exposures outside the home, no ETS exposure other than in the household was included. It is thus likely that many individuals not reporting household ETS exposure were, in fact, exposed to smoke.

Kronqvist et al., 1999. Recent epidemiological studies have evaluated the impact of ETS exposure on new-onset adult asthma. A population-based cross-sectional study aimed to elucidate environmental risk factors for asthma and allergic rhinitis among Swedish dairy farmers. By postal questionnaire, asthma was defined as self-reported episodic respiratory symptoms, such as wheezing and dyspnea. ETS exposure was assessed for the current period (home and work) and during childhood. In this study, no measure of ETS exposure, past or present, was associated with the risk of asthma (OR or RR not reported) (Table 6.51).

Hu et al. (1997b) evaluated a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. At baseline, ETS exposure status was determined by parental reports of personal smoking. During young adulthood (seven years later), self-reported physician diagnosed asthma was ascertained by written questionnaire. Exposure to parental ETS at baseline was associated with an increased risk of subsequent asthma. Compared with no maternal smoking or light smoking at baseline ($\leq$ one-half pack per day), heavier maternal smoking was associated with an increased risk of self-reported asthma in young adulthood (OR 1.8; 95% CI 1.1-3.0). Similarly, heavy paternal smoking was related to a greater risk of asthma (OR 1.6; 95% CI 1.1-2.4). In addition, they observed an exposure-response relationship between number of parents smoking at baseline and the risk of asthma seven years later.

Flodin et al., 1995. A population-based case-control study from semi-rural Sweden evaluated ETS exposure as a risk factor for adult onset asthma ($\geq$ age 20 years). During a 9 month period, cases were identified from all persons filling a prescription for beta-agonist medications in two communities. The diagnosis of asthma was confirmed by a pulmonary specialist. Controls were randomly selected from a general population register and matched to cases by age (of asthma diagnosis), gender, and community. ETS exposure at both home and work was assessed by

written questionnaire, which was defined as exposure for at least 3 years prior to the age at asthma diagnosis (or comparable age for controls). Workplace ETS exposure was associated with an increased risk of asthma (OR 1.5; 95% CI 0.8-2.5), but the confidence interval did not exclude no relationship. Exposure to ETS at home was not associated with a greater risk of asthma (OR 0.9; 95% CI 0.5-1.5).

Greer et al., 1993; McDonnell et al., 1999. A longitudinal cohort study of 3,914 adult non-smoking Seventh-Day Adventists living in California evaluated the relationship between ETS exposure and the incidence of self-reported physician diagnosed asthma during a 15-year period. The investigators reported the 10-year (Greer *et al.*, 1993) and 15-year cohort follow-up (McDonnell *et al.*, 1999). As reported in the 1997 Cal/EPA report, duration of working with a smoker was associated with an increased risk of developing asthma (OR 1.5 per 10-year increment; 95% CI 1.2-1.8). Since the 1997 Cal/EPA report, longer-term follow-up of the cohort has been reported. At 15-year follow-up, duration of working with a smoker was associated with an increased risk of incident asthma for women only (OR 1.21; 95% CI 1.04-1.39). In both analyses, there was no reported relationship between duration of residence with a smoker and risk of asthma.

There is no "gold standard" for defining asthma in epidemiological research. Although self-reported asthma is commonly used in survey research, this definition may not detect all persons with asthma (McWhorter *et al.*, 1989; Toren *et al.*, 1993). Respondents' reports of respiratory symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma (Toren *et al.*, 1993). Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (Burney *et al.*, 1989).

The previous 1997 Cal/EPA report reviewed studies that support the relationship between ETS exposure and wheezing among adults (Comstock *et al.*, 1981; Jaakkola *et al.*, 1996; Kauffmann *et al.*, 1989; Leuenberger *et al.*, 1994; Ng *et al.*, 1993). Two recent studies further support the adverse impact of ETS exposure on the risk of wheezing among adults (Table 6.53).

Table 6.53 ETS and New Onset of Wheezing Among Adolescents and Adults

Reference Country	Study description	Exposure to smoke	Findings and OR (95% CI)	Comments
Withers *et al* 1998 U.K.	Cohort: 6-8 yr followed 8 yrs n = 2,289	Parent report Maternal ETS Paternal ETS	Wheeze 1.48 (1.17-1.88) Asthma 1.50 (1.14-1.98) New onset wheeze 1.55 (1.03-2.32)	ETS associated w/current and new wheeze. Maternal ETS w/current asthma; Paternal w/new wheeze.
Strachan *et al* 1996 U.K.	Cohort: 0-adult Adult wheeze n = 18,559	Maternal ETS Child at 16 yr Prenatal + 16	New onset wheeze at 33 1.19 (0.86-1.65) 1.40 (1.08-1.82)	Combined pre- and post-natal maternal ETS raise wheeze risk at 33 yrs.

FEV_1 forced expiratory volume in one second; FVC forced vital capacity

Withers et al., 1998. A population-based longitudinal cohort study from the U.K. followed children aged 6-8 years into adolescence (age 14-16 years) to examine factors associated with the development of respiratory symptoms. In adolescence, ETS exposure was cross-sectionally

associated with current wheeze (OR 1.48; 95% CI 1.17-1.88). Maternal smoking was related to a greater risk of parent-reported physician-diagnosed asthma (OR 1.50; 95% CI 1.14-1.98). There was no apparent impact of paternal smoking on current asthma. Among previously asymptomatic persons, paternal smoking was associated with new-onset wheeze during prospective follow-up (OR 1.55; 95% CI 1.03-2.32). Maternal smoking, however, was not associated with new-onset wheeze. New-onset asthma was not examined.

Strachan et al., 1996. Another population-based U.K. cohort study followed 18,559 children born during a single week in March, 1958 through age 33 (31% complete follow-up). The study examined the association between household ETS exposure and the future incidence of wheezing. At both age 7 and 33 years, maternal smoking during pregnancy was associated with an increased risk of incident wheezing illness (OR 1.72; 95% CI 1.11-2.67 and OR 1.71; 95% CI 0.97-3.0, respectively). At age 33, maternal smoking at subject age 16 was associated with an increased incidence of wheezing (OR 1.19; 95% CI 0.86-1.65), although the 95% C.I. includes no effect. ETS exposure both during pregnancy and age 16 was related to a greater risk of incident wheezing (OR 1.4; 95% CI 1.08-1.82). This study is limited by the low follow-up at age 33, which could have biased the results if ETS exposure was related to the probability of study participation.

In the 2004 Surgeon General's report on the health consequences of smoking (DHHS, 2004b), the role of active smoking in the etiology of adult-onset asthma was examined. From a survey of 14 longitudinal and cross-sectional studies published between 1988 and 2001, the report concluded that "the evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults." For most of the studies cited, the risks for asthma induction were elevated but in several, the confidence intervals included no effect. The report mentioned that various methodological limitations, biases, differences in study designs, and varying definitions of asthma likely contributed to the apparent inconsistencies in the findings. This update presents several newer studies (Eagan *et al*., 2004; Jaakkola *et al*., 2003; Iribarren *et al.*, 2001; Larsson *et al*, 2001) not included in the Surgeon General's report that better address the limitations noted above, and find a significant association between ETS exposure and adult-onset asthma.

6.5.2.2. Conclusions – Asthma Induction in Adolescents and Adults

A number of the studies in this section included adolescents as adults, thus in the discussion that follows, the term "adult" applies to the combined group. In interpreting these epidemiological studies, a critical issue is whether the observed association between ETS exposure and adult asthma could be explained by confounding factors. ETS exposure has been associated with younger age, female gender, non-white race, lower education, lower income, blue-collar occupation, and personal cigarette smoking (Hole *et al.*, 1989; Iribarren *et al.*, 2001; Mannino *et al.*, 1997; Sippel *et al.*, 1999). Many of these factors have also been associated with an increased prevalence of asthma and asthma-related morbidity (Mannino *et al.*, 1997). As a result, a given risk estimate for ETS exposure could be potentially explained by confounding. Although these studies had variable control for confounding factors, most investigators examined at least some potential confounders. Overall, the observed relationship between ETS exposure and asthma is probably not explained by confounding.

Measurement of ETS exposure by self-report is potentially subject to bias, which limits interpretation of all the studies reviewed. The impact of exposure misclassification may be particularly problematic in cross-sectional studies. For example, adults with asthma might be more likely to remember and report ETS exposure, whereas asymptomatic persons might underreport ETS exposure. This bias would inflate the estimated risk associated with ETS exposure. In all studies examined, systematic misclassification of ETS exposure cannot be excluded. The prospective data, however, should be less affected by this potential bias. Moreover, studies that employed direct markers of ETS exposure, such as cotinine or personal nicotine exposure, would not be affected by this reporting bias.

Examination of the Bradford Hill (Hill, 1971) criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger *et al.*, 1994), number of smokers in the environment (Hu *et al.*, 1997a; Leuenberger *et al.*, 1994), duration of exposure to smokers (Iribarren *et al.*, 2001; Janson *et al.*, 2001; Kunzli *et al.*, 2000; Leuenberger *et al.*, 1994), duration of working with a smoker (Greer *et al.*, 1993; McDonnell *et al.*, 1999), measured nicotine levels (Eisner *et al.*, 2001), and an ETS exposure index that incorporates both intensity and duration of exposure (Jaakkola *et al.*, 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larson 2001), a defined period prior to the diagnosis of asthma (Flodin *et al.,* 1995, Thorn *et al.,* 2001, Hu *et al.,*1997b, Greer *et al.,* 1993, McDonnell *et al.,* 1999), or a defined period prior to the development of asthma-like symptoms (Withers *et al.,* 1998, Strachan *et al.,* 1996). In these studies, exposure to ETS clearly predated the development of asthma.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a deleterious causal effect of ETS exposure on adult asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (Cal/EPA, 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biologic plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function (Hole *et al.* 1989; Comstock *et al.* 1981; Ng *et al.* 1993; Masi *et al.* 1988; O'Connor *et al.* 1987; Xu and Li 1995; Schilling *et al.* 1977; Kauffmann *et al.* 1989; Brunekreef

et al. 1985; Abbey *et al.* 1998; Carey *et al.* 1999; Jaakkola *et al.* 1995; Eisner *et al.* 1998; Eisner 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

A key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease. Several studies directly support the impact of ETS exposure on incident adult asthma (Thorn *et al.,* 2001; Hu *et al.,* 1997b, Greer *et al.,* 1993; McDonnell *et al.,* 1999; and Jaakkola *et al.,* 2003). Other studies have prospectively examined the relation between ETS exposure and incident wheezing (Withers *et al.,* 1998, Strachan *et al.,* 1996). The population-based study by Jaakkola and colleagues provides the strongest evidence to date that links ETS exposure to incident adult asthma. The investigators used a systematic surveillance system to identify newly diagnosed adult asthma cases in a region of Finland and to exclude pre-existing asthma cases. ETS exposure assessment ascertained exposure history during the past 12 months and the entire lifetime. Taken together, these studies indicate that ETS exposure is associated with the subsequent development of adult asthma.

In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship.

The long-term health consequences of ETS exposure have been established over the past two decades. Consistent epidemiological evidence links ETS exposure with serious chronic health effects, including lung cancer and cardiovascular disease (Cal EPA, 1997; Hackshaw *et al.*, 1997; Kawachi *et al.*, 1997). As discussed in depth in each of the previous sections in the present review, the evidence is consistent with a causal relationship between ETS exposure and new-onset asthma and asthma exacerbations in young and older children. In addition, the new studies also provide evidence for a causal relationship between ETS exposure and new-onset asthma and asthma exacerbation among adults. Despite the growing knowledge of ETS-related health effects, smoking is still permitted in many public locations and workplaces (Emmons *et al.*, 1996; Gerlach *et al.*, 1997). Because asthma is a visible condition among the general public, the evidence linking ETS exposure with adverse asthma health outcomes should provide policymakers with additional impetus for regulating public smoking and creating smoke-free public environments.

6.6. Susceptible Populations

From the body of research reviewed here, it is evident that there are populations with enhanced susceptibility to the deleterious effects of ETS. These groups are defined by age, predisposing conditions and previous exposures. ETS exposure puts neonates and infants at greater risk for the onset and exacerbation of asthma (Stoddard and Miller, 1995; Wennergren *et al.*, 1997; Mannino *et al.*, 2001). Young children are especially impacted by asthma; they have the highest

hospitalization rates compared to older children and adults, probably at least in part due to their smaller airways resulting in more serious obstruction. Compared to older children and adults, ETS exposure puts neonates and infants at greater risk for respiratory tract infections (Li *et al.*, 1999), otitis media, and symptoms of respiratory illness (Gergen *et al.*, 1998). Individuals with preexisting allergies or atopy tend to be more severely affected by ETS exposure (Jedrychowski and Flak, 1997; Lindfors *et al.*, 1995; Hajnal *et al.*, 1999). As reviewed above, both children and adults with current asthma are especially susceptible to ETS.

In addition to these conditions, an individual's susceptibility to ETS exposure is enhanced by prior exposure to tobacco products early in development. Children exposed to tobacco smoke constituents *in utero* through either active or passive maternal smoking during pregnancy are even more affected by subsequent ETS exposure with more pronounced respiratory symptoms (Hajnal *et al.*, 1999), higher respiratory infection rates (Jedrychowski and Flak, 1997; Strachan and Cook, 1997; Gilliland *et al.*, 2001), and decreased pulmonary function (Mannino *et al.*, 2001; Li *et al.*, 2000; Rizzi *et al.*, 2004; Svanes *et al.*, 2004). Thus maternal exposure to tobacco smoke during pregnancy helps create a population at greater risk for the subsequent development of ETS-associated diseases.

6.6.1. ETS and Cystic Fibrosis

The 1997 document (CalEPA 1997) summarized the extent and magnitude of the effects of ETS on individuals with cystic fibrosis (CF) as uncertain. While the evidence for an effect of ETS on CF-related hospitalizations was reportedly compelling, it was less conclusive regarding effects on pulmonary function or disease severity. The two additional studies described below do little to change that assessment. While the study by Beydon *et al*. (2002) suggests a negative effect of ETS exposure in CF, the study by Smyth *et al.* (2001) finds no ETS effect on two measures of lung function in children with CF.

Beydon et al. (2002) conducted pulmonary function tests in 39 preschool children with, and 79 without CF. All children received a physical examination during which height, weight and history of ETS exposure were recorded. For CF children additional information collected included CF transmembrane conductance regulator gene mutations, circumstances of diagnosis, pancreatic insufficiency, CF-related respiratory symptoms, history of respiratory infection, intravenous antibiotic use, and anti-asthma treatments. The pulmonary function tests included measures of functional residual capacity (FRC) and expiratory interrupter resistance ($Rint_{exp}$) for which both absolute values and Z-scores were presented. Children with CF had significantly higher $Rint_{exp}$ values and $Rint_{exp}$ Z-scores than did healthy children ($p<0.0001$). Increases in $Rint_{exp}$ or its Z-score reflect occlusion of the lower airways. Of the 39 children with CF, 8 had ETS exposure and higher baseline $Rint_{exp}$ Z-scores than the other 31 (median $Rint_{exp}$ Z-scores 2.4 (0.8-3.5) versus 0.6 (0-1.7); $p < 0.03$). An analysis of the effects of genotype and passive smoking among CF children indicated that passive smoking was the main risk factor for having a $Rint_{exp}$ Z-score greater than 2 (OR 9.5, $p < 0.03$). The significant elevation of the $Rint_{exp}$ Z-score in CF children with ETS exposure was not observed among control children with, versus without, ETS exposure. This study was small and not specifically designed to examine the effects of passive smoking. Thus information on the degree of ETS exposure is limited. Nevertheless, ETS exposure was associated with significant airway obstruction in preschool children with CF.

Smyth et al. (2001) investigated trends in ETS exposure in children with cystic fibrosis (CF) over a five-year period. Smoke exposure was assessed both by questionnaire and by measures of urinary and salivary cotinine. Cross-sectional data were obtained on 52 children with CF in 1993 (ages 5-16 years). Similar cross-sectional data were collected on 56 children in 1998 (ages 5-18 years), 34 of whom were included in the 1993 group. Lung function tests were performed on both occasions to measure FEV_1 and FVC. Family smoking behavior was not different between the groups examined in 1993 and 1998. Among the 34 children tested on both occasions, there was no significant change in the log urinary cotinine values (5.03 ng/ml vs. 4.76 ng/ml, $p = 0.4$). However, these values were apparently not corrected for volume. Measures of FEV_1 and FVC declined in children from both smoking and non-smoking households and there was no significant difference in the decline between the two.

In healthy children, FEV_1 and FVC normally increase as the child grows while ETS exposure decreases this expected increase (Tager *et al*., 1983). By contrast, children with CF typically show a decrease in lung function with age. In this study, children with CF showed a decrease in lung function of approximately the same amount (10-11%) whether or not they were exposed to ETS. Thus ETS exposure was not seen to exacerbate the CF-associated decrease in lung function. The authors observed that it is not known to what extent parents of children with mild symptoms were less likely to modify their smoking behaviors, and hence the child's ETS exposure, compared to parents of severely affected children. Such an effect could mitigate any negative effects of ETS exposure.

6.7. Chapter Summary and Conclusions

6.7.1. Effects of ETS on Children

ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract, especially in children. The number and severity of these effects appear to be inversely related to the age at which tobacco exposure commences, with the greatest susceptibility associated with exposure starting *in utero*. This age-related sensitivity to ETS undoubtedly reflects not only the developmental susceptibility of the very young but also changing patterns of exposure as growing children spend less time in close proximity to sources of ETS.

In the context of lung development, data presented in the previous document were deemed to be suggestive of a causal association. Based on the studies in this update, OEHHA finds that the data still suggest a causal association between ETS exposure and decrements in measures of lung development, and in fact strengthen the suggestive finding of the 1997 report. In all the reviewed studies using forced expiratory volume (FEV) as a measure of lung function, significant decrements were observed in children exposed to ETS. Two studies measured cotinine in children and found that decrements in the spirometric measures were associated with elevated cotinine indicating recent exposure to tobacco smoke. It was difficult for most studies to subtract effects of prenatal exposure from maternal active smoking, which seem to be larger than effects of postnatal ETS exposure. Nonetheless, a few studies reported statistically significant decrements in lung function from postnatal exposure to ETS.

As seen in this review, ETS continues to be causally associated with the onset and exacerbation of asthma, and increased frequency of respiratory infections and disease symptoms in children.

With current asthma, ETS exposure worsened symptoms, increased the number of symptomatic days and increased usage of healthcare services. That recent ETS exposure contributed to these endpoints was indicated by the positive association of cotinine with asthma symptoms in children.

The case for the involvement of ETS in new-onset asthma has been most compellingly made for children, especially young children and those whose mothers smoked during pregnancy. Of the 37 studies included in this review, nearly all showed a positive correlation with postnatal ETS (OR >1.0 or $p<0.05$). In the OEHHA meta-analysis, a summary of which is presented here, an analysis based on 29 studies that controlled for the child's history of atopy and personal smoking, and in which all ages were combined, gave a pooled OR for new-onset asthma of 1.32 (95% CI, 1.24; 1.41). Studies allowing stratification by age indicated that the earlier a child is exposed to ETS, the greater the risk for asthma induction. In another sub-analysis in the OEHHA meta-analysis, postnatal-only exposure resulted in elevated asthma risk in seven of eight studies, and that risk was statistically significant in three of the studies.

In children, ETS is also associated with otitis media. In California, ETS-related otitis media cases are estimated to result in 30,820 to 78,877 office visits per year among children less than three years of age.

The studies in children reviewed here all indicate that smoke exposure increases the risk of respiratory illness by 26 to 113%. This effect was dose-related and especially pronounced in young children and children with atopy.

6.7.2. Effects of ETS on Adults

For two respiratory outcomes in adults, asthma induction and asthma exacerbation, the research published since the 1997 Cal/EPA document supports a change in the estimation of the causal association from suggestive to conclusive. In adults, diagnosed asthma or wheeze was significantly associated with ETS exposure in 8 of 10 studies, especially where exposure started *in utero*, in childhood, and/or where there was a family history of asthma. In adult asthmatics, nicotine exposure (as monitored by personal badge) was linearly correlated with respiratory symptoms. Collectively the studies of ETS and adult-onset asthma satisfy the Bradford Hill criteria for a causal association in that they have demonstrated temporality, exposure-response relationship, consistency, coherence, and biological plausibility.

While lung function effects are less pronounced in adults than in children, ETS exposure appears to play a role in the genesis of chronic lower respiratory tract symptoms in otherwise healthy individuals and produces small, but measurable, decrements in pulmonary function. In adults, exposure to ETS at home and/or work was less associated with the onset of respiratory illness but rather with the aggravation of the symptoms and severity of existing bronchitis, sinusitis and emphysema. Among adult nonsmokers exposed to ETS, eye, nose and throat irritation, as well as odor annoyance, are the most commonly reported health complaints. These complaints occur at levels near or overlapping the odor threshold for ETS, making their prevention technically difficult in smoking-permitted buildings.

This section thus finds ETS exposure in adults to be causally associated with asthma induction and exacerbation, and sensory irritation. An association with the worsening of respiratory symptoms is also strongly indicated.

6.8. References

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Chapter 7. Carcinogenic Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and various cancers from the 1997 OEHHA report and this update are provided below in Table 7.0A. These findings are based on a weight of evidence approach. In summary, there is evidence that ETS exposure causes lung and nasal cancer. Epidemiologic studies, supported by animal data on carcinogenicity of ETS components, provide evidence consistent with a causal association between ETS exposure and breast cancer in younger primarily pre-menopausal women. In addition, there is evidence suggestive of an association between exposure to ETS and brain cancer and lymphomas in children.

Table 7.0A ETS and Cancer: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Findings OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
All cancers - Adult	5	1	Suggestive	Suggestive
All cancers - Childhood				
Mother (smoker)	7	6	Inconclusive	Inconclusive
Father (smoker)	1	6	Inconclusive	Suggestive
Lung	19	22 (7 meta)[a]	Conclusive	Conclusive (strengthened)
Breast	4	22 (4 meta)	Inconclusive	
Younger/pre-menopausal				Conclusive
Older/post-menopausal				Inconclusive
Head and Neck	0	2	Not reviewed	Inconclusive
Nasal sinus	3	0	Conclusive	Conclusive
Nasopharynx	0	4	No studies	Suggestive
Cervical	4	2	Suggestive	Suggestive
Lymphomas Children	6	6	Inconclusive	Suggestive*
Brain Children	10	12	Inconclusive	Suggestive*
Brain Adult	3	0	Inconclusive	Inconclusive
Bladder	2	1	Inconclusive	Inconclusive
Stomach	1	3	Inconclusive	Inconclusive
Leukemia Childhood	8	10	Inconclusive	Inconclusive

* May reflect an association with paternal pre-conceptional smoking rather than ETS exposure.

a. Meta = meta-analyses – not included in study counts

7.0. Introduction

Primary tobacco smoking is an established human carcinogen (IARC 2004a; U.S. DHHS 1989). Environmental tobacco smoke (ETS) has been established as a cause of lung cancer in nonsmokers (U.S. DHHS 1986e; NRC 1986e; U.S. EPA 1992a), most recently by IARC (2004a). This chapter updates the previous OEHHA review (Cal/EPA 1997) on the role of ETS in the etiology of cancers in nonsmokers.

One of the required elements in commonly used criteria for evaluating the possible causality of observed epidemiological associations is biological plausibility (see Chapter 1). In favorable cases, this may involve identification of a detailed mechanism by which a given exposure could produce the observed result. Even where this is not available, the observation of similar effects in other more closely controlled circumstances such as laboratory experiments may be regarded as evidence of biological plausibility. Thus, a carcinogenic effect in laboratory animals in the course of a well-designed bioassay (where other factors such as timing, dose level, consistency of subject groups and potential confounding exposures can be tightly controlled) is regarded as supporting the biological plausibility of an association between increased cancer incidence and exposure of humans seen in an epidemiological study.

In reviewing the case for a causal association between exposure to ETS and various cancers, OEHHA (Cal/EPA, 1997) noted the occurrence of a number of established carcinogens as ingredients of both direct and sidestream tobacco smoke. The list, presented as Table 2.2 in the 1997 document, includes 38 organic compounds and 5 inorganic elements or classes of compounds classified by IARC as 2B or higher, by U.S. EPA as B2 or higher, and/or listed as a carcinogen under Proposition 65. This probably under-represents the true number of carcinogenic components of tobacco smoke by a significant margin, both because tobacco smoke is a complex mixture, many components of which have not been conclusively identified, and also because many identified components have not been exhaustively tested for carcinogenicity. Since IARC monograph 38 (IARC 1986a), that agency has substantially increased the number of materials it has evaluated, and in some cases upgraded earlier evaluations in the light of new evidence or revised evaluation protocols. A further indication of the number and type of potentially carcinogenic components in tobacco smoke may be obtained from Table 7.0B below. This lists, as far as possible, those compounds present in tobacco smoke which have been evaluated by IARC. It is based on Appendix 2 of IARC (1986a), with some additions based on data on occurrence in tobacco smoke from U.S. EPA (1992g) and from IARC (2004a), Table 1.14. The evaluations were updated to reflect changes and additions listed in Supplement 6 (1987), Supplement 7 (1987), and in recent monographs up to and including Vol. 84

As with the previous OEHHA review (Cal/EPA, 1997), this chapter updates the data on the relationship between ETS and all cancers combined, in adults (Section 7.1.1) and in children (Section 7.1.2). Later sections present any additional published data on the role of ETS in the etiology of lung cancer (Section 7.2), cancer sites other than lung causally linked to active smoking (Section 7.3), and cancer sites which have been equivocally or suggestively linked to active smoking (Section 7.4). Section 7.4 also includes the evidence on ETS exposure and risk of specific childhood cancers. In addition, we discuss new studies on the impact of exposure misclassification on the results of epidemiological investigations into ETS exposure and human disease (Section 7.0).

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
1. Aliphatic hydrocarbons			
1,3-butadiene (20-40) (4)	Sufficient	Limited	Vol. 39, p.155-179; Suppl. 7, p. 136; Vol. 54, pp. 237-285; Vol. 71, pp. 109-225.
ethylene (200-400) (3)	Inadequate	Inadequate	Vol. 19, pp. 157-186, Suppl.7, p. 63, Vol. 60 pp. 45-71.
propylene (50-100) (3)	Inadequate	Inadequate	Vol. 19, pp. 213-230; Suppl.7, pp. 70-71, Vol. 60 pp. 161-180.
2. Aromatic hydrocarbons			
Monocyclic aromatic hydrocarbons			
benzene (12-50) (4)	Sufficient	Sufficient	Vol. 7, pp. 203-221; Vol. 29, pp. 93-148, 391-397; Suppl. 4, p. 56; Suppl. 6, pp. 91-95; Suppl. 7, pp.120-122.
styrene (14-19) (4)	Limited	Limited	Vol. 19, pp. 231-274; Suppl. 4, pp. 229-233; Suppl. 7, 345-347; Vol. 60, pp. 233-319; Vol. 82, 437-550.
Di- and polycyclic aromatic hydrocarbons			
anthanthrene (0.002-0.02) (2)	Limited	No data	Vol. 32, pp. 95-104; Suppl. 7, p. 57.
anthracene (0.023-0.23) (2)	Inadequate	No data	Vol. 32, pp. 105-121; Suppl. 7, p. 57.
benz[a]anthracene (0.02-0.07) (4)	Sufficient	No data	Vol. 3, pp. 45-48; Vol. 32, pp. 135-145; Suppl. 7, p. 58.
benzo[b]fluoranthene (0.004-022) (4)	Sufficient	No data	Vol. 3, pp. 69-81; Vol. 32, pp. 147-153; Suppl. 7, p. 58.
benzo[j]fluoranthene (0.006-021) (4)	Sufficient	No data	Vol. 3, pp. 82-90; Vol. 32, pp. 155-161; Suppl. 7, p. 58.
benzo[k]fluoranthene (0.006-0.012) (4)	Sufficient	No data	Vol. 32, pp. 163-170; Suppl. 7, p. 58.
benzo[ghi]fluoranthene (0.001-0.004) (2)	Inadequate	No data	Vol. 32, pp. 171-175; Suppl. 7, p. 58.
benzo[a]fluorene (0.049-0.18) (2)	Inadequate	No data	Vol. 32, pp. 177-182; Suppl. 7, p. 58.
benzo[b]fluorene (0.02) (2)	Inadequate	No data	Vol. 32, pp. 183-187; Suppl. 7, p. 58.
benzo[c]fluorene (2)	Inadequate	No data	Vol. 32, pp. 189-193; Suppl. 7, p. 58.
benzo[ghi]perylene (0.06) (1)	Inadequate (co-carcinogen)	No data	Vol. 32, pp. 195-204; Suppl. 7, p. 58.
benzo[c]phenanthrene (2)	Inadequate (initiator)	No data	Vol. 32, pp. 205-209; Suppl. 7, p. 58.
benzo[a]pyrene (0.0085-0.011) (4)	Sufficient	No data	Vol. 3, pp. 91-136; Vol. 32, pp. 211-224; Suppl. 4, pp. 227-228; Suppl. 7, p. 58.
benzo[e]pyrene (0.002-0.03) (2)	Inadequate (initiator?, promoter)	No data	Vol. 3, pp. 137-158; Vol. 32, pp. 225-237; Suppl. 7, p. 58.
chrysene (0.04-0.06) (1)	Limited (initiator, co-carcinogen)	Inadequate	Vol. 3, pp. 159-177; Vol. 32, pp. 247-261; Suppl. 7, p. 60.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
coronene (0.001) (2)	Inadequate (initiator)	No data	Vol. 32, pp. 263-268; Suppl. 7, p. 61.
dibenz[a,c]anthracene (present) (2)	Limited (initiator)	No data	Vol. 32, pp. 289-297; Suppl. 7, p. 61.
dibenz[a,h]anthracene (0.004) (4)	Sufficient	No data	Vol. 3, pp. 178-196; Vol. 32, pp. 299-308; Suppl. 7, p. 61.
dibenz[a,j]anthracene (0.01) (2)	Limited	No data	Vol. 32, pp. 309-313; Suppl. 7, p. 61.
dibenzo[a,e]fluoranthene (present) (4)	Limited (initiator)	No data	Vol. 32, pp. 321-325; Suppl. 7, p. 61.
dibenzo[a,e]pyrene (present) (4)	Sufficient	No data	Vol. 3, pp. 201-206; Vol. 32, pp. 327-330; Suppl. 7, p. 62.
dibenzo[a,h]pyrene (present) (2)	Sufficient	No data	Vol. 3, pp. 207-214; Vol. 32, pp. 331-335; Suppl. 7, p. 62.
dibenzo[a,i]pyrene (0.0017-0.0032) (4)	Sufficient	No data	Vol. 3, pp. 215-223; Vol. 32, pp. 337-342; Suppl. 7, p. 62.
dibenzo[a,l]pyrene (present) (2)	Sufficient	No data	Vol. 3, pp. 224-228; Vol. 32, pp. 343-347; Suppl. 7, p. 62.
1,4-dimethylphenanthrene (present) (2)	Inadequate (initiator)	No data	Vol. 32, pp. 349-353; Suppl. 7, p. 62.
fluoranthene (0.1-0.26) (1)	Inadequate (co-carcinogen)	No data	Vol. 32, pp. 355-364; Suppl. 7, p. 63.
fluorene (present) (2)	Inadequate	No data	Vol. 32, pp. 365-371; Suppl. 7, p. 63.
indeno[1,2,3-cd]pyrene (0.004-0.02) (2)	Sufficient	No data	Vol. 3, pp. 229-237; Vol. 32, pp. 373-379; Suppl. 7, p. 64.
1-methylchrysene (0.003) (2)	Inadequate (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
2-methylchrysene (0.001) (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
3-methylchrysene (0.006) (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
4-methylchrysene (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
5-methylchrysene (≤0.0006) (4)	Sufficient	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
6-methylchrysene (0.007) (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
2-methylfluoranthene (2)	Limited (initiator)	No data	Vol. 32, pp. 399-404; Suppl. 7, p. 66.
3-methylfluoranthene (2)	Inadequate	No data	Vol. 32, pp. 399-404; Suppl. 7, p. 66.
1-methylphenanthrene (0.03) (2)	Inadequate	No data	Vol. 32, pp. 405-409; Suppl. 7, p. 66.
naphthalene (53 – 177) (8)	Sufficient	Inadequate	Vol. 82, pp. 367-435.
perylene (0.003-0.005) (2)	Inadequate	No data	Vol. 32, pp. 411-418; Suppl. 7, p. 69.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
phenanthrene (0.09- 0.6) (2)	Inadequate	No data	Vol. 32, pp. 419-430; Suppl. 7, p. 69.
pyrene (0.05-0.2) (1)	Inadequate (co-carcinogen)	No data	Vol. 32, pp. 431-445; Suppl. 7, p. 71.
triphenylene (2)	Inadequate	No data	Vol. 32, pp. 447-451; Suppl. 7, p. 73.
3. Phenols and phenol ethers			
caffeic acid (<3) (4)	Sufficient	No data	Vol. 56, pp. 115-129
catechol (59-81) (4)	Sufficient	No data	Vol. 15, pp. 155-175; Suppl. 7, p. 59; Vol. 71, pp. 433-451.
eugenol (2-4) (2)	Limited	No data	Vol. 36, pp. 75-97; Suppl. 7, p. 63.
hydroquinone (88-155) (2)	Limited	Inadequate	Vol. 15, pp. 155-175; Suppl. 7, p. 64; Vol. 71, pp. 691-719.
resorcinol (8-80) (2)	Inadequate	No data	Vol. 15, pp. 155-175; Suppl. 7, p. 71; Vol. 71, pp. 1119-1131.
cholesterol (22) (2)	Inadequate	Inadequate	Vol. 10, pp. 99-111; vol. 31, pp. 95-132; Suppl. 7, 161-165
4. Aldehydes			
acetaldehyde (770-864) (4)	Sufficient	Inadequate	Vol. 36, pp. 101-132; Suppl. 7, 77-78; Vol. 71, p. 319-335.
acrolein (25-140) (4)	Inadequate	Inadequate	Vol. 19, pp. 479-494; Vol. 36, pp. 133-161; Suppl 6, pp.21-23; Suppl. 7, p. 78; Vol. 63, p. 337 -372 (correction Vol. 65, p.549).
crotonaldehyde (55-67) (4)	Inadequate	Inadequate	Vol. 63, pp. 373-391.
formaldehyde (10.3-25) (4)	Sufficient	Limited	Vol. 29, pp. 345-389; Suppl. 4, pp. 131-132; Suppl. 6, pp.321-324; Suppl. 7, pp. 211-216; Vol. 62, pp. 217-362 (corrections Vol. 65, p.549 and 66, p. 485).
5. Lactones, esters, epoxides, furans etc.			
benzofuran (present) (4)	Sufficient	No data	Vol. 63, pp. 431-441
γ-butyrolactone (10) (2)	Evidence sug-gesting lack of carcinogenicity	Inadequate	Vol. 11, pp. 231-240; Suppl. 7, p. 59; Vol. 71, pp. 367-382.
coumarin (3)	Limited	No data	Vol. 10, pp. 113-119; Suppl. 7, p. 61; Vol. 77, pp. 193-225.
ethylene oxide (7) (4)	Sufficient	Limited	Vol. 11, pp. 157-167; Vol 36, pp. 189-226; Suppl. 7, pp. 205-207; Vol. 60, pp. 73-159.
furan (20 - 40) (4)	Sufficient	No data	Vol. 63, pp. 393-407
propylene oxide (0 - 0.1) (4)	Sufficient	Inadequate	Vol. 11, pp. 191-199; Vol 36, pp. 227-243; Suppl. 7, pp. 328-329; Vol. 60, pp. 181-213
methyl acrylate (present) (2)	Inadequate	No data	Vol. 19, p. 52; Vol. 39 pp. 99-112; Suppl. 7, p. 66; Vol. 71, p. 1489-1496.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
6. Nitrogen compounds			
N-Nitroso compounds			
4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) (0.08-0.7) (2)	Sufficient	No data	Vol. 37, pp. 209-223; Suppl. 7, p. 68.
N'-nitrosoanabasine (0-0.2) (2)	Limited	No data	Vol. 37, pp. 225-231; Suppl. 7, p. 67.
N'-nitrosoanatabine (0-3.7) (1)	Inadequate	No data	Vol. 37, pp. 233-240; Suppl. 7, p. 67.
N'-nitrosodimethylamine (0.001-0.2) (1)	Sufficient	No data	Vol. 1, pp. 95-106; Vol. 17, pp. 125-175; Suppl. 7, p. 67.
N-nitrosodiethylamine (0-0.01) (1)	Sufficient	No data	Vol. 1, pp 107-124; Vol. 17, pp. 83-124; Suppl. 7, p. 67.
N-nitrosodi-n-propylamine (0-0.001) (2)	Sufficient	No data	Vol. 17, pp. 177-189; Suppl. 7, p. 68.
N-nitrosodi-n-butylamine (0-0.003) (1)	Sufficient	No data	Vol. 4, pp. 197-210; Vol. 17, pp. 51-75; Suppl. 7, p. 67.
N-Nitroso-N-methylethylamine (0.0001- 0.01) (1)	Sufficient	No data	Vol. 17, pp. 221-226; Suppl. 7, p. 68.
N'-nitrosonornicotine (0.13-0.25) (1)	Sufficient	No data	Vol. 17, pp. 281-286; Vol. 37, pp. 241-261; Suppl. 7, p. 68.
N-nitrosodiethanolamine (0-0.09) (2)	Sufficient	Inadequate	Vol. 17, pp. 77-82; Suppl. 7, p. 67; Vol. 77, pp. 403-438.
N-nitrosopyrrolidine (0.002-0.042) (1)	Sufficient	No data	Vol. 17, pp. 313-326; Suppl. 7, p. 68.
N-nitrosopiperidine (0-0.009) (1)	Sufficient	No data	Vol. 17, pp. 287-301; Suppl. 7, p. 68.
Polycyclic aza-arenes			
carbazole (1) (2)	Limited	No data	Vol. 32, pp. 239-245; Suppl. 7, p. 59; Vol. 71, pp.1319-1323.
dibenz[a,h]acridine (≤0.0001) (4)	Sufficient	No data	Vol. 3, pp. 247-253; Vol. 32, pp. 277-281; Suppl. 7, p. 61.
dibenz[a,j]acridine (≤0.010) (4)	Sufficient	No data	Vol. 3, pp. 254-259; Vol. 32, pp. 283-288; Suppl. 7, p. 61.
7H dibenzo[c,g]carbazole (≤0.0007) (4)	Sufficient	No data	Vol. 3, pp. 260-268; Vol. 32, pp. 315-319; Suppl. 7, p. 61.
benz[a]acridine (2)	Inadequate	No data	Vol. 32, pp. 123-127; Suppl. 7, p. 58.
benz[c]acridine (2)	Limited	No data	Vol. 3, pp. 241-246; Vol. 32, pp. 129-134; Suppl. 7, p. 58.
Amino acid pyrolysis products			
3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) (0.0003-0.0005) (4)	Sufficient	No data	Vol. 31, pp. 247-254; Suppl. 7, p. 73
2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) (0.00037-0.00089) (4)	Sufficient	No data	Vol. 40, pp. 223-233; Suppl. 7, p. 64

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
2-aminodipyrido[1,2-a:3',2'-d] imidazole (Glu-P-2) (0.00025-0.00088) (4)	Sufficient	No data	Vol. 40, pp. 235-243; Suppl. 7, p. 64
2-amino-3-methyl-3H-imidazo [4,5-f]quinoline (IQ) (0.00026) (4)	Sufficient	No data	Vol. 40, pp. 261-273; Suppl. 7, p. 64: Vol. 56, pp. 165-195
2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (0.011-0.023) (4)	Sufficient	No data	Vol. 56, pp. 229-242
2-amino-3-methyl-9H-pyrido [2,3-b]indole (MeA-α-C) (0.002-0.037) (4)	Sufficient	No data	Vol. 40, pp. 253-259
3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2) (0.0008-0.0011) (4)	Sufficient	No data	Vol. 31, pp. 255-263; Suppl. 7, p. 73
2-amino-9H-pyrido[2,3-b] indole (A-α-C) (0.025-0.26) (4)	Sufficient	No data	Vol. 40, pp. 245-252
Aromatic amines			
4-aminobiphenyl (0.002-0.005) (4)	Sufficient	Sufficient	Vol. 1, pp. 74-79; Suppl. 4, pp. 37-38; Suppl. 6, 60-63; Suppl. 7, 91-92.
ortho-anisidine (1-amino-2-methoxybenzene)	Sufficient	Inadequate	Vol. 27, pp. 63-80; Suppl. 7, p. 57; Vol. 73, pp. 49-58.
aniline (0.1-0.4) (2)	Limited	Inadequate	Vol. 4, pp. 27-39; Vol. 27, pp. 39-61; Suppl. 6, 68-70; Suppl. 7, 99-100.
2,6-dimethylaniline (4-50) (4)	Sufficient	No data	Vol. 57., pp. 323-335
1-naphthylamine (0.003-0.004) (1)	Inadequate	Inadequate	Vol. 4, pp. 87-96; Suppl. 4, pp. 164-165; Suppl. 6, 406-409; Suppl. 7, 260-261.
2-naphthylamine (0.001-0.022) (4)	Sufficient	Sufficient	Vol. 4, pp. 97-111; Suppl. 4, pp. 166-167; Suppl. 6, 410-414; Suppl. 7, 261-263.
N-phenyl-2-naphthylamine (2)	Limited	Inadequate	Vol. 16, pp. 325-341; Suppl. 4, pp. 213-215; Suppl. 6, 461-462; Suppl. 7, 318-319.
ortho-toluidine (2-methylaniline) (0.03-0.2) (4)	Sufficient	Limited	Vol. 16, pp. 349-366; Vol. 27, pp. 155-175; Suppl. 4, pp. 245-246; Suppl. 6, 523-527; Suppl. 7, 262-263; Vol. 77, pp. 267-322.
Miscellaneous nitrogen compounds			
acetamide (38-56) (4)	Sufficient	No data	Vol. 7, pp. 197-202; Suppl. 7, pp. 389-390; Vol. 71, pp. 1211-1221.
acrylamide (present) (4)	Inadequate	Sufficient	Suppl. 7, p. 62; Vol. 60, pp. 389-433:
acrylonitrile (3-15) (4)	Sufficient	Inadequate	Vol. 19, pp. 73-113; Suppl. 4, pp. 25-27 Suppl. 6, 27-31; Suppl. 7, 79-80; Vol. 71, pp. 43-108.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
hydrazine (0.024-0.043) (4)	Sufficient	Inadequate	Vol. 4, pp. 127-136; Suppl. 4, pp. 136-138; Suppl. 6, 341-343; Suppl. 7, 223-224; Vol. 71, pp. 991-1013.
1,1-dimethylhydrazine (present) (4)	Sufficient	No data	Vol. 4, pp. 137-143; Suppl. 7, p. 62; Vol. 71, pp. 1425-1436.
nitrobenzene (25) (4)	Sufficient	Inadequate	Vol. 65, pp 381-408
nitromethane (0.5-0.6) (4)	Sufficient	Inadequate	Vol. 77, pp. 487-501
2-nitropropane (0.0.0007-0.0012) (4)	Sufficient	Inadequate	Vol. 29, pp. 331-343; Suppl. 7, p. 67; Vol. 71, p. 1079-1094.
urethane (0.020-0.038) (4)	Sufficient	No data	Vol. 7, pp. 111-140; Suppl. 7, p.73.
7. Agricultural chemicals and derivatives			
captan (0.4-34) (2)	Limited	No data	Vol. 30, pp. 295-318; Suppl. 7, p. 59.
DDT (0.7-1.2) (2)	Sufficient	Inadequate	Vol. 5, pp. 83-124; Suppl. 4, pp. 105-108; Suppl. 6, 212-215; Suppl. 7, 186-189; Vol. 53, p. 179-249.
endrin (2)	Inadequate	No data	Vol. 5, pp. 157-166; Suppl. 7, p.63.
malathion (2)	Inadequate	No data	Vol. 30, pp. 103-129; Suppl. 7, p.65.
maleic hydrazide (0.1-2.1) (2)	Inadequate	No data	Vol. 4, pp. 173-179; Suppl. 7, p.65.
succinic anhydride (2)	Limited	No data	Vol. 15, pp. 265-271; Suppl. 7, p.72.
8. Halogen compounds			
vinyl chloride (0.011-0.015) (4)	Sufficient	Sufficient	Vol. 7, pp. 291-318; Vol. 19, pp. 377-438; Suppl. 4, pp. 260-262; Suppl. 6, 566-569; Suppl. 7, 373-376.
9. Inorganic elements			
Arsenic (0.040-0.12) (4)	Sufficient	Sufficient	Vol. 1, p. 41; Vol. 2, pp. 48-73; Vol. 23, pp. 39-141; Suppl. 4, pp. 50-51, Suppl. 6, 71-76; Suppl. 7, 100-106, Volume 84 pp 39-267.
Cadmium (0.041-0.062) (4)	Sufficient	Sufficient	Vol. 2, pp. 74-99; Vol. 11, pp. 39-74; Suppl. 4, pp. 71-73; Suppl. 6, 132-135; Suppl. 7, 139-142; Vol. 58, pp. 119-237.
Chromium VI (0.004-0.07) (4)	Sufficient	Sufficient	Vol. 2, pp. 100-125; Vol. 23, pp. 205-323; Suppl. 4, pp. 91-93; Suppl. 6, 168-175; Suppl. 7, 165-168; Vol. 49, p. 49-256 (correction Vol. 51, p. 483).
Lead (0.034-0.085) (4) Inorganic Pb: Organic Pb:	 Sufficient Inadequate	 Limited Inadequate	Vol. 1, pp. 40-50; vol. 2, p. 52; vol. 23, pp. 40, 209, 325-415; Suppl. 4, pp. 149-150; Suppl. 6, 351-354; Suppl. 7, 230-232, Vol 87, in preparation.
Nickel (≤0.6) (4)	Sufficient	Sufficient	Vol. 2, pp. 126-149; Vol. 11, pp. 75-112; Suppl. 4, pp. 167-170; Suppl. 6, 417-420; Suppl. 7, 264-269; Vol. 49, p. 257-445 (correction Vol. 67, p. 395).

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
^{210}Polonium (0.03-1.0 pCi) (4)	Sufficient	Sufficient	Vol. 78, pp. 465-477. (Group 1 lisitng is of all internally deposited α-emitting radionuclides, considered as a group.
Selenium (≤0.012) (4)	Inadequate	Inadequate	Vol. 9, pp. 245-260; Suppl. 7, p.71.

Footnotes to Table 7.0B

[a] In parentheses: concentration expressed as μg in the mainstream smoke of one cigarette; exceptionally, as μg/g tobacco smoked. Second parentheses refer to the following references:
1. Wynder & Hoffmann (1982), Wynder & Hoffmann (1979)
2. Wynder & Hoffmann (1967)
3. IARC (1983c)
4. IARC (2004a)

[b] IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volumes 1-84 and Supplements 4, 6 and 7. See Table 7.6.1 for full citations.

7.0.1. Misclassification of Smoking Status

As discussed in Chapter 1, the accurate classification of an individual's smoke exposure is critical to the determination of the degree of association between ETS and disease. For example, the estimate of relative risk of disease from exposure to ETS will be overestimated if active smokers are misclassified as passive smokers. Similarly, if light or infrequent smokers or passive smokers are included in the control non-smoke-exposed group, the relative risks from exposure will be underestimated and biased toward the null.

7.0.1.1. Summary of Previous Findings on Misclassification of Smoking Status

Previously, OEHHA concluded that collective evidence from the two most recent studies examined (Riboli *et al.*, 1995; Nyberg *et al.*, 1997), as well as studies reviewed by the U.S. EPA (1992d), demonstrated that misclassification of smoking status, particularly the potential for identifying smokers as nonsmokers, remains low and does not explain the lung cancer risk associated with ETS exposure (Cal/EPA, 1997).

7.0.1.2. Recent Data on Misclassification of Smoking Status and of Exposure

The parameters utilized to define the referent population in epidemiological studies may have an important impact on the ability to uncover an association with ETS exposure. In many, particularly older studies, the referent (non-exposed) population is defined in ways that include many significantly ETS-exposed individuals. An example of this is utilizing a single question, "Does your spouse smoke?", to define the non-exposed referent group, ignoring other household, workplace or outside exposures. In many studies, exposure is identified for only a single point in time. Since carcinogenesis often involves a long latency period, the exposure periods of interest may include decades. Prior to the last decade, the prevalence of smoking and therefore ETS exposure was much higher, making it difficult to define a truly non-exposed referent group.

Failure to correct for this background exposure will bias results toward the null. The impact of such referent group "misclassification" has been examined within individual studies (Johnson *et al.* 2001; Morabia *et al.*, 1998) and shown to lead to an underestimation of the effect (see further discussion in Section 7.4.1.3).

In a study comparing self-reported smoking status and cotinine levels from seven studies of lung cancer in a U.S. EPA report (U.S. EPA, 1992) and three newer studies, Wells *et al.* (1998) noted differences in the smoking misclassification rates associated with majority/minority classification. Among females, the misclassification rate of regular smokers as never smokers was 0.8% for majority females and 2.8% for minority females, while misclassification of occasional smokers as nonsmokers was higher, 6.0% and 15.3%, respectively. The respective misclassification rates among males were generally higher (1.4%, 3.7%, 5.1% and 19.7%). These data suggest that the ethnic make-up of study subjects should be considered when adjusting for misclassification bias. They also confirm the conclusion in the EPA report that misclassification bias is small and unlikely to account for the increased risk of lung cancer associated with ETS exposure.

In a more recent review of exposure misclassification bias in studies of ETS and lung cancer, Wu (1999) found that the proportion of ever smokers reported as never-smokers, the proportion of nonsmokers misclassified as ever-smokers, and the risk of lung cancer among misclassified smokers were all low (≤ 5%). One of the studies reviewed by Wu (1999) was a case-control study of active and passive smoking in lung cancer (Nyberg *et al.* 1998b). This study compared subjects' self-reported smoke exposure with reports from next of kin and found a very low proportion (1.2%) of misclassified ever-regular smokers among reported never-smokers. They also estimated the misclassification associated with occasional smoking using an exclusion criterion of >400 cigarettes to be 2.6%. After exclusion of potentially misclassified subjects, very little change was found in the effect estimates associated with ETS exposure. These observations support the conclusion in the previous document that smoker misclassification cannot explain the ETS effect on lung cancer in never-smokers.

In a study of ETS exposure as assessed by salivary cotinine, measures of airborne nicotine and exposure self-classification, Jenkins and Counts (1999) report misclassification rates of subjects claiming to be lifetime never-smokers based on salivary cotinine cutoffs of 106, 35, 15, and 10 ng/ml ranged from 3.22% to 5.94%. The effect again is to bias toward the null.

7.1. All Cancers (Combined)

The following background information is reiterated from the earlier OEHHA report (Cal/EPA, 1997):

> "Overall 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 1986f), 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) (See Chapter 2, Exposure Measurement and Prevalence). 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 a lifetime accumulation of exposures and resulting biological effects, including those due to exposures occurring transplacentally, during childhood and/or adulthood. Earlier studies examining the potential role of ETS exposure in the etiology of various cancers in adults have focused on the association between adult exposure to ETS and cancer risk (Hirayama, 1984; Sandler *et al.,* 1985a; Reynolds *et al.*, 1987; Sandler *et al.*, 1989), with more limited work on the role of childhood ETS exposure and subsequent adult onset cancers (Sandler *et al.*, 1985b). More recent epidemiological studies on adult cancers and ETS exposure have focused on individual anatomic sites, such as lung (Section 7.2) or breast (Section 7.4.1.2), with increasing focus on lifetime and/or multiple sources of ETS.

7.1.1.1. Overall Cancer Risk in Adults: Previous Findings

In 1997, OEHHA determined that the epidemiological evidence for a relationship between ETS and overall cancer risk in adults was limited (Cal/EPA, 1997). Three of the five studies summarized, including two based on cancer mortality, determined that exposure to spousal smoking may increase the overall cancer risk among women (Hirayama, 1984; Sandler *et al.* 1985a; Reynolds *et al.,* 1987). These studies lacked information on other sources of ETS exposure, were based on a limited number of smoking-related cancers, and often lacked data on other known cancer risk factors.

7.1.1.2. Overall Cancer Risk in Adults: Recent Epidemiological Findings

As described in section 7.2.3, Nishino *et al*. (2001) conducted a population-based prospective study on the effects of exposure to spousal smoking among 9,675 Japanese women between 1984 and 1992. After adjusting for age, alcohol use, intake of green and yellow vegetables, and

fruit intake, an RR of 1.1 (95% CI 0.91-1.4) was reported for cancer at all sites in association with ETS exposure. For smoking-related cancers, the adjusted RR was 1.7 (95% CI 0.94-3.1).

7.1.1.3. Summary on Overall Cancer Risk in Adults

In 1997, OEHHA concluded:

> "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% of all cancers. In the study by Sandler *et al.* (1985a), increased risks were observed for both smoking-related (lung, cervix), and non-smoking-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 in further studies should be more carefully researched. 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."

While the study by Nishino *et al*. (2001) suggests a weak association between ETS exposure and all cancers, no other additional studies were found that reported on overall adult cancer risk associated with ETS exposure. Thus, no compelling evidence exists for modifying the above conclusions regarding the potential role of ETS of increasing adult onset cancer risk for all malignancies combined.

7.1.2. All Cancers in Children

As outlined in the previous OEHHA report (Cal/EPA, 1997), as well as more recently published quantitative and qualitative reviews (Thornton and Lee, 1998b; Sasco and Vainio, 1999; Boffetta *et al.*, 2000), ETS exposure has been investigated as a risk factor for all childhood cancers combined and for specific childhood tumors (see Sections 7.1.2 to 7.1.2.5). However, difficulties exist in distinguishing the effects of ETS on children, both prior to and after birth, by various exposures routes, including preconceptional, transplacental prenatal, and postnatal exposure from a variety of sources, i.e., mothers' smoking, fathers' smoking, other ETS sources. As with many studies on childhood cancer and ETS exposure, the previous OEHHA report also considered parental smoking during pregnancy as a surrogate measure of postnatal parental smoking, and thereby childhood ETS exposure. Limited data exist to support the assumption that smoking habits during pregnancy represent an unbiased estimate of smoking habits after pregnancy (Cal/EPA, 1997).

Historically, most studies only reported on ever-maternal active smoking, ever-paternal active smoking, or maternal active smoking during the pregnancy. More recent studies have attempted to analyze maternal smoking prior to or at conception (Filippini *et al.*, 1994; Shu *et al.*, 1996; Sorahan *et al.*, 1995; Sorahan *et al.*, 2001), maternal active smoking during pregnancy (Bunin *et al.*, 1994; Brondum *et al.*, 1999; Cordier *et al.*, 1994; Filippini *et al.*, 1994; Infante-Rivard *et al.*, 2000; Klebanoff *et al.*, 1996; Norman *et al.*, 1996; Schuz *et al.*, 1999; Sorahan *et al.*, 1995; Sorahan *et al.*, 2001) or postnatal exposures (Cordier *et al.*, 1994; Infante-Rivard *et al.*, 2000), and to a more limited extent, pre- or postnatal paternal ETS exposure (Ji *et al.*, 1997). Other studies on childhood cancers obtained information on both maternal and paternal smoking habits during various time periods relative to the pregnancy (Bunin *et al.*, 1994; Brondum *et al.*, 1999; Filippini *et al.*, 1994; Infante-Rivard *et al.*, 2000; Shu *et al.*, 1996; Schuz *et al.* 1999; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a; b; Sorahan *et al.*, 2001). As with earlier studies, the relatively rare nature of childhood cancer and the overwhelming reliance on case-control study design led to the majority of data on parental smoking habits being ascertained retrospectively, after cancer diagnosis or cancer-related death.

Studies also varied substantially in the age range of cases; the majority included children under age 15, while others were restricted to infants (Shu *et al.*, 1996), children under age six or eight or ten years of age (Klebanoff *et al.*, 1996; Infante-Rivard *et al.*, 2000; Bunin *et al.*, 1994), or adolescents up to age 15 (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.* 1997a;b; Sorahan *et al.* 2001; Brondum *et al.*, 1999; Cordier *et al.*, 1994; Filippini *et al.*, 1994; Schuz *et al.*, 1999) or 19 (Linet *et al.*, 1996; Norman *et al.*, 1996). Patterns of cancer occurrence, with respect to overall incidence, anatomic site, or specific histology, vary substantially by age. Age-specific incidence rates for all cancer sites combined peak by age 5, decline until age 14, prior to rising again during adolescence continuing through adulthood (Campleman *et al.*, 1999; Ries *et al.*, 1999). Therefore, making any comparison between these individual studies analyzing for excess in overall cancer risk in different age groups at varying risk for individual cancer types remains difficult.

7.1.2.1. Biomarker Studies of Exposure to Tobacco Smoke Constituents *In Utero* and Postnatally: Previous Findings.

Several studies, described previously in Cal/EPA (1997), investigated the availability of biological markers of tobacco smoke exposure in newborns (Eliopoulos *et al.*, 1994), fetal blood samples (Coghlin *et al.*, 1991; Hammond *et al.*, 1993), or young, pre-school age children (Crawford *et al.*, 1994). Nicotine and cotinine levels in newborns (obtained from hair shaft samples) were highest among smokers, followed by those exposed to passive smoke and non-smokers (Eliopoulos *et al.*, 1994). In another cross-sectional study, levels of 4-amino-biphenyl (4-ABP) hemoglobin adducts were identified in the maternal-fetal paired blood samples of both smoking and non-smoking mothers. 4-ABP hemoglobin adduct levels in the blood of nonsmoking women and their fetuses were 12% and 9%, respectively, of the levels found in smokers (Hammond *et al*., 1993). In the third study, Crawford *et al.* (1994) evaluated levels of serum cotinine and polycyclic aromatic hydrocarbon (PAH)-albumin adducts in preschool children and their mothers. Maternal mean serum cotinine, childhood mean serum cotinine, and PAH-albumin adducts levels all demonstrated a decreasing gradient by active smoking, passive smoking and nonsmokers with no ETS exposures. Comparisons between the three groups of mothers and of preschool children demonstrated statistically significant differences in levels of

cotinine and PAH-albumin adducts. Adduct levels were higher in smokers (or their children) than in passive smokers and nonsmokers not exposed to ETS (or their children). Another recent study measured BaP-DNA adducts and cotinine levels in paired maternal and fetal blood (Perera *et al*., 2004). They found higher BaP-DNA adducts in the newborns than in the mothers despite an estimated 10 fold higher dose to the mother as well as significantly higher level of maternal cotinine. These results are indicative of both a reduced ability to clear ETS constituents and an increased susceptibility to DNA damage in the fetus.

These studies provide evidence that constituents of tobacco smoke are present in the biological fluids of nonsmokers exposed to ETS, that such chemicals readily cross the human placenta in both nonsmoking and smoking mothers, and that young children may carry a biological burden from exposure to ETS that exceeds that of the parent.

7.1.2.2. Biomarker Studies of Exposure to Tobacco Smoke Constituents *In Utero* and Postnatally: Recent Data.

Two additional studies have reported on the levels of two different biomarkers of tobacco smoke exposure in pregnant women and their offspring, one in the fetus (Pinorini-Godly and Myers, 1996), and the other in newborns (Whyatt *et al.*, 1998b), while a third study reported on the uptake of a tobacco-related carcinogen by school age children exposed to ETS (Hecht *et al.*, 2001). These studies, in particular Pinorini-Godley and Myers (1996) and Hecht *et al.* (2001), further demonstrate transplacental transfer of tobacco-related constituents, and carcinogen uptake by children exposed to ETS.

Table 7.1A. 4-Aminobiphenyl hemoglobin adduct concentrations in pregnant women and fetuses by exposure to tobacco smoke[1]

	HPLC[2] (pg ABP/g Hb)[3] Mean ± Standard Deviation	GC/MS[2] (pg ABP/g Hb)[3] Mean ± Standard Deviation
Maternal Blood		
nonsmokers (n = 21)	24 ± 14	30 ± 16
smokers (n = 21)	423 ± 154	488 ± 174
Fetal Blood		
nonsmokers (n = 21)	10 ± 5	14 ± 7
smokers (n = 21)	197 ± 77	244 ± 91

[1] Source: Pinorini-Godly and Myers (1996). [2] Data analyzed by two methods, high pressure liquid chromatography and gas chromatographic/mass spectrometry [3] ABP = 4-aminobiphenyl hemoglobin adducts; Hb = hemoglobin; pg ABP/g HB = picograms ABP adduct per gram hemoglobin

Pinorini-Godly and Myers, 1996. Maternal-fetal exchange of the tobacco-related carcinogen, 4-aminobiphenyl (4-ABP), was analyzed in a small group of women (21 smokers, 21 nonsmokers) and their corresponding fetuses during pregnancy. Maternal smoking status was determined via questionnaire and through immunoassay of serum cotinine in maternal/fetal blood samples. The mean level of 4-ABP in smoking women was significantly higher than nonsmoking women, 488 (± 174 pg 4-ABP/g Hb) versus 29.6 (± 16.2 pg 4-ABP/g Hb), respectively. A similar result was found among fetal samples, 244 (± 91 pg 4-ABP/g Hb) versus 14.0 (± 6.5 pg 4-ABP/g Hb), among fetuses of smokers and nonsmokers, respectively (Table 7.1A). Maternal and fetal

exposures were significantly correlated (GC/MS, R^2=0.95). This study confirmed that 4-ABP readily crosses the human placenta and binds to fetal hemoglobin in significantly larger amounts in smoking versus nonsmoking women.

Whyatt et al., 1998b. As part of a larger study investigating the relationship between ambient air pollution and DNA damage in Polish mothers and newborns, DNA adducts of polycyclic aromatic hydrocarbons (PAHs) were measured in maternal and umbilical white blood cells. This cohort included 70 mothers and newborns in Krakow, Poland. Smoking status (active and passive) was quantified via questionnaire with plasma cotinine used to verify questionnaire data. Maternal smoking (active and passive) significantly increased maternal adduct levels among current smokers compared to both nonsmokers and ex-smokers, including those who quit smoking during pregnancy. DNA adduct levels in newborns also increased with maternal exposure to active or passive smoking, but after adjusting for dietary PAHs, use of coal in the home, and home or occupational exposure to PAHs, the association became non-significant. In nonsmokers, maternal DNA-PAH adducts were significantly higher in women reporting exposure to ETS. However, no association was reported between maternal white blood cell DNA adduct levels and maternal plasma cotinine levels. Additionally, the study analyzed for the potential modulation of DNA-PAH adducts by two polymorphic metabolic enzymes, genotyping for glutathione S-transferase M1 (GSTM1) and cytochrome P4501A1 (CYP1A1) MspI. Neither polymorphism was associated with maternal adduct levels. However, in newborns the CYP1A1 RFLP was positively associated with higher adduct levels (heterozygotes and homozygotes), possibly due to low or absent levels of the conjugating enzyme, GSTM1, in the fetus. Thus, although this study did not find a statistically significant association between maternal ETS exposure and DNA adduct formation in newborns, any effect may have been masked by the effects of the ambient pollution, as suggested by a study by Vork *et al.* (2002), as well as limitations of the measurement techniques employed.

Hecht et al., 2001. A U.S. study utilized a series of biomarkers to investigate the uptake of the tobacco-related carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in elementary aged children. Urinary analysis assayed levels of two NNK metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide (NNAL-Gluc), as well as total cotinine (cotinine and cotinine glucuronide). Seventy of the 204 children assayed (34%) had a total cotinine level ≥ 5 ng/mL, and among these children NNAL and NNAL-Gluc metabolites were identified in the majority of samples analyzed (96%). Additionally, partial analysis for NNAL/NNAL-Gluc among children with < 5 ng/mL total urinary cotinine found half the samples (10/20) also positive for the carcinogenic metabolites, indicating the potential widespread distribution of this tobacco-specific carcinogen in elementary-school-aged children. Children identified as "ever exposed to ETS" via interviewer questionnaire had significantly higher mean urinary levels of NNAL (0.032 ± 0.039 vs 0.010 ± 0.020 pmol/ml), NNAL plus NNAL-Gluc (0.095 ± 0.088 vs 0.035 ± 0.058 pmol/ml), and total cotinine (24.5 ± 22.4 vs 5.0 ± 8.7 µg/ml), relative to "unexposed" children. Levels detected in this study were comparable with levels previously identified in the urine of women with spousal ETS exposure (Anderson *et al.* 2001).

7.1.2.3. Overall cancer risk in children/adolescents: previous findings

In the 1997 report, OEHHA reviewed a total of 21 published studies examining the potential relationship between ETS exposure and the risk of developing childhood cancer, both for all cancer types combined and for specific childhood tumors (Cal/EPA, 1997). In summary, the previous report found only inconclusive evidence for an association between parental smoking and childhood cancers (all cancer sites combined). One of the two cohort studies reviewed found an elevated, but statistically non-significant association between maternal smoking and all cancer sites combined (Neutel and Buck, 1971), while the second cohort found no association between maternal smoking and the risk of all cancers combined (Pershagen *et al.*, 1992). Two of the five case-control studies reviewed reported significant associations between mother's smoking during pregnancy and risk of childhood cancers (Stjernfeldt *et al.*, 1986b; Golding *et al.*, 1990). A third case-control study (John *et al.*, 1991), the only to assess paternal smoking independently from maternal smoking, found no association with maternal smoking but a statistically non-significant increased risk with paternal smoking.

7.1.2.4. Overall cancer risk in children/adolescents: recent epidemiological findings

Seven newer studies not previously reviewed in Cal/EPA (1997) are described below. The six studies with data on smoking during the index pregnancy are summarized in Table 7.1C.

Klebanoff et al., 1996. This United States study was based on a prospective, multi-center cohort, the Collaborative Perinatal Project. The cohort, 44,621 pregnant women enrolled from 1959 to 1966 at 12 university-affiliated medical centers, was initially selected to study risk factors for neurodevelopmental disorders, not cancer. All 54,795 live born children were eligible for enrollment. Maternal smoking data available for 54,306 births indicated that 52% of the mothers smoked during pregnancy (smoking determined at each prenatal visit). No data on paternal or other passive smoking exposure were available. Follow up was limited, with children followed to either age 7 (80%) or 8 years (36%). Fifty-one cancer cases were reported (17 leukemia cases). No overall association (RR 0.67, 95% CI 0.38-1.17) (Table 7.1C) or dose-response gradient (0, 1-10, >10) was found for all cancers combined. Limited covariate analysis was presented, but did not alter the risk estimates to any substantial degree.

Ji et al. 1997. A population based case control study in Shanghai, People's Republic of China, studied the association between parental smoking and childhood cancer incidence diagnosed between 1981 through 1991 (1985-1991 only for acute leukemia). Cases were ascertained from a population based cancer registry for children under the age of 15 at diagnosis. A total of 680 cases were eligible with 642 participating. Population controls were matched to cases based on age, sex and local governmental sampling unit. Only paternal smoking was analyzed in this study. Three mothers that reported ever smoking were excluded, all other mothers were considered nonsmokers.

Paternal smoking status (ever versus never) was positively associated with increased risk for all childhood cancers combined [adjusted RR 1.3 (95% C.I. 1.0-.7)]. Adjusted risk estimates were highest among fathers that started smoking under age 20 [RR 1.9 (95% C.I. 1.3-2.7)], smoked 15 or more years, [RR 1.7 (95% C.I. 1.2-2.5)], or smoked more than 10 pack years [RR 1.6 (95% C.I. 1.1-2.4)]. Additional analysis examining the cancer risk among children according to

exposure period, either before conception or after birth, found the greatest risk associated with preconception smoking (adjusted for birth weight, income, paternal age, education and alcohol consumption). Among offspring of fathers smoking more than 5 pack-years before conception, an elevated risk of 1.7 (95% C.I. 1.2-2.5) was observed (Table 7.1C). When childhood cancers were analyzed by age of diagnosis, there was a highly significant association between paternal preconception smoking and incidence of childhood cancer (all sites) in children diagnosed before 5 years of age (see Table 7.1B). The greatest risk was noted with fathers smoking ≥ 5 pack-years preconception [RR = 3.5 (CI 1.8-6.6)]. This association shows a strong dose-response with a p-value of 0.0002 for trend. No significant associations were noted between paternal preconception smoking and age of cancer diagnosis at older ages (5-14 years). These findings suggest prezygotic genetic damage. See further discussion of Ji *et al.* (1997) in Section 7.4.3.4.

Table 7.1B. Age-specific odds ratios (adjusted for birth weight, income, paternal age, education, and alcohol drinking) and 95% confidence intervals for childhood cancers (all sites combined) in relation to paternal smoking before conception[1].

Pack-years	Age at diagnosis of cancer		
	0-4 years OR (95%CI)	5-9 years OR (95%CI)	10-14 years OR (95%CI)
≤ 2	1.6 (1.0-2.7)	0.7 (0.3-1.7)	0.8 (0.1-4.2)
> 2 and < 5	1.8 (1.8-3.1)	1.0 (0.5-2.1)	0.8 (0.2-2.8)
≥ 5	3.5 (1.8-6.6)	0.7 (0.3-1.6)	0.9 (0.4-2.4)
(p for trend)	0.0002	0.71	0.77

[1]Source: Table 5 of Ji *et al.* (1997)

Sorahan et al. 1995; 1997a; 1997b. Three United Kingdom case-control studies of childhood cancer deaths in relation to reported parental tobacco consumption have been published from the Oxford Survey of Childhood Cancers (OSCC) (Sorahan *et al.*, 1995; Sorahan *et al.* 1997a;b). The survey was initiated in 1956 with interviews conducted with the parents of any child dying of cancer prior to age 16. Controls were selected from the birth register in the same local authority matched on sex and date of birth.

In the 1995 report, a subset of cases was utilized. There were 3,364 childhood cancer deaths which occurred between 1977 and 1981, with 1,816 case parents interviewed (60.5% all cases) however, only 1,641 matched pairs were available (48.8% of all cases). Case and control interview data were reviewed to abstract data on parental alcohol consumption and tobacco consumption (prior to pregnancy) for reanalysis. Maternal consumption of cigarettes before pregnancy was not associated with an increased risk of childhood cancer death. However, paternal smoking was significantly associated with overall cancer death, with a positive trend of association between risk and daily cigarette consumption (p = 0.003), and risk estimates ranging from 1.17 to 1.39. Analysis combining maternal and paternal smoking habits, with and without adjustment for social class and maternal age, was the same for paternal only [RR 1.37 (95% C.I. 1.12-1.68) and both parents combined [RR 1.37 (95% C.I. 1.13-1.67)] (Table 7.1C).

The two 1997 publications analyzed childhood cancer deaths from two other periods, 1953 to 1955 (Sorahan *et al.*, 1997a) and 1971 to 1976 (Sorahan *et al.*, 1997b). The study focusing on 1953 to 1955 included 1,549 childhood cases from the 3,364 period deaths with controls matched on child age, residence and sex. Exposure consisted of maternal and paternal postnatal smoking.

No significant association was seen for maternal smoking either alone, in combination with paternal smoking, or adjusted for other factors including maternal/paternal age, parity, social class and obstetric x-ray. Positive associations with childhood cancer were seen for paternal smoking alone [1.30 (95% CI 1.10-1.53)], or in combination with maternal smoking [1.70 (95% CI 1.32-2.18)]. There was a statistically significant dose-response trend between paternal daily cigarette consumption (current habit at interview) and the overall risk of childhood cancer ($p<0.001$) after adjustment for several factors including social class, maternal smoking, parental age, birth order and obstetric radiography (Sorahan *et al.*, 1997a).

The later analysis (Sorahan *et al.*, 1997b) incorporated data on 2,587 matched pairs (from 5,111 total number of period deaths). As with the previous study (Sorahan *et al.*, 1997a), smoking questions were on current habits at time of interview. However, reliability of the smoking data was examined by comparing birth weight to reported smoking habits. Among both case and control groups, mean birth weight was significantly associated with reported daily maternal cigarette consumption (negative trend $p<0.001$). Relative risks for death due to all types of childhood cancer combined were analyzed by maternal smoking alone, paternal smoking alone, and combined parental smoking, with and without adjustment for other factors (parental ages, social class, parity and obstetric radiography). As with the previous OSCC analyses, maternal cigarette consumption was not significantly associated with risk of childhood cancer [adjusted RR 0.94 (95% C.I. 0.78-1.12)] and the study found no significant trend with increasing daily maternal smoking. Paternal cigarette smoking was again statistically significantly associated with risk of childhood cancer when analyzed alone [RR 1.29 (95% C.I. 1.10-1.51)] or combined with maternal smoking [RR 1.27 (95% C.I. 1.09-1.48)](Table 7.1C). Significantly elevated risk estimates were derived for four out of five paternal daily consumption categories (10-19, 20-29, 30-39, $\geq$ 40 cigarettes per day), whether analyzed alone, combined with maternal smoking, or adjusted for other factors. A positive significant trend for paternal smoking was observed in all three analyses ($p<0.001$).

All three OSCC studies found no association between maternal smoking and risk of childhood cancer deaths for the three time periods individually, 1953 to 1955 deaths, 1971 to 1976 deaths, and 1977 to 1981 deaths. However, the studies did find paternal smoking associated with childhood cancer death (all sites combined), including a statistically significant positive trend associated with daily cigarette consumption in the three separate analyses (Sorahan *et al.*, 1997b). Pooled estimates of risk comparing paternal smokers versus paternal nonsmokers also gave a significant estimate [RR 1.29 (95% C.I. 1.19-1.41)] for all cancer sites combined (Sorahan *et al.*, 1997b). The consistent parental results from the three OSCC analyses are unlikely due to chance, as each gave positive significant trends with parental smoking. The newer study adjusted for several important confounders, including social class and paternal age, with little effect on the risk estimates (Sorahan *et al.*, 1997b). The study related maternal smoking data to mean birth weights as a test of reliability, however no similar surrogate test was available for paternal smoking data. A concern for all three OSCC subsets remains the modest response rate in some subsets and the potential influence of non-responders on any true estimate of risk.

Seersholm et al., 1997. A cohort study from the Danish Cancer Registry investigated the incidence of childhood cancer in the offspring of lung cancer patients (under age 56), under the assumption that such children were likely exposed to ETS; no direct assessment of ETS exposure

was included. The study included 3,348 lung cancer cases and 6,417 children born between 1953 and 1991. Follow up continued until death, emigration, 35th birthday, or December 31, 1999. Total follow up was 135,333 person-years. In all, 26 malignancies were identified among the children, with no overall increased cancer risk for children of the lung cancer cases [SIR 0.9 (95% CI 0.6-1.2)]. A stratified analysis by sex of the lung cancer patients identified an elevated, but non-significant overall cancer risk, among children of female lung cancer patients [SIR 1.2 (95% CI 0.8-1.8)].

Sorahan et al., 2001. Another set of data from the United Kingdom, the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC), was reanalyzed for the association between parental smoking and childhood cancer (Birch *et al.*, 1985; McKinney and Stiller, 1986; Sorahan *et al.*, 2001). The authors report that some data overlap exists between this data set and one OSCC study (Sorahan *et al.*, 1995). Additionally, the previous OEHHA report (Cal/EPA 1997) details an earlier analysis from this study. IRESCC was designed to investigate etiological factors of childhood cancer. The original study included incident cases of childhood cancer. Study data were re-abstracted from the original interview data. Two controls were selected for each case, one hospital (same region, acute surgical/accident) and one general practitioner (same GP practice list as case, considered as a population based control). Participation rates were 97% for cases, 74% for GP controls and 64% for hospital controls. Maternal and paternal smoking habits were analyzed separately, combined, with and without adjustment for other factors (maternal/paternal age, socioeconomic status based on paternal occupation, and ethnicity).

Five hundred fifty-five incident childhood cancer cases diagnosed before their fifteenth birthday between January 1980 and January 1983 were included in the study (615 eligible). Two separate matched pair analyses were reported, one for each control group. Maternal smoking was not positively associated with increased risk of childhood cancer. In the GP control analysis, paternal smoking was significantly associated with overall risk of childhood cancer, with a positive significant trend (p=0.02) and significant point estimates for two daily consumption categories [10-19 cigarettes/day, RR 1.63 (CI 1.10-2.41); and 20-29 cigarettes/day, RR 1.46 (1.05-2.03)] (Table 7.1C). Adjustment for other potential confounding factors did not influence the estimates. Simultaneous analysis of parental smoking habits also gave a positive significant trend for childhood cancer risk and paternal smoking (p=0.003), again for GP control analysis.

The choice of control group substantially influenced analysis results. Comparing cases to hospital controls gave a statistically significant negative trend between the risk of childhood cancer and both maternal and parental smoking. The study authors admit that "confident interpretation of these data is difficult in that the two sets of controls produced very different findings: the analyses with GP controls supported the hypothesis under test, the analyses with hospital controls did not" (Sorahan *et al.*, 2001). However, the parents of hospital controls had an "unusually" high prevalence of smoking relative to national smoking surveys, and therefore may not have been as representative as the population at risk relative to the GP controls. Overall, the analysis with the population based GP controls supports an association between daily paternal cigarette smoking and increased overall risk of childhood cancer.

Table 7.1C. Parental smoking during index pregnancy and risk of all childhood cancers combined.

Cohort Study (Age of Subjects)	# Cases/ #Controls	Smoking Habits	RR (95% CI) Maternal Smoking	RR (95% CI) Paternal Smoking
Klebanoff *et al.*,1996	51	During pregnancy	0.67 (0.38-1.17)[a]	Not available
(Deaths, age < 8)		Daily cigarettes per day:		
		1-10 cpd	0.45[b]	Not available
		>10 cpd	0.83	Not available
Ji *et al.* (1997)	642/642	Never Active		1.0 (Referent)[c]
(Deaths, age <15)		Ever Active	Not available	1.3 (1.0-1.7)
		Cigarettes per day:		
		<10 cpd	Not available	1.5 (1.1-2.3)
		10-14cpd	Not available	1.1 (0.8-1.6)
		>15 cpd	Not available	1.5 (1.0-2.3)
				p trend=0.07
		Duration (years):		
		<10	Not available	1.2 (0.7-1.8)
		10-14	Not available	1.1 (0.8-1.7)
		>15	Not available	1.7 (1.2-2.5)
				p trend=0.007
		Pack-year prior conception:		
		≤2	Not available	1.2 (0.8-1.8)
		>2-<5	Not available	1.3 (0.9-2.0)
		≥5	Not available	1.7 (1.2-2.5)
				p trend=0.006
Sorahan *et al.*, 1995; 1997a; 1997b				
(Deaths, age < 15)		Current at interview (after death of child)		
1953-1955 (1997a)	1549/1549	Current Daily Use:		
		<1 cpd	1.0 (Referent) [d]	1.0 (Referent)
		1-9 cpd	0.99 (0.83-1.18)	1.03 (0.81-1.29)
		10-20 cpd	1.23 (0.98-1.54)	1.31 (1.06-1.62)
		>20 cpd	1.28 (0.71-2.32)	1.42 (1.08-1.87)
			p trend=0.092	p trend<0.001
		Unknown	0.65 (0.28-1.48)	1.89 (0.84-4.24)
		Moderate/Heavy Smokers		
		Both parents ever smoked	1.70 (1.32-2.18)	
		Father only ever smoked	1.30 (1.10-1.53)	
		Mother only ever smoked	1.21 (0.84-1.75)[d]	

[a] RR (Proportional hazards ratio) adjusted for maternal age, other factors adjusted one at a time also presented, Table 2 Klebanoff *et al.* (1996).

[b] 95% CI was not stated in the original paper.

[c] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

[d] RRs adjusted for social class, paternal/maternal age, birth order, obstetric radiography; Tables 1 and 3, Sorahan *et al.* (1997a).

Table 7.1C. Parental smoking during index pregnancy and risk of all childhood cancers combined.

Cohort Study (Age of Subjects)	# Cases/ #Controls	Smoking Habits	RR (95% CI) Maternal Smoking	RR (95% CI) Paternal Smoking
Sorahan *et al.*, 1995; 1997a; 1997b (cont.)				
1971-1976 (1997b)	2128/2128	Current Daily Use:		
		1-9 cpd	0.92 (0.75-1.13)[e]	1.02 (0.78-1.34)[e]
		10-19 cpd	1.00 (0.85-1.19)	1.37 (1.13-1.65)
		20-29 cpd	1.03 (0.87-1.22)	1.33 (1.13-1.55)
		30-39 cpd	0.75 (0.52-1.09)	1.42 (1.09-1.84)
		>40 cpd	1.48 (0.89-2.44)	1.63 (1.23-2.15)
			p trend=0.909	p trend < 0.001
		Both parents ever smoked	1.27 (1.09-1.48)[e]	
		Father only ever smoked	1.29 (1.10-1.51)	
		Mother only ever smoked	0.94 (0.78-1.12)	
1977-1981 (1995)	1641/1641	Daily Prenatal Use:		
		<10 cpd	1.04 (0.78-1.38) [f]	1.23 (0.82-1.86)
		10-19 cpd	1.21 (0.98-1.49)	1.17 (0.92-1.49)
		20-29 cpd	1.01 (0.81-1.25)	1.24 (1.02-1.49)
		30-39 cpd	0.98 (0.60-1.60)	1.30 (0.98-1.73)
		>40 cpd	1.70 (0.91-3.20)	1.39 (1.00-1.92)
			p trend=0.796	p trend=0.003
		Both parents ever smoked	1.37 (1.13-1.67)[g]	
		Father only ever smoked	1.37 (1.12-1.68)	
		Mother only ever smoked	1.22 (0.95-1.56)	
Pooled Estimate: Three time-periods				
(1997b)	5640/5673 (M)[h]	Current at interview:		
	5504/5572 (P)		1.02 (0.94-1.10)[i]	1.29 (1.19-1.41)
Sorahan *et al.*,		At conception:		
2001	549/549(M)	Non-smoker	1.0 (Referent)[j]	1.0 (Referent)[j]
(Deaths, age < 15)	555/555 (P)	<10 cpd	1.77 (1.07-2.92)	0.94 (0.53-1.66)
		10-19	1.51 (1.08-2.13)	1.63 (1.10-2.41)
		20-29	1.22 (0.86-1.74)	1.46 (1.05-2.03)
		30-39	0.48 (0.17-1.37)	0.95 (0.52-1.73)
		> 40 cpd	(30+ max)	1.77 (0.94-3.34)
			p trend=0.53	p trend=0.02
	549/549	During pregnancy (5th month):		
		Non-smoker	1.0 (Referent)[j]	
		<10 cpd	1.49 (0.93-2.39)	Not available
		10-19	1.58 (1.09-2.30)	Not available
		20-29	1.02 (0.68-1.54)	Not available
		>30 cpd	0.74 (0.30-1.83)	Not available
			p trend=0.36	

[e] RRs adjusted for social class, paternal/maternal age, birth order, obstetric radiography; Tables 1 and 3, Sorahan *et al.* (1997b).
[f] RRs adjusted for alcohol consumption Table 2 Sorahan *et al.* (1995)
[g] RRs adjusted for daily alcohol/cigarette consumption, social class and maternal age Table 3 Sorahan *et al.* (1995).
[h] (M)=Maternal cases and/or controls, (P)=Paternal cases and/or controls.
[i] RRs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b).
[j] Unadjusted RRs presented in Tables 1 and 2 of Sorahan *et al.* (2001) for GP controls.

7.1.2.5. Summary of Overall Cancer Risk in Children/Adolescents

The risk of childhood cancer due to ETS exposure, via either maternal or paternal smoking, varied across studies, with the majority of studies finding an elevated, and frequently statistically significant increase associated with some measure of parental smoking (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001). In studies where maternal and paternal, or only paternal, smoking data were available, risk estimates usually appeared higher for paternal smoking and were often statistically significant (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001).

Additionally, several studies attempted to identify potential dose-response relationships between either duration or amount of parental smoking and overall cancer risk (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001), with some evidence for a trend in the association between estimated duration of paternal smoking, but not maternal smoking, either prior to (Ji *et al.*, 1997; Sorahan *et al.*, 2001) or during pregnancy (Sorahan *et al.*, 1995) and cancer risk. However, as with the earlier studies reviewed in the previous OEHHA report (Cal/EPA, 1997), several additional limitations still remain in more recent studies between ETS exposure and risk of childhood cancers.

Hospital-based or collaborative studies of childhood cancers may be prone to selection bias of cases if the childhood cancer patients admitted to, and enrolled from, academic institutions are unrepresentative of all childhood cancers in the population (*e.g.,* higher social class). However, this has not been a problem in the U.K. and, within at least the U.S., the likelihood of this bias has declined with time, as the majority of childhood cancer patients, particularly those diagnosed prior to adolescence (under age 15), receive treatment at tertiary or academic cancer centers regardless of social class (Ross *et al.*, 1996). One of the studies summarized above, Klebanoff *et al.* (1996), could be affected by such enrollment bias; however, it was not originally designed to study childhood cancer.

As with studies previously reviewed (Cal/EPA, 1997), parental recall of smoking habits may lead to substantial information bias, particularly if parents of cases were more likely to remember potentially hazardous exposure prior to or during pregnancy (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001). However, the rare nature of childhood cancer, with age-adjusted U.S. incidence rates near 15 new cases per 100,000 children under age 15, inhibits the ability to conduct anything other than case-control studies (Campleman *et al.*, 1999; Ries *et al.*, 1999). In the one recent cohort study at which maternal smoking habits were assessed at each prenatal visit prior to cancer diagnosis, no association was found (Klebanoff *et al.*, 1996). However, this study varied substantially from the other recent studies in size (only 51 total cancers versus hundreds) and population age (only cancer diagnosis up to 8 years of age, compared to other recent studies addressing risk up to mid-adolescence, age 14.) As found previously (Cal/EPA, 1997), the limited exposure assessment, particularly reliance of "ever" or "never" active smoker, continues to inhibit the ability to separate and analyze for effects of ETS temporally (pre-conception, during pregnancy and during childhood); however, a few studies attempted to account for time-specific exposure (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 2001).

Although the majority of these recent publications reported the collection of data on other relevant risk factors, adjusted risk estimates were not always reported (Klebanoff *et al.*, 1996; Sorahan *et*

al., 2001) or reported for some but not all results (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a,b). However, in the three U.K.mortality reports, the adjusted risk estimates for paternal smoking and overall childhood cancer risk remained significantly elevated after adjustment for several factors including parental age and social class (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a,b).

In summary, the evidence for a role of parental smoking and all childhood cancers combined remains inconclusive for maternal smoking, as the majority of studies continue to find either no overall association (Klebanoff *et al.*, 1996) or a slightly elevated, but statistically non-significant risk (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b). Additionally, the studies continue to lack evidence for a dose-response between maternal smoking duration and/or amount smoked with childhood cancer risk.

Figure 7.1.1. Association between paternal smoking and an elevated risk of childhood cancer (all sites combined). These studies used a variety of exposure measures.

Several studies report statistically significant increases in overall cancer risk often with supporting dose-response data (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a,b; Sorahan *et al.*, 2001). Studies identifying positive associations between parental smoking and childhood cancer risk, specifically paternal smoking, usually reported increased risks between 10% and 20%, similar to estimates derived from recent meta-analyses (Thornton and Lee, 1998b; Boffetta *et al.*, 2000). It should be noted that since the increase is relatively small, it remains difficult to rule out bias and confounding as contributing to this overall risk of childhood cancer. However, as evident in Figure 7.1.1 above, there are a number of studies with adequate sample size that show statistically significant increases in cancer risk with paternal smoking. A pooled estimate indicates tight confidence limits. Thus, data provide evidence suggestive of a causal relationship between paternal smoking and overall childhood cancer. However, this may be the result of a potential heritable mutation in germ cells, as implied by data in Ji *et al.* (1997), rather than an effect of ETS exposure directly on the child. Thus, we consider the data suggestive of an association between ETS and childhood cancers, rather than conclusive.

7.2. ETS and Lung Cancer

Active smoking is firmly established as a causal factor for lung cancer. The Surgeon General (U.S. DHHSa, 1986), the National Research Council (NRC, 1986e), the U.S. EPA (U.S. EPA, 1992a), OEHHA (Cal/EPA, 1997), and most recently, the International Agency for Research on Cancer (IARC, 2004a) have reviewed epidemiological studies investigating the role of ETS exposure as a cause of lung cancer in nonsmokers. IARC (2004a) recently determined that ETS is a probable human lung carcinogen. This current review focuses on studies published since the previous OEHHA report (Cal/EPA, 1997), including a large Canadian population-based case-control study (Johnson *et al.*, 2001), a multi-center, pooled analysis from twelve European sites in seven countries (Boffetta *et al.*, 1998), and five individual European case-control studies (Jockel *et al.*, 1998; Nyberg *et al.*, 1998b; Zaridze *et al.*, 1998; Kreuzer *et al.*, 2000; Rachtan, 2002). Additionally, brief summaries are presented for six case-control (Du *et al.* 1995; Du *et al.*, 1996; Rapiti *et al.*, 1999; Zhong *et al.*, 1999; Lee *et al.*, 2000; Wang *et al.*, 2000), two population and four hospital-based, and two cohort studies (Jee *et al.*, 1999; Nishino *et al.*, 2001), from Asia. No recent primary U.S. studies on ETS exposure and lung cancer risk were identified.

7.2.1. ETS and Lung Cancer: Previous Findings

The previous OEHHA report reviewed in detail three large U.S. population-based case-control studies designed specifically to investigate the association between ETS exposure and lung cancer published since 1991 (Cal/EPA, 1997). These studies were conducted in Florida (Stockwell *et al.*, 1992), Missouri (Brownson *et al.*, 1992), and a multicenter study 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) (Fontham *et al.*, 1991; Fontham *et al.*, 1994). A smaller, hospital-based study (Kabat *et al.*, 1995), as well as several other smaller studies were also summarized (Liu *et al.*, 1993; Schwartz *et al.*, 1996; Ko *et al.*, 1997). The results of one U.S. cohort study were also discussed (Cardenas *et al.*, 1997).

OEHHA determined that these three population-based studies successfully addressed many of the weaknesses (*i.e.*, small sample size, possible selection bias, possible misclassification biases, inadequate adjustment for potential confounders) found in previous studies on ETS and lung cancer. All three case-control studies identified a statistically significant association between increased risk of lung cancer and long-term ETS exposures. Additionally, lung cancer risk increased with increasing ETS in all three studies. The cohort study reported an elevated, but statistically non-significant, risk for lung cancer associated with ETS exposure. All five studies reported about a 20% increased risk of lung cancer in nonsmokers due to ETS exposure, which is the same as the excess risk identified in the U.S. EPA pooled estimate (U.S. EPA, 1992c).

7.2.2. Recent Epidemiological Studies

7.2.2.1. Case-Control Studies on ETS and Lung Cancer

No new U.S. population-based case-control studies designed specifically to investigate the association between ETS exposure and lung cancer have been published since the previous OEHHA review (Cal/EPA, 1997). However, a large population-based Canadian study was

conducted in 8 of 10 provinces through the National Enhanced Cancer Surveillance System (Johnson *et al.*, 2001). Six published reports described results from case-control studies in Europe and Russia (Jockel *et al.*, 1998; Nyberg *et al.*, 1998a; Zaridze *et al.*, 1998; Kreuzer *et al.*, 2000; Kreuzer *et al.*, 2001), which overlap to varying degrees with the pooled multicenter International Agency for Research on Cancer (IARC) analysis (Boffetta *et al.*, 1998), and two additional hospital-based studies were available from Czechoslovakia (Kubik *et al.*, 2001) and Poland (Rachtan, 2002). Four reports based on two case-control studies, one population-based mortality study (Du *et al.*, 1995;1996) and two hospital-based incidence studies (Wang *et al.*, 1996a,b), were published prior to, but not reviewed in, the previous OEHHA report. More recent studies from China were population-based (Zhong *et al.*, 1999) and hospital-based (Wang *et al.*, 2000). Other studies briefly summarized below include hospital-based studies from Taiwan (Lee *et al.*, 2000) and India (Rapiti *et al.*, 1999).

For these recently published studies, the respective study designs and the main findings are summarized in Tables 7.2A-D. As in the previous OEHHA review, the evaluation of the methodological issues related to the study of ETS exposure will focus on the sources of cases and controls, the methods used to obtain information on the exposure, the verification of the exposure and of the diagnosis of lung cancer, and the consideration of potential confounding variables in the analysis of ETS exposure.

Brennan et al. (2004) conducted a pooled analysis of data from two large published case-control studies on the association of lung cancer with passive smoking. The data set analyzed included 1,263 lung cancer cases and 2,740 controls recruited in 1985-1994, and represented 5 metropolitan areas in the U.S. and 11 areas in 7 European countries. The analysis examined passive exposure at home (years a subject lived with a smoking spouse), at work (years working in an environment where others smoked), and years of exposure to ETS in other areas (at least 2 hrs per week in the US study). Nonsmokers were defined as having smoked less than 100 cigarettes in their lifetime.

For exposure to spousal smoking, the OR for lung cancer was 1.18 (95% CI 1.01-1.37). There was evidence of an exposure-response trend ($p = 0.07$) with the greatest risk in the highest tertile of exposure (>30.9 yr): OR 1.23 (95% CI 1.01-1.51). Exclusion of proxy data from the analysis gave similar results, while exclusion of data from hospital-based centers gave a higher risk in the upper tertile (OR 1.30, 95% CI 1.04-1.63) and a statistically significant exposure response trend ($p = 0.04$).

Ever exposure to ETS in the workplace resulted in elevated risk that did not achieve statistical significance (OR 1.13, 95% CI 0.97-1.31). However, the exposure-response trend from workplace exposure was significant ($p = 0.01$) with a risk in the highest tertile ($\geq$ 21 yrs) of 1.25 (95% CI 1.03-1.51). Similarly, the risk associated with ever exposure in other settings was 1.17 (95% CI 1.00-1.36), with a significant exposure-response trend ($p = 0.02$), and an OR of 1.26 (95% CI 1.01-1.58) for > 20 yrs exposure.

The ORs presented above and in Table 7.2A were adjusted for age, center and gender. The authors report that analyses adjusted for employment in high risk occupations, education, and vegetable consumption gave similar results, suggesting little confounding from these variables. For example, the OR for lung cancer with any exposure from the three sources combined was

identical (1.22, 95% CI 0.99-1.51) with or without adjustment for these potential confounders. In addition, the exposure-response trend was significant (p = 0.01) with an OR of 1.32 (95% CI 1.04-1.66) for the greatest exposure (≥ 39 yrs). However, it is not clear why the adjusted data were not presented.

As with other interview-base studies, since the duration but not the intensity of ETS exposure was determined it is not known how the intensity of exposure may have affected risk estimates. The intensity of current exposures was reflected in the urinary cotinine levels determined in the U.S. study but used only to validate current nonsmoking status. In three European centers, validation of nonsmoking status was achieved through cross interviews with next of kin. Potential misclassification bias associated with the inclusion of proxy-based interviews, as well as bias associated with the use of hospital-based controls was examined and found to likely cause a slight attenuation of risk estimates.

The analyses were also stratified by histological type of cancer, and it was noted that ETS exposure from any sources increased risk in an exposure-dependent fashion for both adenocarcinomas and squamous/small cell carcinomas. Overall, this analysis found an association between ETS exposure from any source and lung cancer that was significant with the longest exposures, and that demonstrated a significant exposure-response trend.

Table 7.2A. Risk of Lung Cancer with ETS Exposure from Three Sources

Exposure	Duration	Cases/Ctrls	OR (95% CI)
Spousal	Ever	764/1,458	1.18 (1.01-1.37)
	<16 yr	246/457	1.18 (0.97-1.44)
	16-30.9	224/480	1.05 (0.86-1.29)
	≥ 31	264/491	1.23 (1.01-1.51)
		Trend	p = 0.07
Work	Ever	729/1,560	1.13 (0.97-1.31)
	< 8.0 yr	198/472	0.94 (0.76-1.15)
	8-20.9	267/544	1.17 (0.97-1.42)
	≥ 21	262/543	1.25 (1.03-1.51)
		Trend	p = 0.01
Other	Ever	407/904	1.17 (1.00-1.36)
	< 8.0 yr	123/287	1.04 (0.84-1.32)
	8-19.9	128/290	1.20 (0.95-1.52)
	≥ 20	154/320	1.26 (1.01-1.58)
		Trend	p = 0.02
Any	Ever	1,102/2,351	1.22 (0.99-1.51)
	< 20.0	329/752	1.09 (0.86-1.39)
	20.0-38.9	348/768	1.21 (0.96-1.54)
	≥39.0	413/817	1.32 (1.04-1.66)
		Trend	p = 0.01

Boffetta et al., 1998. The International Agency for Research on Cancer coordinated a multicenter case-control study of lung cancer among nonsmokers. Twelve centers from seven European countries participated in the study, contributing a total of 650 nonsmoking cases and 1,542 nonsmoking controls. Cases were enrolled from 1988 to 1994 varying by study center. Study design did vary by site, particularly selection of controls - four sites utilized hospital controls, and one site used hospital and community controls, with the remaining seven centers relied only on community controls. The majority of cases (96.5%) were microscopically confirmed. Again control matching varied by site, with some centers conducting individual matching based on age and sex, while other study sites used frequency matching. Response rate varied by site from <50% to 95%.

Data on ETS exposure in childhood and adulthood, including residential, occupational, and other settings were obtained via interview with a common questionnaire based on data from a previous urinary cotinine/ETS study (Riboli *et al.*, 1990). A subset of study centers also collected dietary data on the consumption of vegetables, fruits and related nutrients (Boffetta *et al.*, 1998).

Individuals were considered eligible for study enrollment (e.g., were "nonsmokers") if lifetime cigarette consumption did not exceed 400 cigarettes. Additionally, three centers conducted validation of never-smoking status through secondary confirmation interviews with next of kin for comparison with subject responses. Childhood ETS exposure (up to age 18 years) variables were either binomial ("ever" versus "never") or based on number of household smokers and years exposed weighted by identity of smoker (mother 1.0 > father 0.75 > other adults 0.25). Weighting was based on urinary cotinine concentrations previously found in children (Jarvis *et al.*, 1991). Spousal/cohabitant ETS exposure variables included duration in years, duration as hours/day x year, average daily cigarette consumption, and/or pack-years. Workplace ETS variables were duration in total years and duration in years weighted by hours of daily exposure and subjective index of "smokiness" (Boffetta *et al.*, 1998). Categorical ETS exposure variables were based on the distribution among controls, specifically defined by the 75^{th} and 90^{th} percentiles ($<75^{th}$, 75^{th}-90^{th}, $>90^{th}$), based on previous work in Germany and Poland (Becher *et al.*, 1992). For example cumulative exposure (in weighted smoker years) is divided into "nonexposed", 0.1-14 ($< 75^{th}$ percentile), 14.1-18.0 (75^{th}-90^{th} percentile), and ≥ 18.1 ($>90^{th}$ percentile) categories.

No association between childhood exposure to ETS and lung cancer was observed in Boffetta *et al.* (1998). The overall risk estimate for "ever" exposed to childhood ETS was below unity [adjusted OR 0.78 (95% CI 0.64-0.96) after adjustment for age, and sex-study center interaction]. Risk estimates for paternal specific and maternal specific ETS exposure were similar [adjusted ORs 0.76 (95% CI 0.61-0.94) and 0.92 (95% CI 0.57-1.49), respectively]. No evidence for trend in risk by number of household smokers was evident. Additionally, lung cancer risk decreased with increasing cumulative exposure (weighted smoker-years), p for trend 0.02 (see Table 7.2C). Additional analysis found similar results for subjects also reporting adulthood ETS exposure (data not shown). Stratifying childhood ETS exposure by age of exposure, birth to 10 years and 11 to 18 years, produced estimates similar to those for overall childhood exposure (data not shown).

In the case of spousal ETS exposure, risk estimates for individuals ever married to a smoker were elevated [adjusted OR 1.27 (95% CI 1.00-1.62)], slightly lower in women [adjusted OR

1.11 (95% CI 0.88-1.39)], and higher in men [adjusted OR 1.65 (95% CI 0.85-3.18)]. Heterogeneity across study centers existed (one center OR was below 0.7 and three ORs were above 1.5); however, the tests of heterogeneity were not significant (p=0.42). Evidence of a dose-response was noted for increasing lung cancer risk with increasing duration of exposure (hours/day × years), but not so with duration of exposure in years alone or average daily intake (cigarettes/day; Table 7.2B). The lung cancer risk was statistically significantly elevated for the maximum exposure category based on duration of exposure (hours/day × years) [adjusted OR for all subjects 1.80 (95% CI 1.12-2.90); adjusted OR for women only 1.70 (95% CI 1.05-2.75)], and on cumulative exposure (pack-years), [adjusted OR for all subjects 1.64 (95% CI 1.04-2.59)].

The overall association between lung cancer and spousal ETS may vary by histology, being weakest for adenocarcinoma compared to squamous cell carcinoma or small-cell carcinoma [adjusted ORs were 1.08 (95% CI 0.82-1.42), 1.21 (95% CI 0.77-1.91) and 1.39 (95% CI 0.79-2.45), respectively], but these differences were not statistically significant. While none of these results are statistically significant, they are consistent with point estimates of the meta-analysis of Taylor *et al.* (2001) (Figure 7.2.1).

ETS exposure in the workplace was associated with a slightly elevated, yet statistically non-significant risk of lung cancer [adjusted OR 1.17 (95% CI 0.94-1.45)]. Risk estimates were above unity in eight of twelve study centers, with no statistically significant heterogeneity (p = 0.23). Trend analysis for weighted duration of exposure (total years weighted by hours of daily exposure and subjective "smokiness" scale) demonstrated a statistically significant association with increasing lung cancer risk [0.1-46.1: adjusted OR 0.97 (95% CI 0.76-1.25); 46.2-88.9: adjusted OR 1.41 (95% CI 0.93-2.12); ≥ 89.0: adjusted OR 2.07 (95% CI 1.33-3.21)] (see Table 7.2D). The adjusted OR for "ever" occupational exposure to ETS was highest for squamous cell carcinoma [adjusted OR 1.27 (95% CI 0.82-1.97)] compared to adenocarcinoma [adjusted OR 1.06 (95% CI 0.81-1.40)] or small-cell carcinoma [adjusted OR 1.17 (95% CI 0.67-2.04)]. The authors report that adjustment for additional confounders (education, urban residence, occupational carcinogens, dietary vegetable intake) did not affect the estimated ORs (data not shown).

Adult exposure to spousal and/or workplace ETS was also associated with a slightly elevated but not statistically significant risk of lung cancer [adjusted OR 1.14 (95% CI 0.88-1.47)]; risks were similar for men and women [adjusted ORs 1.13 and 1.15, respectively]. A significant trend between lung cancer risk and duration of either major ETS source was evident in one variable (hours/day × year) but not the other (years) (see Table 7.2E). Duration of exposure to ETS was associated with a higher risk of squamous cell carcinoma [adjusted OR 1.57 (95% CI 0.89-2.76)] and small-cell carcinoma [adjusted OR 1.19 (95% CI 0.62-2.30)] relative to adenocarcinoma [adjusted OR 1.01 (95% CI 0.73-1.40)]; however, the differences were not statistically significant.

Additional estimates for lung cancer risk associated with ETS exposure in vehicles [adjusted OR 1.14 (95% CI 0.88-1.48)] or other public indoor settings [adjusted OR 1.03 (95% CI 0.82-1.29)] were presented.

Jockel et al. 1998. As a subsequent analysis to an occupational study of risk factors for lung cancer, Jockel *et al.* (1998) examined ETS exposure and lung cancer risk among nonsmokers. The original study included 1,004 lung cancer cases and population-based controls in northwestern Germany, with this sub-analysis restricted to subjects who never smoked regularly (71 cases and 236 controls). Occasional smokers were included (at least one cigarette/day, or five cigarettes/week, or one pack/month for at least six months); however, risk estimates were provided for nonsmokers (including occasional) and never smokers separately. All cases were histologically or cytologically confirmed primary malignancies. Additional covariate data collected via interviewer-administered questionnaire included occupational, dietary, active smoking history and demographic characteristics. Several sources of ETS exposure were categorized based on percentile – during childhood (cumulative hours), spousal (cumulative hours), workplace, public transportation, and other public places (weighted duration) – into low or no exposure ($<75^{th}$), intermediate exposure (75^{th}-90^{th}), or high exposure ($>90^{th}$) (as with Boffetta *et al.*, 1998). This no/low exposure group (38 cases, 143 controls with occasional smokers) was used as a referent category. Risk estimates were adjusted for sex, age, region and smoking status (for occasional smokers in the total "nonsmoker" analysis).

In lifetime never-smokers (55 cases, 160 controls), an elevated, statistically significant increase in risk was reported in the "high" total (childhood and adult) ETS exposure group [adjusted OR 3.24 (95% C.I. 1.44-7.32)](Table 7.2B) with no increases in risk for the "intermediate" total ETS exposure group [adjusted OR 0.87 (95% C.I. 0.36-2.07)]. If occasional smokers were included the ORs for "high" and "intermediate" total ETS exposure were 2.09 (95% CI 1.02-4.28) and 1.05 (95% CI 0.52-2.12), respectively. Restricting analysis to never-smokers, there was a slightly increased, but statistically non-significant risk with "ever-exposed" to spousal ETS [adjusted OR 1.12 (95% CI 0.54-2.32)] and "high" spousal ETS [adjusted OR 1.87 (95% CI 0.45-7.74)] (Table 7.2B). In this same never-smoker group, ORs for other adult ETS exposures (workplace, public transit, and other public places) were significantly elevated in the "high" category [adjusted OR 3.10 (95% CI 1.12-8.60)]. Few cases reported childhood exposure to ETS (10 cases, 24 controls among never-smokers); nonetheless, the reported adjusted ORs were elevated [2.02 (95% CI 0.60-6.75) and 1.07 (95% CI 0.35-3.30), "high" and "intermediate" exposure, respectively] (Table 7.2C).

Also, although case numbers were limited, the authors analyzed lung cancer risk in the nonsmokers (including occasional smokers) for total ETS exposure and spousal ETS exposure controlling for dietary intake of fruit and salad. After including education and dietary intake of fruit and salad in the full model, the "high" ETS exposed group (with occasional smokers) had an increased effect estimate that was statistically significant [adjusted OR 2.33 (95% CI 1.11-4.91)]. The "intermediate" ETS exposed group had a statistically non-significant increase in risk [1.08 (95% CI 0.53-2.21)].

Nyberg et al. (1998a) investigated the relationship between ETS exposure and lung cancer among never-smokers in Sweden; these cases were also included in Boffetta *et al.* (1998). Cases were enrolled from Stockholm County and its three hospitals between 1989 and 1995. Cases were either microscopically confirmed or presented with an unambiguous chest radiograph with typical clinical course. In addition, histological or cytological slides were retrieved and underwent pathologic review. Population-based controls were frequency matched by sex, age and hospital catchment area. Smokers were defined as ever having smoked 1 cigarette/day, 10

cigarettes/week, 3 cigars/week, or 4 pipes/week for 1 year or longer. Data were obtained on occasional smoking, residential history, occupational history, and dietary habits. The study enrolled 124 never-smoking cases and 235 never-smoking controls (includes occasional smokers), that underwent either personal or telephone interview (response rate 85.5% and 82.9%).

Residential exposure to ETS with a binomial "ever" or "never" measure was not clearly associated with lung cancer risk for spousal smoking [adjusted RR 1.17 (95% CI 0.73-1.88)], paternal smoking [adjusted RR 1.02 (95% CI 0.63-1.66], or maternal smoking [adjusted RR 0.72 (95% CI 0.28-1.87)]. Risk estimates were adjusted for age, sex, catchment area, occasional smoking, vegetable consumption, urban residence, and years occupational exposure. Low and high exposure categories for spousal ETS exposure based on average daily exposure (cigarettes/day) or duration of exposure (years or hour-years) identified similar elevated, but statistically non-significant risks for the highest exposed group, adjusted RRs 1.16, 1.14 and 1.25 for ≥ 10 cigarettes/day, ≥ 30 years, and ≥ 90 hour-years, respectively (Table 7.2B). Lung cancer risk increased with the cumulative matrix ("pack-years smoked in subject's presence") for the highest exposure category [adjusted RR 1.53 (95% CI 0.76-3.09)].

Occupational ETS exposure ("ever" exposed at work) was associated with elevated, but not statistically significant, lung cancer risk for all subjects combined [adjusted ORs 1.61 (95% CI 0.91-2.85)] (Table 7.2D), increasing slightly in men [adjusted OR 1.89 (95% CI 0.53-6.67)]. Additionally, lung cancer risk increased with increasing duration of occupational ETS measured in either years [< 30 years: adjusted OR 1.40 (95% 0.76-2.56); ≥ 30 years: adjusted OR 2.21 (95% CI 1.08-4.52)], or hour-years, [<30 hour-years: adjusted OR 1.27 (95% 0.69-2.34); ≥ 30 hour-years: adjusted OR 2.51 (95% CI 1.28-4.93)] (Table 7.2D), with statistically significant elevated risk estimates for the high exposure category by either measure.

Additional risk estimates were presented for binomial exposure categories for ETS exposure in other indoor locations [adjusted OR 0.94 (95% CI 0.54-1.63)], or in vehicles (not occupational) [adjusted OR 0.98 (95% CI 0.41-2.37)]. However, risk estimates were higher among men "ever" exposed to either other indoor ETS [adjusted OR 1.31 (95% CI 0.50-3.38)] or vehicle related ETS [adjusted OR 1.71 (95% CI 0.49-5.98)].

As misclassification by individual ETS variable was potentially high when analyzed separately, Nyberg *et al.* (1998b) combined the two major ETS source estimates for each study subject, with major source being either spousal or occupational. In this combined analysis, lung cancer risk tended to be higher in the high exposure groups or with more recent ETS exposure. However, dose response relationships were not consistent (no trend tests reported). When accounting for time since last exposure (years) to either ETS source, spousal or occupational, risk was highest for individuals exposed more recently, ≤ 2 years [adjusted OR 2.12 (95% CI 0.91-4.92)]. In the highest duration ETS category for either spousal or occupational exposure, lung cancer risk was highest among those above the 90th percentile by years [adjusted ORs 1.84 (95% CI 0.77-4.37)] and statistically significant [2.52 (95% CI 1.08-5.85)] by hour-years.

Zaridze et al. 1998. This hospital-based case-control study was conducted in Moscow, Russia among lifetime nonsmoking women. One hundred eighty nine microscopically confirmed primary lung cancer cases and 358 oncology controls (restricted to cancers other than upper

respiratory tumors) underwent in-person interviews on demographic, residential, occupational history and ETS exposures (spousal, parental and occupational). Subjects from this study were included within the IARC multicenter study (Boffetta *et al.*, 1998).

A statistically elevated risk of lung cancer was associated with spousal smoking (yes/no) [adjusted OR 1.53 (95% CI 1.06-2.21)], after adjusting for age and education (Table 7.2B). Stratifying by histology gave a similar risk estimate for spousal ETS and adenocarcinoma [adjusted OR 1.52 (95% 0.96-2.39], increasing for squamous cell carcinoma [adjusted OR 1.94 (95% CI 0.99-3.81)]. No effect on lung cancer risk was observed for other cohabitant smoking or parental smoking.

Occupational ETS exposure, simply measured as yes or no, was not associated with an increased overall lung cancer risk [adjusted OR 0.88 (95% CI 0.55-1.41)] (Table 7.2D), or with adenocarcinoma [adjusted OR 0.99 (95% CI 0.56-1.73)]; a slightly higher, but still statistically non-significant risk was observed for squamous cell carcinoma [adjusted OR 1.20 (95% CI 0.54-2.63)].

Kreuzer et al. 2000, 2001. The study population consisted of 292 lung cancer patients and 1,338 controls, a subset derived from a larger study on lung cancer risk and radon exposure in Germany (Kreuzer *et al.*, 2000; Kreuzer *et al.*, 2001). Incident cases of histologically or cytologically confirmed primary lung cancer cases, diagnosed between 1990 and 1996, were recruited from fifteen medical clinics. The response rate among eligible cases was 76%. Population-based controls were obtained from either random digit dialing or mandatory registries at a 41% response rate. Some overlap exists with the multicenter IARC study (Boffetta *et al.*, 1998), which shared 173 cases and 215 controls. Data on basic demographics, residential history, active/passive smoking history, dietary habits, occupational and medical history were obtained via personal interview. Individuals were classified as "nonsmokers" if they never smoked more than one cigarette/day, four cigarillos/week, three cigars/week, or three pipes/week for longer than 6 months. Occasional smokers were also included if they had not smoked more than 400 cigarettes during a lifetime. The publications presented data for all nonsmoking subjects and nonsmoking women (Kreuzer *et al.*, 2000), and for nonsmoking men separately (Kreuzer *et al.*, 2001).

Several sources of ETS exposure were categorized based on percentile – during childhood, during adulthood at home (spousal or other cohabitants), at the workplace, in public transportation, and other public places. Categories of ETS exposure were derived from quantitative variables for cumulative duration hours (childhood), cumulative hours and duration in pack-years, duration hours and cumulative hours weighted by qualitative smokiness (workplace, other public places, vehicles). Similar to Jockel *et al.* (1998), 75^{th} and 90^{th} percentiles were utilized to create categories, low or no exposure ($< 75^{th}$), medium exposure (75^{th}-90^{th}), or high exposure ($> 90^{th}$). These other categories were combined to derive summary indicators for total ETS exposure. Risk estimates were adjusted for sex, age, region, occupational exposure, and diet. Previous lung disease and social class were entered into the statistical models, but reportedly did not influence the risk estimates.

Childhood exposure to ETS was not associated with increased lung cancer risk [adjusted OR 0.84 (95% CI 0.63-1.11)] for "ever" exposed (up to age 18). Similar risk estimates were

obtained for paternal or maternal exposure [adjusted ORs 0.83 (95% CI 0.62-1.11) and 0.62 (95% CI 0.27-1.44), respectively]. No evidence for a dose-response with childhood duration of exposure (cumulative hours) was observed. Restricting the analysis to either women or men gave similar results (Kreuzer *et al.*, 2000).

Spousal exposure to ETS also gave no indication of an association between "ever" exposed to spousal smoke and lung cancer [adjusted OR 0.99 (95% CI 0.73-1.34)]. No trend was observed between either cumulative exposure in pack-years or duration in hours. The authors indicate that the "high" exposure group for duration among women, cumulative hours > 67,900, had a statistically non-significant increased risk of lung cancer [adjusted OR 1.69 (95% CI 0.94-3.03)], as did the "high" exposure group based on pack-years, > 23 [adjusted OR 1.03 (95% CI 0.48-2.24)] (see Table 7.2B). Risk estimates for "ever" spousal exposure were similar by histopathological type (categorized by adenocarcinoma and other). Also, restricting the analysis to women or men only did not substantially alter the findings (Kreuzer *et al.*, 2000; Kreuzer *et al.*, 2001).

Analysis of workplace exposure to ETS gave some evidence of increased lung cancer risk among nonsmokers with increased exposure, particularly women subjects categorized into the "high" exposure group. For the binomial "ever" exposed in the workplace no increased risk was found for all subjects [adjusted OR 1.03 (95% CI 0.78-1.36)] (Table 7.2D). A slightly elevated but non-significant lung cancer risk was found among women [adjusted OR 1.14 (95% CI 0.83-1.57)]. Some evidence for increasing lung cancer risk by increasing duration of exposure was presented, particularly among women. When cumulative exposure was estimated in total hours, risk estimates for the "medium" category (> 29,000-61,000 hours) and "high" category (>61,000 hours) were elevated [adjusted ORs 1.85 (95% CI 0.96-3.54) and 2.70 (95% CI 1.01-7.18), respectively, with p for trend 0.01]; the highest category OR showed statistical significance. Additionally, a similar dose-response was observed for women with the ETS weighted duration measure (hours x degree of "smokiness") "high" category [adjusted OR 2.52 (95% CI 1.12-5.71), P for trend 0.04] (Kreuzer *et al.*, 2000) (Table 7.2D).

ETS exposures in other settings, e.g. in vehicles or other indoor public settings (bars, restaurants), were estimated both binomially, "ever" or "never", and weighted duration cumulative exposure (hours × level of "smokiness"); however, only a small subset of cases and controls reported "ever" exposure within vehicles, 35 cases and 167 controls, or other public settings, 82 cases and 454 controls (Kreuzer *et al.*, 2000). Slightly elevated, non-significant risk estimates were associated with "ever" exposure in vehicles [adjusted OR 1.15 (95% CI 0.76-1.75)] for all subjects combined but not for women only [adjusted OR 0.96 (95% CI 0.57-1.60)]. In the highest weighted duration of exposure category (hours × level of smokiness, >10,950), risk estimates were significantly increased for all subjects and in women only [adjusted ORs 2.64 (95% CI 1.30-5.36) and 2.63 (95% CI 1.04-6.68), respectively]. Lung cancer risk due to ETS exposure in other indoor public settings was not elevated except in the highest weighted duration of exposure group (hours × level of smokiness, >19,710), for all subjects combined [adjusted OR 1.48 (95% CI 0.65-3.36)] (Kreuzer *et al.*, 2000).

Kreuzer *et al.* (2000, 2001) estimated ETS exposure from all sources and all outside the home sources (workplace, vehicles, and other public settings) during adulthood. Risk estimates adjusted for age, sex and region were presented by exposure category "no/low" (referent group),

"medium", and "high". Risk estimates for those from all adulthood ETS sources were elevated, but not significantly, in the highest exposure group for all subjects combined and for women only [adjusted ORs 1.39 (95% CI 0.96-2.01) and 1.51 (95% CI 0.97-2.33)]. Estimates were similar when stratified by histology, adenocarcinoma or other carcinomas, again in the highest exposure category. Restricting the summary ETS adulthood exposure to nonresidential sources gave higher risk estimates which were statistically significant for the high exposure group [adjusted OR 1.29 (95% CI 0.79-2.09) and 1.78 (95% CI 1.05-3.04), medium and high exposure groups for all subjects]. Again, risk estimates were similar between the two histology groups, adenocarcinoma and other carcinomas, except among women with cancer other than adenocarcinoma [adjusted OR 2.22 (95% CI 1.03-4.80) and 2.35 (95% CI 0.88-6.80), medium and high exposure groups].

Johnson et al. 2001. This case-control study utilized female cases obtained from the population-based Canadian National Enhanced Cancer Surveillance System diagnosed between 1994 and 1997. 61.6% of cases contacted by the registry responded. Controls were obtained via publicly funded health insurance plans (5 of 8 provinces), provincial property assessment files (1 province) or random-digit dialing (2 provinces). The response rate for controls was 70.2%. Demographic, dietary, lifetime passive smoking, residential and occupational history data were collected via mailed questionnaire from a total of 1,558 cases and 2,531 controls. The final analysis utilized 71 never active smoking cases and 761 never active smoking controls with relatively complete residential lifetime passive smoking exposure history (90% complete). The study created two summary passive smoking variables each for residential and occupational ETS exposures: duration total years (total years × number of regular smokers in residence) and smoker-years (total years × number of regular smokers at work). An additional summary ETS variable combined residential and occupational exposure.

Never-smoking women exposed to passive smoke as both a child and an adult had an elevated lung cancer risk [adjusted OR 1.63 (95% CI 0.8-3.5)] compared to adult only exposure [adjusted OR 1.20 (95% CI 0.5-3.0)]; however, neither risk estimate was statistically significant (adjusted for age, province, education and dietary fruit and vegetable consumption) (Table 7.2B).

The risk estimate for lifetime residential ETS exposure was elevated, but not significantly, across the exposure categories in years, with no statistical evidence of trend [1-20 years: adjusted OR 1.10 (95% CI 0.4-2.8); 21-38 years: adjusted OR 1.52 (95% CI 0.6-3.6); ≥ 39 years: adjusted OR 1.29 (95% CI 0.5-3.2)] (Table 7.2B). Similar results were observed for the smoker-years variable. Although longer residential ETS exposure generally had higher risk estimates, no statistical evidence of a dose-response was demonstrated. Similarly, occupational years of ETS exposure also gave non-significantly elevated adjusted risk estimates with no evidence of trend [1-7 years: adjusted OR 1.24 (95% CI 0.5-3.3); 8-19 years: adjusted OR 1.71 (95% CI 0.7-4.3); ≥ 20 years: adjusted OR 1.71 (95% CI 0.7-4.3)]; with the smoker-years occupational variable, the two highest exposure categories gave similar risk estimates [adjusted ORs 1.98 (95% CI 0.8-4.9) and 1.58 (95% CI 0.6-4.0), respectively] (Table 7.2D). Combined smoker-years of residential and occupational exposure did demonstrate a statistically significant trend (p=0.05) [1-36 smoker-years: adjusted OR 0.83 (95% CI 0.3-2.1); 37-77 smoker-years: adjusted OR 1.54 (95% CI 0.7-3.5); ≥ 78 smoker-years: adjusted OR 1.82 (95% CI 0.8-4.2)] (Table 7.2E).

Rachtan 2002. This hospital-based case-control study consisted of 242 Polish women with newly diagnosed lung cancer (March 1991 through December 1997) and 352 healthy controls. Controls were a convenience sample derived from the next-of-kin of other hospital patients diagnosed without tobacco-related cancers. Cancer diagnosis was based on surgical resection/staging or histology samples. Data on demographics, residential and health histories, family history of cancer, occupational exposures, diet, alcohol use, and active and passive smoking were obtained through interviewer-administered questionnaires. Smokers were defined as ever smoking one or more cigarettes per day for at least seven months.

ETS exposure was defined as residential/domestic exposure during childhood (before age 18). The majority of ETS-related analyses presented used women "never-exposed" to passive smoking prior to age 18, regardless of active smoking or other ETS exposure after age 18. After adjusting for age and pack-years of active smoking, women exposed to ETS prior to age 18 had a significantly higher lung cancer risk (all cell types combined) [RR 2.31 (95% CI 1.47-3.63)], relative to women unexposed to ETS during childhood. A multivariate analysis identified a similar risk estimate [RR 2.49 (1.36-4.54)] after adjusting for age, alcohol consumption, dietary components, family history, occupational exposures, and pack-years smoking. In a smaller subset analysis, restricted to lifetime non-smokers (54 cases/251 controls), the age-adjusted lung cancer risk for childhood ETS exposure was also elevated [RR 2.53 (95% CI 1.45-4.41)]. After including the other potential risk factors in a multivariate analysis, the estimated lung cancer risk (all histological types combined) associated with childhood ETS exposure increased to RR 3.31 (95% CI 1.26-8.69) (Table 7.2C).

7.2.2.2. Other Case-Control Studies Conducted in Asia and India

Five reports based on three case-control studies, one population-based mortality (Du *et al.*, 1995, 1996) and two hospital-based incidence studies (Wang *et al.*, 1996a; Wang *et al.*, 1996b), were published prior to, but not reviewed in, the previous OEHHA report (Cal/EPA, 1997). More recent reviewed studies from China were population-based (Zhong *et al.*, 1999; Wang *et al.*, 2000). Other studies summarized below include smaller hospital studies from Taiwan (Lee *et al.*, 2000) and India (Rapiti *et al.*, 1999).

The series of registry-based case-control lung cancer mortality analyses by Du *et al.* (1995) included either 120 cases among nonsmoking residents, or 75 lung cancer cases among nonsmoking women married to smokers, all in Guangzhou, China during 1985-1986. Controls were deaths due to either non-respiratory disease or other non-respiratory cancer-related deaths. In the first analysis, no effect of ETS exposure on lung cancer death was reported (no risk estimates presented). In the second study, spousal ETS exposure was associated with an elevated, statistically non-significant increase in the risk of death due to lung cancer among nonsmoking women [OR 1.19 (95% CI 0.66-2.16)] with risk increasing as the number of cigarettes smoked/day by the spouse increased [ORs 0.72 and 1.62, <20 and ≥ 20 cigarettes/day, respectively (using non-tumor related death controls)]. Point estimates were not statistically significant (Table 7.2B).

A more recently published population-based case-control study among nonsmoking women in Shanghai, China included 504 women diagnosed between 1992 and 1994 (Zhong *et al.*, 1999). Controls were obtained from a residential registry (n = 601). Data on lifetime residential and

occupational exposure to ETS were obtained via interview. Risk estimates were adjusted for age, income, vitamin C intake, smokiness during cooking, family history of lung cancer and high-risk occupations. ETS exposure during childhood (up to age 23) was not associated with an elevated risk of lung cancer [adjusted OR 0.9 (95% CI 0.5-1.6)] (Table 7.2C). There was evidence of a significant dose-response effect from ETS exposure when analyzed by both number of hours exposed per day (p for trend = 0.001) and number of co-workers who smoked (p for trend < 0.001) (see Table 7.2D). Lung cancer risk was not statistically significantly associated with adult residential ETS exposure [adjusted OR 1.2 (95% CI 0.8-1.8)] (Table 7.2C) or occupational ETS exposure alone [adjusted OR 1.9 (95% CI 0.9-3.7)] (Table 7.2D). However, the risk due to adult ETS exposure at work and at home combined was significantly elevated [adjusted OR 1.9 (95% CI 1.1-3.5)] (Table 7.2E).

Another recent report by Wang *et al.* (2000) identified 233 lung cancer cases among never-smokers from hospitals and clinics throughout Gansu Province in 1995; the authors' considered their case-ascertainment as population-based. The lung cancer risk for "ever" exposure to ETS was slightly elevated, but not statistically significantly [adjusted for age and place of residence OR 1.19 (95% CI 0.7-2.0)] (Table 7.2C). Risk estimates were similar for men and women. ETS exposure in childhood was associated with a significantly elevated lung cancer risk [adjusted OR 1.52 (95% CI 1.1-2.2)], with evidence for a trend ($p<0.01$) with increasing exposure duration (expressed as pack-years) [adjusted ORs 1.43, 1.81, and 2.95] (Table7.2C). No elevated risk was observed for ETS exposure exclusively in adulthood [adjusted OR 0.90 (95% CI 0.6-1.4)].

Two smaller hospital-based studies conducted in China, one in Guangzhou, between 1990 and 1993 (Wang *et al.*, 1996a) and another in Shenyang, between 1992 and 1994 (Wang *et al.* 1996b), found contrasting results. The first study reported that spousal ETS exposure was significantly related to elevated lung cancer risk among nonsmoking women, while the second study did not find a significant association (Table 7.2B). Additionally, a small hospital study from Chandigarh, India, based on 58 nonsmoking lung cancer patients (microscopically confirmed), found a strong association between childhood ETS exposure [adjusted OR 3.9 (95% CI 1.9-8.2)], with risk highest for cigarette smoke [adjusted OR 12 (95% CI 4.2-34)] after adjustment for sex, age, residence and religion (Rapiti *et al.*, 1999) (Table 7.2C). Increased risk due to exposure to a smoking spouse was significantly elevated for individuals exposed to cigarette smoke [OR 5.1 (95% CI 1.5-17)] .

A hospital-based study in Taiwan based on 268 cases and 445 controls evaluated the risk of lung cancer in nonsmoking women due to lifetime ETS exposure (Lee *et al.*, 2000). Risk estimates were adjusted for residential area, education, occupation, tuberculosis, and cooking related variables (cooking fuels and fume extractor). Childhood exposure (≤ 19 years) to ETS was associated with a statistically elevated lung cancer risk [adjusted OR 1.7 (95% CI 1.1-2.6)]. Cumulative childhood exposure gave evidence of trend [1-20 smoker-years: adjusted OR 1.8 (95% CI 0.9-3.6); > 20 smoker-years: adjusted OR 2.2 (95% CI 1.4-3.4), p for trend 0.001] (Table 7.2C). Adult exposure to spousal ETS was also significantly associated with increased lung cancer risk [adjusted OR 2.2 (95% CI 1.5-3.3)], however, workplace exposure was not [adjusted OR 1.2 (95% CI 0.5-2.4)] (Table 7.2D). Among women with husbands that smoked in their presence, the risk of lung cancer increased with increasing pack-years [1-20: adjusted OR 1.5 (95% CI 0.9-2.4); 21-40: adjusted OR 2.5 (95% CI 1.5-4.2); > 40: adjusted OR 3.3 (95% CI 1.7-6.2)] (Table 7.2B). Combined adult life exposure (home and workplace) demonstrated a

trend for increasing cancer risk with increasing smoker-years [1-20 smoker-years: adjusted OR 1.3 (95% CI 0.7-2.5); 21-40 smoker-years: adjusted OR 1.5 (95% CI 0.9-2.4); ≥ 40 smoker-years: adjusted OR 2.6 (95% CI 1.6-4.2), p for trend 0.001] (Table 7.2E). Cumulative lifetime exposure to ETS (childhood and adulthood) demonstrated a similar trend [1-20 smoker-years: adjusted OR 1.3 (95% CI 0.6-2.6); 21-40 smoker-years: adjusted OR 1.6 (95% CI 0.9-2.6); 41-60: adjusted OR 2.0 (95% CI 1.2-3.5); > 60 smoker-years: adjusted OR 2.8 (95% CI 1.6-4.8), p for trend 0.001] (Table 7.2E).

7.2.3. Recent Cohort Studies of ETS and Lung Cancer

Since the prior review by OEHHA, only three reports from cohort studies examining ETS exposure and lung cancer risk were available for review, two investigating cancer incidence among non-smoking women married to smokers, the third involving both genders with smoking spouses. The Korean study addressed the effects of spousal smoking on lung cancer risk in a group of health plan enrollees (Jee *et al.*, 1999), while the population-based Japanese study enrolled women from three cities (Nishino *et al.*, 2001). The third study utilized data from the American Cancer Society's CPS-I study (Enstrom and Kabat, 2003).

Jee et al. (1999) investigated the effects of spousal smoking in Korean women receiving health benefits through the Korea Medical Insurance Corporation (KMIC). Approximately 11% of the population of Korea was eligible for KMIC in 1992. This study enrolled 160,130 non-working spouses; among these 157,436 women were non-smokers. KMIC enrollees (husbands) and dependents (wives) received questionnaires on smoking, dietary, and health habits. Lung cancer cases were ascertained through hospital discharge summaries through a unique personal identification number from July 1994 through December 1997. A total of 79 lung cancer cases were identified during the 3.5 years of follow-up. The adjusted relative risk of lung cancer among women married to current smokers was statistically elevated [RR 1.9 (95% CI 1.0-3.5)] after adjustment for age, socioeconomic status, residency, vegetable consumption, and husband's occupation (Table 7.2B). Lung cancer risk increased among women with increasing years of spousal smoking [adjusted RRs 1.6 (95% CI 0.8-3.0) and 3.1 (95% CI 1.4-6.6), 1-29 and ≥ 30 years among current smokers, respectively ($p < 0.01$)]. Although the follow up period was limited, less than four years, the high follow up rates, large sample size, and repeated measures of smoking habits (1992 and 1994) increase the reliability of the risk estimates.

Nishino et al. (2001) investigated the effects of spousal smoking among 9,675 women completing mailed questionnaires (total response rate of 96% for men and women). Individuals were followed for 9 years with cancer cases identified through record linkage with a population cancer registry. ETS exposure was based on spousal smoking at time of initial survey.

Twenty-four lung cancers were identified within the cohort, eleven in women reporting spousal exposure. The age-adjusted relative risk for lung cancer associated with having a smoking husband was elevated, but not significantly [RR 1.9 (95% CI 0.81-4.4)]. A similar, non-significantly elevated lung cancer risk was reported after additional adjustment for alcohol, dietary factors, past history of lung disease and residential area [RR 1.8 (95% CI 0.67-4.6)] (Table 7.2B).

This study identified an elevated, but statistically non-significant lung cancer risk, based on only 24 lung cancer cases. Although the study adjusted for several potentially important confounding factors, including dietary intake of vegetables, it was limited by a single ETS exposure indicator (spousal smoking) at baseline.

Enstrom and Kabat (2003) examined ETS exposure and long-term mortality from CHD, lung cancer and chronic obstructive pulmonary disease (COPD) in a prospective cohort study of the adult Californians enrolled in 1959 in the American Cancer Society's Cancer Prevention Study (CPS-I). Never smokers married to current or former smokers were compared to never smokers married to never smokers, with the former group subdivided based on the smoking status of the spouse (1-9, 10-19, 20, 21-39, ≥ 40 cigarettes per day). Former smokers were considered in a separate category. The relative risk of death was calculated as a function of the spouse's smoking status and adjusted for age and seven potential confounders at baseline: race, education, exercise, BMI, urbanization, fruit or fruit juice intake, and health status (good, fair, poor, sick).

The adjusted RR for lung cancer death among all men married to a formerly smoking spouse was 0.82 (95% CI 0.29-2.26). With a currently smoking spouse, the RR was 0.57 (95% CI 0.26-1.26), while with an ever-smoking spouse the RR was 0.63 (95% CI 0.33-1.22). In never-smoking women, there was a slight but non-significant risk associated with previous exposure from a formerly smoking spouse (1.04, 95% CI 0.69-1.57), but not with exposure to a currently or ever-smoking spouse (0.88, 95% CI 0.60-1.28 and 0.94, 95% CI 0.66-1.33, respectively) (see Table 7.2E).

There are several concerns with this study. It is based on data from which it is not possible to distinguish ETS-exposed from truly non-exposed individuals. At the start of CPS-I, the only information regarding potential ETS exposure was the smoking habits of the spouse. At that time, cigarette smoking was more prevalent, and ETS much more pervasive than it is now. As a result, the control group, defined as non-ETS-exposed based on the absence of spousal smoking, would include individuals with extensive ETS exposure outside the home, at work and elsewhere. As noted by Thun (2003), the potential misclassification of smoke exposure was enhanced by the absence of spousal smoking data after 1972 (an additional 26 years of study follow-up, representing two-thirds of the study length). A re-survey of 681 subjects in 1999 comprised only 7% of the original 9,619 life-long nonsmokers at enrollment, lending little assurance about the validity of exposure measurements. Thus, individuals no longer married to a smoking spouse, married to a spouse who had quit smoking, or whose spouse had died, were still classified as ETS-exposed. As both duration of exposure and total dose measurements are important factors, the resulting misclassification would be a major liability to this study. Similarly, analyses were adjusted for the factors listed above at baseline and while exercise, weight, height, and fruit intake reportedly changed little over time, changes in health status or in other lifestyle factors that could affect survival were not included in the adjustment. There was, for example, a large increase between 1959 and 1999 in the proportion of the population using vitamin pills (38.3% and 81.2%, respectively), which may have partly mitigated the effects of smoke exposure. In addition, the category of current smokers may include intermittent smokers and those who started smoking relatively recently, potentially leading to wide variations in the duration of ETS exposure among never smokers, and a dilution of effects. The problems noted above result in a study that is uninformative with respect to the health outcomes related to ETS exposure.

7.2.4. ETS Exposure from Spouses

7.2.4.1. Spousal ETS and Lung cancer: Previous Findings

In the previous OEHHA report (Cal/EPA, 1997), the population-based case-control studies reported that risks for lung cancer associated with ETS exposure from spousal smoking ranged from 1.0 to 1.6 for "ever" exposed or cumulative exposure estimates (Brownson *et al.*, 1992; Stockwell *et al.*, 1992; Fontham *et al.*, 1991; Kabat *et al*., 1995), which were comparable with the pooled estimate of the U.S. EPA report (U.S. EPA, 1992c). Statistical significance was achieved in the overall estimate only in the largest study [OR 1.29, (95% CI 1.04-1.60)] (Fontham *et al.*, 1994) and for the highest exposure categories [OR 2.4, (95% CI 1.1-5.3) (Stockwell *et al.*, 1992) and OR 1.3 (95% CI 1.0-1.7) (Brownson *et al.*, 1992)]. Odds ratios from the hospital-based study were elevated but not statistically significantly, OR 1.60 and 1.08, males and females, respectively (Kabat *et al.*, 1995). The U.S. cohort study showed a similar, statistically non-significant increased risk of lung cancer associated with spousal smoking [RR 1.2 (95% CI 0.8-1.6)] (Cardenas *et al.*, 1997).

Additionally, the OEHHA report supported that either individually, or as a group, the studies reviewed, particularly the population based studies, addressed criticisms directed at earlier, smaller case-control studies including: diminishing selection bias by being population based; diminishing misclassification bias of smokers as non-smokers by improving smoking definition criteria; utilizing corroborative or multiple measures of smoking; diminishing misclassification of cases by improving diagnostic review; and improving adjustment for potential confounders.

The previous OEHHA report found that the concordance in the studies' results, in combination with improvements in study design and analysis, was indicative of a causal association between spousal ETS exposure and the risk of lung cancer (Cal/EPA, 1997).

7.2.4.2. Spousal ETS and Lung Cancer: Recent Primary Epidemiological Studies

Table 7.2B summarizes recent studies addressing spousal ETS exposure and lung cancer. These studies are improved over the earliest studies by having larger sample sizes and/or better case definition, and less misclassification bias, although the latter is still somewhat problematic. The newer reviewed studies provide additional evidence that exposure to ETS is causally related to development of lung cancer.

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Du *et al.* (1995,1996)	Residential exposure	OR[a]	Spouse cigarettes/day	OR
Mortality	Spousal smoking		(28/53)	1.0 (Referent)
Case-control	No (28/53)	1.0 (Referent)	< 20 (13/34)	0.72
China	Yes (47/75)	1.19 (0.66-2.16)	0 ≥ 20 (30/35)	1.62 (0.83-3.15)
Population			Residential years	
			< 30	1.39 (0.61-3.16)
			≥ 30 (29/47)	1.17 (0.60-2.29)
Wang *et al.* (1996a)	Home and/or work (99/99)	2.5 (1.3; 5.1)		
Case-control- China				
Wang *et al.* (1996b)	Spousal smoking	OR (Crude)[b]	Years lived with smoking spouse	OR (Crude)
Case-control	No (NA)	1.0 (Referent)	< 20 (NA)	1.0 (Referent)
China	(92/89)	1.11 (0.65-1.88)	(21/16)	1.41 (0.68-1.94)
Hospital Based			(32/32)	1.08 (0.58-2.00)
	Yes		20-29 ≥ 40 (17/17)	1.08 (0.37-3.14)
Boffetta *et al.* (1998)	Spousal smoking	OR[c]	Duration exposure years	OR
Pooled case-control	Ever exposed (Women Only)		30-39	0.99 (0.77-1.27)
Multiple country	No (187/376)	1.00 (Referent)		1.57 (1.06-2.31)
	Yes (321/632)	1.11 (0.88-1.39)	1-34 ≥ 43	1.05 (0.66-1.68)
			Duration hours/day × yrs	
			35-42	p trend=0.19
				0.80 (0.61-1.06)
				1.12 (0.72-1.74)
			1-135 ≥ 224	1.70 (1.05-2.75)
			136-223	p trend=0.03

[a] Crude odds ratio; ORs from Table 2 Du *et al.* (1995) and Table 13 Du *et al.* (1996).
[b] Unadjusted ORs from Table 1 and 2 Wang *et al.* (1996b).
[c] ORs adjusted age and sex-study center interaction from Table 3 Boffetta *et al.* (1998).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Boffetta *et al.* (1998) (continued)			Average exposure (cig/day)	OR[c]
			Unexposed	1.00 (Referent)
			0.1-10.0	1.00 (0.77-1.31)
			10.1-18.0	0.57 (0.34-0.93)
			≥18.1	1.34 (0.83-2.17)
			Cumulative exposure (pack-yrs)	p trend=0.97
			0.1-13.0	0.91 (0.70-1.19)
			13.1-23.0	0.83 (0.52-1.30)
			≥23.1	1.54 (0.97-2.44)
				p trend=0.15
Jockel *et al.* (1998)	Spousal exposure	OR[d]	Spousal exposure	OR
Case-control	Never (99/25)	1.00 (Referent)	No/low (142/49)	1.00 (Referent)
Germany[*]	Ever/smoking spouse (61/30)	1.12 (0.54-2.32)	Intermediate (13/2)	0.22 (0.05-1.07)
	All other sources (11/9)	3.10 (1.12-8.60)	High (5/4)	1.87 (0.45-7.74)
	High		Total exposure	
			High (21/17)	3.24 (1.44-7.32)
Nyberg *et al.* (1998a)	Spouse ever smoker	OR[e]	Average daily spousal exposure	OR[f]
Case-control	Women		(66/127)	1.0 (Referent)
Sweden	(39/71)	1.0 (Referent)	< 10 cpd (40/83)	0.96 (0.57-1.61)
	(50/92)	1.05 (0.60-1.86)	≥ 10 cpd (15/24)	1.16 (0.55-2.45)
			Unexposed	
	Never			
	Ever			

[c] ORs adjusted age and sex-study center interaction from Table 3 Boffetta *et al.* (1998).

[*] Included in Boffetta *et al.* (1998).

[d] ORs adjusted for sex, age and region; Table 3 Jockel *et al.* (1998); estimated for both sexes.

[e] ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 2 Nyberg *et al.* (1998a); OR for men 1.96 (0.72-5.36).

[f] Both genders combined; ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 3 Nyberg *et al.* (1998a).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)		Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Nyberg *et al.* (1998a) (continued)	Both Genders	1.17 (0.73-1.88)	Total duration spousal exposure		OR[f]
			< 30 years	(39/74)	1.01 (0.60-1.70)
			≥ 30 years	(19/34)	1.14 (0.56-2.29)
			Total weighted duration spousal Exposure ("hours-years")		
			< 90 HY	(36/84)	0.85 (0.50-1.44)
			≥ 90 HY	(16/23)	1.25 (0.59-2.66)
			Cumulative exposure to spousal ETS (pack-years in presence)		
			< 9 PY	(35/82)	0.84 (0.49-1.43)
			≥ 9 PY	(20/25)	1.53 (0.76-3.09)
Zaridze *et al.* (1998)	Spousal smoking	OR[g]	Husband's smoking duration (yrs)		OR[g]
Case-control		1.0 (Referent)	None	(195/80)	1.0 (Referent)
Russia[*]	(195/80)			(39/31)	1.86 (1.07-3.22)
	(163/109)	1.53 (1.06-2.21)	> 15	(124/78)	1.42 (0.95-2.12)
	No		Husband's smoking quantity		
	Yes		1-15	(195/80)	1.0 (Referent)
			1-10 cpd	(90/66)	1.66 (1.09-2.52)
			None > 10 cpd	(73/43)	1.35 (0.84-2.18)

[f] Both genders combined; ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 3 Nyberg *et al.* (1998a).

[*] Included in Boffetta *et al.* (1998).

[g] OR adjusted for age and education; Table 3 Zaridze *et al.* (1998).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Jee *et al.* (1999)	Spousal smoking:	RR[i]	Spouse cigarettes/day (current):	RR[j]
Cohort Study	Non-smoker (12/36,109)[h]	1.0 (Referent)	Non-smoker (12/36,109)	(Referent)
Korea	Ex-smoker (16/36,802)	1.3 (0.6-2.7)	1-19 (35/72,254)	2.0 (1.1-3.9)
Health Insurance	Current smoker (51/84,525)[h]	1.9 (1.0-3.5)	≥ 20 (16/12,271)	1.5 (0.7-3.3) p < *0.1*
			Residential years (current):	
			(36/53,881)[e]	1.6 (0.8-3.0)
			≥ 30 (15/30,644)[e]	3.1 (1.4-6.6) p< *0.01*
Rapiti *et al.* (1999)	Spousal smoking	OR[k]		
Case-control	Husband non-smoker (28/46)	1.0 (Referent)	1-29	
India	Husband smoker (13/21)	1.2 (0.5-2.9)		
Hospital Based	(11/5)	5.3 (1.6-18)		
Zhong *et al.* (1999)	Spousal smoking:	OR[l]	Years lived with smoking spouse:	OR[l]
Case-control	Women only spousal	1.1 (0.7-1.7)	None (114/85)	1.0 (Referent)
China	exposure		(86/82)	1.1 (0.7-1.8)
Population	(116/89)		(102/74)	1.0 (0.6-1.6)
			> 35 (108/83)	1.1 (0.7-1.8)
			Cigarettes per day:	
			(90/88)	1.4 (0.9-2.2)
			(174/123)	0.9 (0.6-1.4)
			> 20 (32/28)	1.4 (0.7-2.6)

Cigarettes only
1-20
21-35
1-10
11-20

[h] ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 2 Nyberg *et al.* (1998a); OR for men 1.96 (0.72-5.36).
[i] Cases of lung cancer and size cohort.
[j] RR from Table 1 Jee *et al.* (1999); RR = rate ratio; adjusted for age husband, age wife, socioeconomic status, residency, husband's vegetable consumption and occupation.
[k] ORs from Table 3 Rapiti *et al.* (1999); adjusted for age, residence and religion.
[l] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history lung cancer, and high-risk occupations; from Tables 2 and 4, Zhong *et al.* (1999).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Lee *et al* (2000)[m]	Spousal smoking[n]:	OR[o]	Spousal pack-years	OR
Case-control	Husband non-smoker	(Referent)	0	(Referent)
Taiwan	(82/192)		(55/89)	1.5 (0.9-2.4)
Hospital Based	Husband smoker		(53/51)	2.5 (1.5-4.2)
	(40/89)	1.2 (0.7-2.0)	> 40 (38/25)	3.3 (1.7-6.2)
	"absence" (146/164)	2.2 (1.5-3.3)	1-20	
	"presence"		21-40	
Wang *et al.* (2000)	Spousal smoking[p]	OR	Spousal smoking pack-years[q]	OR
Case-control	No (31/70)	1.0 (Referent)	(52/122)	0.81 (0.5-1.4)
China	Yes (169/337)	1.03 (0.6-1.7)	(Wells *et al.* 1998)	1.00 (0.6-1.8)
Hospital Based			≥ 20 (58/102)	1.03 (0.6-1.8)
			1-9	
			10-19	
Kreuzer *et al.* (2000; 2001)	Spousal smoking:		Duration exposure (hours)	OR[r]
Case-control	Ever exposed (Women only)	OR[q]		1.00 (Referent)
Germany[*]	(95/219)	1.00 (Referent)	> 49,400-67,900	0.98 (0.53-1.81)
	No (139/316)	0.96 (0.70-1.33)	≥ 67,900	1.69 (0.94-3.03)
	Yes		0-49,400	p trend=0.16
			Cumulative (pack-yrs)	
				1.00 (Referent)
				0.85 (0.46-1.57)
			≥ 23	1.03 (0.48-2.24)
			1-10.0	
			10.1-23.0	p trend=0.85

[m] Appears some case overlap with Ko *et al.* (1997).
[n] Smoker in the presence of passive smokers were classified as "presence", otherwise reported as "absence"; Lee *et al.* (2000).
[o] ORs from Table 3 Lee *et al.* (2000); adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor.
[p] ORs from Table II Wang *et al.* (2000); adjusted for childhood exposure, age, residence and socioeconomic factors. Adult residential exposure based after age 18 exposure to smoking cohabitants (spouse or others). Estimate presented for non-smoking women. Estimate for non-smoking men OR=0.56 (0.2-1.4) and non-smoking men/women combined OR=0.90 (0.6-1.4).
[q] Exposure included cigarettes and pipe exposure divided by 20 times duration of exposure in adulthood.
[r] ORs adjusted for sex, age, and region; Table 3, Kreuzer *et al.* (2000) [*] Included in Boffetta *et al.* (1998).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Johnson *et al.* (2001)	Residential exposure	OR[s]	Residential years	OR[t]
	Never Exposed (10/135)	1.0 Referent)	Never exposed(10/135)	1.0 (Referent)
Case-control	Child Only (2/56)	0.54 (0.1-2.7)	(13/171)	1.10 (0.4-2.8)
Canada	Adult Only (13/159)	1.20 (0.5-3.0)	(21/189)	1.52 (0.6-3.6)
Population	Child and Adult (46/411)	1.63 (0.8-3.5)	≥ 39 (20/183)	1.29 (0.5-3.2)
			1-20	
			Residential smoker-years	
			21-38	
			Never exposed(10/135)	1.0 (Referent)
			(16/176)	1.33 (0.4-4.0)
			(13/182)	0.93 (0.4-2.4)
			≥ 48 (25/185)	1.64 (0.7-3.9)
			1-23	
			24-47	
Nishino *et al.* (2001)	Spousal smoking	RR[u]		
	Husband smoker at baseline	1.8 (0.67-4.6)		

[s] ORs adjusted for age, province, education and total fruit/vegetable consumption. Childhood defined as age 0-19. ORs are from Table II of Johnson *et al.* (2001).

[t] Sum over subject's lifetime of residential exposure (i.e. number of regular smokers living in the subject's home multiplied by the number of years in that home; ORs from Table III of Johnson *et al.* (2001); ORs adjusted for age, province, education and total fruit/vegetable consumption

[u] Relative risk adjusted for age, alcohol, fruit and vegetable intake, age at first birth, parity, age at menarche and BMI.

Results from these recent Canadian and European studies are comparable to the previous pooled estimate of the U.S. EPA (U.S. EPA, 1992c) report, summary OR of 1.19 (90% CI 1.04-1.35) for "ever" exposed to ETS from spouses (for U.S. studies). In the population-based case-control study of Johnson *et al.* (2001), the OR for adult exposure to residential ETS was 1.20 (95% CI 0.5-3.0) after adjustment for age, province, education and total fruit/vegetable consumption. Combining adult and childhood residential exposure increased this adjusted risk estimate [OR 1.63 (95% CI 0.8-3.5)], but the point estimate remained non-significant. Among the individual European population based case-control studies, risk estimates (range 0.96 to 1.17) were somewhat lower and usually non-significant (Jockel *et al.*, 1998; Kreuzer *et al.*, 1998; Kreuzer *et al.* 2000; Nyberg *et al.*, 1998a), similar to the pooled estimate from the multicenter study [OR 1.11 (95% CI 0.88-1.39)] (Boffetta *et al.*, 1998). The one Russian study did find a significant elevation of risk [OR 1.53 (95% CI 1.06-2.21)] (Zaridze *et al.*, 1998). Case-control studies from Asia varied more substantially, with hospital-base studies ORs ranging from 1.0 to 1.2 without statistical significance (Rapiti *et al.*, 1999; Wang *et al.*, 1996b; Wang *et al.*, 2000), to a statistically significant OR of 2.2 (95% CI 1.5-3.3) in Lee *et al.* (2000). Population-based estimates also gave similar non-significant risk estimates (range ORs 1.1 to 1.2) (Du *et al.*, 1995, 1996; Zhong *et al.*, 1999). Both cohort studies from Asia identified increased risks for lung cancer, with one being statistically significant; both estimates [adjusted RR 1.9 (95% CI 1.0-3.5) (Jee *et al.*, 1999) and adjusted RR 1.8 (95% CI 0.67-4.6) (Nishino *et al.*, 2001)] were higher than that reported in the earlier U.S. cohort study by Cardenas *et al.* (1997) [RR 1.2 (95% CI 0.8-1.6)].

In addition, several of these recent studies, including the prospective cohort (Jee *et al.*, 1999), provided evidence of positive increasing trends in lung cancer risk in nonsmokers with increasing ETS exposure, with some but not all exposure indices of duration, daily amount, or cumulative dose (7.2B). The large multicenter IARC study (Boffetta *et al.* 1998) did not find a trend with ETS exposure for three of four matrices: duration (years), average exposure (cigarettes/day), or cumulative exposure (pack-years). However, ETS exposure duration estimated in hours/day × years exposed was suggestive of a dose-response relationship (p for trend 0.03). Furthermore, the "non-exposed" referent group by definition contained people exposed to ETS.

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 (U.S. EPA, 1992a) and previous Cal/EPA (1997) reports.

As with the studies previously reviewed in the Cal/EPA (1997) report, these more recently published studies continue to improve on criticisms of earlier studies, particularly those published prior to 1991, including larger sample sizes, more attention to defining and improving on selection bias, confirmation of primary lung cancers, and adjustment for potential confounders. The individual population-based case-control studies conducted in Canada and Europe attempted to minimize selection bias associated with hospital-based cases and controls (Jockel *et al.*, 1998; Nyberg *et al.*, 1998a; Zaridze *et al.*, 1998; Kreuzer *et al.*, 2000; Johnson *et al.*, 2001). These studies also attempted to address bias due to the misclassification of nonsmokers as smokers by defining lifetime smokers; however, concerns continue to be raised regarding this issue (Boffetta *et al.*, 1998). The majority of studies also continue to address the

issue of microscopic confirmation of primary lung cancer by requiring microscopic confirmation or additional tissue review.

Additionally, several studies attempted to adjust for potential confounding factors, including dietary consumption of fruits, vegetables or other estimates of micronutrient intake (Nyberg *et al.*, 1998a; Jee *et al.*, 1999; Zhong *et al.*, 1999; Johnson *et al.*, 2001; Nishino *et al.*, 2001), education (Zhong *et al.*, 1999; Lee *et al.*, 2000; Johnson *et al.*, 2001), occupation (Nyberg *et al.*, 1998a; Jee *et al.*, 1999; Zhong *et al.* 1999; Lee *et al.*, 2000), socioeconomic status or income (Jee *et al.*, 1999; Zhong *et al.*, 1999), urban residence or region (Nyberg *et al.*, 1998a; Jee *et al.*, 1999; Lee *et al.*, 2000; Johnson *et al.*, 2001; Nishino *et al.*, 2001), or history of lung disease or family history of lung cancer (Zhong *et al.*, 1999; Lee *et al.*, 2000; Nishino *et al.*, 2001). Although the individual European studies tended to adjust for several factors, the multicenter IARC pooled study reported estimates adjusted for only age and sex-study center interaction as sites did vary in the type of data collected and methods of control assignment (Boffetta *et al.*, 1998).

The previous OEHHA report (Cal/EPA, 1997) summary states that there is a causal association between spousal ETS exposure and lung cancer, and "that either individually, or as a group, the studies reviewed, particularly the population based studies addressed criticisms directed at earlier, smaller case-control studies including diminishing selection bias by being population based; misclassification bias of smokers as non-smokers by improving smoking definition criteria, utilizing corroborative or multiple measures of smoking; misclassification of cases by improving diagnostic review; improved adjustment for potential confounders." No compelling evidence exists for modifying the above conclusion that there is a causal association between spousal ETS exposure and lung cancer risk.

7.2.4.3. Spousal ETS and Lung Cancer: Recent Meta-Analyses

Several meta-analyses of lung cancer risk among female spouses (or cohabitants) of male smokers have been published in the peer-reviewed literature subsequent to the Cal/EPA review in 1997 (Mengersen, 1995; Law and Hackshaw, 1996; Rundle *et al.*, 2002; Hackshaw *et al.*, 1997; Hackshaw, 1998; Boffetta *et al.*, 1998; Taylor *et al.*, 2001). Each publication included all studies available at the time of meta-analyses, thus the most recent meta-analysis (Taylor *et al.*, 2001) is the most comprehensive. The investigators analyzed a total of 43 epidemiological studies (4 cohort and 39 case-control) published between 1981 and 1999 of cancer risk among nonsmoking female spouses of male smokers. They estimated the overall rate ratio to be 1.29 (95% CI 1.17 – 1.43), which was consistent with, but a little higher than, summary rate ratios estimated by the other recent meta-analyses mentioned above (rate ratios ranged from1.14 to 1.26).

Male spouses of female smokers were the subject of a meta-analysis by Mengersen *et al.* (1995), who estimated the overall rate ratio for lung cancer to be 1.42 (95% CI 1.01-1.99), based on eight case-control and two cohort studies.

The sensitivity of the association found in meta-analyses between ETS and lung cancer to methods and potential biases were quantified in several papers. Mengersen *et al.* (1995) found small differences in the overall rate ratio estimate for 31 studies as a result of choosing fixed or

random effect models, use of exact or approximate confidence intervals for the primary studies, taking study quality into account, inclusion of unadjusted primary data, and adjustment for potential publication bias. They found some evidence of publication bias (large relative risks were favored for studies with small sample size), but they estimated that 80 additional negative studies would be required to reduce the summary risk to below statistical significance. Tweedie *et al.* (1996) compared the traditional methods of meta-analyses to Bayesian methods in a statistical paper that found very similar results. For 38 studies of female spouses of male smokers they estimated the overall rate ratio to be 1.20 (95% CI 1.07-1.34) with traditional methods and 1.22 (95% CI 1.08-1.37) with Bayesian methods. Hackshaw *et al.* (1997) found that adjustment for the potential effects of exposure misclassification and dietary confounding changed the rate ratio very little (from 1.24 to 1.26) in a meta-analysis of 37 studies of lung cancer among female spouses of male smokers. These recent meta-analyses strengthen the case for a causal association between exposure to spousal ETS and elevated lung cancer risk.

7.2.5. Other Sources of ETS Exposure

7.2.5.1. Other Sources of ETS and Lung Cancer: Previous Findings

Although the majority of studies published prior to 1991 addressing the potential associations between ETS and lung cancer focused on the risks associated with spousal smoking, comprehensive measures of lifetime ETS exposure also include assessment of other home (lifetime spousal, parental and other household sources), workplace and social exposures (Cummings *et al.*, 1989; Cal/EPA, 1997).

As reviewed in Cal/EPA (1997), ETS exposure from parents and/or other household members has not been consistently associated with an increased risk of lung cancer. However, among the four post-1991 U.S. case-control studies previously summarized, parental smoking was statistically associated with increased lung cancer risk in women in two studies, with 22 years childhood/adolescent exposure [OR 2.4 (95% CI 1.1-5.4)] (Stockwell *et al.*, 1992), and with combined childhood/adult exposure (48 years or more) [OR 3.25 (95% CI 1.42-7.46)] (Fontham *et al.*, 1994). The quality of data, particularly quantitative aspects of parental smoking, varied substantially by how exposure was ascertained, particularly declining with the use of surrogate respondents versus the lung cancer cases themselves. Such decreasing reliability of exposure data regarding household sources, compared to the more reliable data obtained regarding spousal smoking, was considered to limit the ability to identify strong or consistent associations (Cal/EPA, 1997).

Similar difficulties and limitations in assessing lifetime ETS work exposures exist, particularly when utilizing surrogate respondents. Often studies utilized indicators for most recent job, last job, or lacked information on the temporal relationship between exposure and diagnosis (Cal/EPA, 1997). However, in three studies reviewed, lifetime occupational history and assignment of workplace exposure were obtained (Wu *et al.*, 1985; Wu-Williams and Samet, 1990; Fontham *et al.*, 1994). OEHHA determined that the assessment of ETS workplace exposure in these studies was complete, and that the studies supported the association between workplace ETS exposure and an elevated risk of lung cancer (Cal/EPA, 1997).

More limited data were available to assess the potential association between ETS exposure in social settings with an elevated risk of lung cancer (Cal/EPA, 1997). One population-based case control study found an increased risk of lung cancer among women with increasing years of ETS exposure, 1-15, 16-30, and >30 years exposure, in social settings, ORs of 1.45, 1.59 and 1.54, respectively (p for trend 0.0002) (Fontham *et al.*, 1994). Also, one hospital-based case control study reported a non-significant elevated lung cancer risk associated with ETS in social settings, for males and females analyzed separately (Kabat *et al.*, 1995). However, OEHHA reported that this risk was significant for both sexes combined [calculated crude OR 1.73 (95% CI 1.03-2.29)]. This study also addressed ETS exposure in "other modes of transportation" among women (no men reported this exposure); associated lung cancer risk was significantly elevated [OR 5.17 (95% CI 1.46-18.24)] (Kabat *et al.*, 1995).

Overall, OEHHA found the evidence for an association between other, non-spousal, sources of ETS exposure and elevated lung cancer risk was supportive for workplace exposure and other household exposures, specifically when cumulative lifetime measures were analyzed. Data on ETS from social settings were also limited, but again, indicative of an elevated risk, particularly for cumulative exposures (Cal/EPA, 1997).

7.2.5.2. ETS Exposure from Parents and Other Household Members

Table 7.2C summarizes studies that included analysis of residential ETS exposure during childhood. Among the recent case-control studies, several of the population-based (Jockel *et al.*, 1998; Kreuzer *et al.* 1998; Nyberg *et al.* 1998a; Zhong *et al.*, 1999; Kreuzer *et al.*, 2000; Johnson *et al.*, 2001) and hospital-based studies (Wang *et al.*, 1996b; Lee *et al.*, 2000; Wang *et al.*, 2000; Rachtan 2002) attempted to evaluate the lung cancer risk associated with childhood exposure to ETS, including in combination with adult residential ETS exposure (Zhong *et al.*, 1999; Wang *et al.*, 2000; Johnson *et al.*, 2001). Most studies reported non-significant risk estimates of childhood ETS exposure as "ever" versus "never" for at least one parent, with ORs near 1, range 0.5 to 1.14 (Wang *et al.* 1996b; Kreuzer *et al.* 1998; Nyberg *et al.* 1998a; Zhong *et al.*, 1999; Lee *et al.*, 2000; Johnson *et al.*, 2001). Three studies reported elevated statistically significant risk estimates for childhood ETS exposure, OR 1.52 (95% CI 1.1-2.2) (Wang *et al.*, 2000), OR 1.7 (95% CI 1.1-2.6) (Lee *et al.*, 2000), and RR 3.31 (95% CI 1.26-8.69) (Rachtan, 2002). The European pooled analysis found an elevated non-significant risk for both sexes, OR 1.17 (95% 0.64-1.96), and a lowered, statistically significant risk for women only [OR 0.77 (95% CI 0.61-0.98)] (Boffetta *et al.*, 1998)

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Table 7.2C. Association between risk of lung cancer and ETS exposures from parents and other household members

Study	ETS Exposure	#Cases/ #Controls	OR (95% CI) for exposed
Johnson *et al.* (2001)	Period passive exposure[a]		OR
Case-control	Never exposed	10/135	(Referent)
Canada	Child only	2/56	0.54 (0.1-2.7)
Population	Adult only	13/159	1.20 (0.5-3.0)
	Child and Adult	46/411	1.63 (0.8-3.5)
Wang *et al.* (1996a)	Passive smoking in home		OR (Crude OR) [b]
Case-control	Total	Not presented.	1.91 (p<0.01)
China	Male		1.02 (p>0.05)
Hospital Based	Females		2.54 (p<0.05)
Wang *et al.* (1996b)	Childhood exposure ETS		OR (Crude) [cc]
Case-control	Non-smoking women	80/83	0.91(0.55-1.49)
China	(Prior to marriage)		
Hospital Based			
Zhong *et al.* (1999)	Childhood residential		OR[d]
Case-control	Childhood exposure only	64/44	0.9 (0.5-1.6)
China	Years childhood ETS		
Population	None	114/85	1.0 (Referent)
	1-19	33/20	0.9 (0.5-1.8)
	20-23	31/24	0.9 (0.5-1.9)
	Residential Total ETS		
	Adult only	162/132	1.2 (0.8-1.8)
	Childhood and Adult	134/107	1.0 (0.7-1.6)
Lee et al (2000)[e]	Childhood exposure home[f]		OR[f]
Case-control	Father		
Taiwan	Non-smoker	136/245	1.0 (Referent)
Hospital Based	Absence	36/96	0.8 (0.5-1.3)
Non-smoking women	Presence	96/104	1.7 (1.1-2.6)
	Mother		
	Non-smoker	260/436	1.0 (Referent)
	Absence	2/2	0.9 (0.1-7.8)
	Presence	6/7	0.9 (0.3-3.1)
	1-20 smoker years	27/33	1.8 (0.9-3.6)
	> 20 smoker years	90/94	2.2 (1.4-3.4)

[a] ORs adjusted for age, province, education and total fruit/vegetable consumption. Childhood defined as age 0-19. ORs are from Table II of Johnson *et al.* (2001).

[b] Unadjusted OR from Table 2, Wang *et al.* (1996a).

[c] Unadjusted OR from Table 1, Wang *et al.* (1996b).

[d] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history of lung cancer, and high-risk occupations, from Tables 2 and 3 Zhong *et al.* (1999). Childhood <23 years old.

[e] Appears some case overlap with Ko *et al.* (1997).

[f] ORs from Table 3 Lee *et al.* (2000). Adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor. Smoker in the presence of passive smokers were classified as "presence", otherwise reported as "absence", Lee *et al.* (2000).

Table 7.2C. Association between risk of lung cancer and ETS exposures from parents and other household members

Study	ETS Exposure	#Cases/ #Controls	OR (95% CI) for exposed
Wang *et al.* (2000)	Childhood ETS[g]		OR
Case-control	No	12/58	1.0 (Referent)
China;	Yes	20/56	1.52 (1.1-2.2)
Hospital Based	Childhood ETS pack-yrs[h]		
	1-9	91/203	1.43 (1.0-2.1)
	10-19	28/44	1.81 (1.0-3.3)
	> 20	8/8	2.95 (1.0-8.9)
			p trend < 0.01
	Lifetime ETS [i]		OR
	No	28/85	1.0 (Referent)
	Yes	200/436	1.19 (0.7-2.0)
	Lifetime ETS pack-yrs		
	1-9	50/130	1.04 (0.6-1.8)
	10-19	45/110	1.13 (0.6-2.2)
	≥ 20	76/141	1.51 (0.9-2.7)
			p trend < 0.05
Boffetta *et al.* (1998)	Childhood (<19 yrs) Ever		OR[j]
Pooled Case-control;	No	252/496	1.00 (Referent)
Multiple Countries in	Yes	389/1021	0.78 (0.64-0.96)
Europe	Women Only		
	No	187/295	1.00 (Referent)
	Yes	314/700	0.77 (0.61-0.98)
	Cumulative (smoker-yrs)		
	0	252/496	1.00 (Referent)
	0.1-14.0	248/582	0.83 (0.66-1.04)
	14.1-18.0	104/332	0.68 (0.51-0.92)
	≥ 18.0	37/107	0.80 (0.51-1.24)
			p trend=0.02
Jockel *et al.* (1998)	Childhood exposure		OR[k]
Case-control	No/low	136/45	1.00 (Referent)
Germany[*]	Intermediate	14/5	1.07 (0.35-3.30)
	High	10/5	2.02 (0.60-6.75)

[g] ORs from Table 2 Wang *et al.* (2000). Adjusted for adult exposure, age, residence and socioeconomic factors. Residential exposure based on exposure to smoking cohabitants (parents or others) prior to age 19. Estimates presented for both sexes combined. Estimate for non-smoking men OR=1.46 (0.6-3.7) and non-smoking women OR=1.51 (1.0-2.2).

[h] Exposure included cigarettes and pipe exposure divided by 20 times duration of exposure during childhood (or adulthood).

[i] ORs adjusted as above (plus childhood exposure) estimates presented for both sexes combined.

[j] ORs adjusted for age and sex-study center interaction from Table 2 Boffetta *et al.* (1998).

[*] Included in Boffetta *et al.* (1998)

[k] ORs adjusted for sex, age and region Table 3 Jockel *et al.* (1998).

Table 7.2C. Association between risk of lung cancer and ETS exposures from parents and other household members

Study	ETS Exposure	#Cases/ #Controls	OR (95% CI) for exposed
Nyberg *et al.* (1998a)	Childhood exposure to		OR[l]
Case-control	smoking father		1.00 (Referent)
Sweden[*]	Never	55/106	1.02 (0.63-1.66)
	Ever	59/107	
	Childhood exposure to smoking mother		1.00 (Referent)
	Never	55/106	0.72 (0.28-1.87)
	Ever	10/21	
Rapiti *et al.* (1999)	Childhood exposure ever	31/30	3.9 (1.9-8.2)
Case-control	Cigarettes	20/9	12 (4.2-34)
India			
Rachtan (2002)	Lifetime non-smokers		RR
Case-control			3.31 (1.26-8.69)
Poland			
Kreuzer *et al.*	Childhood Ever exposed		OR[m]
(2000;1998)	No	110/476	1.00 (Referent)
Case-control	Yes	182/862	0.84 (0.63-1.11)
Germany	Women only		
	No	88/171	1.00 (Referent)
	Yes	148/364	0.78 (0.56-1.08)
	Duration exposure (hours)		
	Childhood Total		
	0-12,000	235/1,124	1.00 (Referent)
	> 12,000-22,500	22/103	1.06 (0.63-1.76)
	> 22,500	16/85	0.92 (0.51-1.65)
	Childhood Women		p trend=0.89
	0-12,000	188/452	1.00 (Referent)
	> 12,000-22,500	16/39	0.94 (0.51-1.73)
	> 22,500	13/33	0.97 (0.49-1.90)
			p trend=0.86

[*] Included in Boffetta *et al.* (1998)

[l] Both genders combined, ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations Table 2 Nyberg *et al.* (1998a).

[m] ORs adjusted for sex, age and region Table 2 Kreuzer *et al.* (1998).

The three individual population-based studies (Jockel *et al.*, 1998; Kreuzer *et al.*, 1998; Zhong *et al.*, 1999), as well as the pooled analysis (Boffetta *et al.*, 1998), did not find evidence of a dose-response between cancer risk and cumulative exposure (years, cumulative hours, combination). One hospital-based case-control study from China did report a significant trend between risk of lung cancer and childhood years of ETS exposure [1-9 pack-years: adjusted OR 1.43 (95% CI 1.0-2.1); 10-19 pack-years: adjusted OR 1.81 (95% CI 1.0-3.3); >20 years: adjusted OR 2.95 (95% CI 1.0-8.9), p for trend <0.01] (Wang *et al.*, 2000).

Three studies, two population-based and one hospital-based, reported lung cancer risk estimates for residential ETS exposure for childhood and adulthood combined (Zhong *et al.*, 1999; Wang *et al.*, 2000; Johnson *et al.*, 2001). In the Canadian population study of women, the combined risk estimate was elevated but statistically non-significant [adjusted OR 1.63 (95% 0.8-3.5)], as well as larger than the adult only point estimate [adjusted OR 1.20 (95% CI 0.5-3.0)] (Johnson *et al.*, 2001). The two case-control studies from China identified null [adjusted OR 1.0 (95% 0.7-1.6)], or elevated, but again statistically non-significant risk [adjusted OR 1.19 (95% CI 0.7-2.0)] (Zhong *et al.*, 1999; Wang *et al.*, 2000).

In summary, the majority of individual studies reported null or slightly elevated, but non-significant, risk estimates for "ever" exposure to ETS during childhood, including the large pooled European study (Boffetta *et al.*, 1998). A similar null result [RR 0.91 (95% CI 0.80-1.05)] was reported in a meta-analysis of eleven studies on lung cancer in nonsmokers and childhood ETS exposure (Boffetta *et al.*, 2000). As discussed previously in Cal/EPA (1997), the difficulty in accurately assessing childhood ETS exposure among adult lung cancer cases (and controls) may help explain this inconsistency in risk estimates, and potentially the failure to observe any stronger associations that may exist. However, in several instances, significantly elevated risks were noted for childhood exposure (Rapiti *et al.*, 1999; Rachtan, 2002; Lee *et al.*, 2000; Wang *et al.*, 2000). These studies are suggestive of an association between childhood ETS exposure and later development of lung cancer.

7.2.5.3. Workplace ETS Exposure

Table 7.2D summarizes results from studies reporting risk estimates for lung cancer associated with workplace exposure to ETS. Five population-based and three hospital-based case-control studies reported risk estimates for workplace ETS exposure at least as "ever" or "never" exposed (Wang *et al.* 1996a;b; Kreuzer *et al.*, 1998; Nyberg *et al.*, 1998a; Zaridze *et al.*, 1998; Zhong *et al.*, 1999; Lee *et al.*, 2000; Wang *et al.*, 2000; Johnson *et al.*, 2001). The pooled European estimate found elevated, non-significant risk, similar to the spousal risk estimates, for "ever" exposed [adjusted OR 1.17 (95% CI 0.94-1.45)] for both sexes or among women only [adjusted OR 1.19 (95% CI 0.94-1.51)] (Boffetta *et al.*, 1998). Among the three individual European case-control studies reporting "ever" workplace exposure estimates, one was non-significantly below null [adjusted OR 0.88 (95% CI 0.55-1.41)](Zaridze *et al.*, 1998), one was slightly elevated, particularly among women [adjusted OR 1.14 (0.83-1.57)] (Kreuzer *et al.*, 1998), and the third study was non-significantly elevated for both genders [adjusted OR 1.61 (95% CI 0.91-2.85)] (Nyberg *et al.*, 1998a). One population-based case-control study from China reported a statistically elevated lung cancer risk with workplace exposure ("ever") [adjusted OR 1.7 (95% CI 1.3-2.3)]. The hospital-based binomial risk variable estimates from China ranged from 0.89

to 1.90 (Wang *et al.*, 1996a,b; Lee *et al.*, 2000), with only the crude unadjusted estimate from Wang *et al.* (1996a) being statistically significant ($p<0.05$).

Limited evidence for a dose-response trend for increasing lung cancer risk with increasing duration of workplace exposure (by various indices) was observed in the Canadian population study (Johnson *et al.*, 2001), two European population studies (Nyberg *et al.*, 1998a; Kreuzer *et al.*, 1998), and the pooled European study (Boffetta *et al.*, 1998). Johnson *et al.* (2001) found increasing lung cancer risk estimates after eight years of workplace exposure measured in years [1-7: adjusted OR 1.24 (95% CI 0.5-2.8); 8-19: adjusted OR 1.71 (95% CI 0.7-4.3); ≥20: adjusted OR 1.71 (95% CI 0.7-4.3)] or smoker-years [1-23: adjusted OR 1.16 (95% CI 0.4-3.1); 24-47: adjusted OR 1.98 (95% CI 0.8-4.9); ≥48: adjusted OR 1.58 (95% CI 0.6-4.0)]. Using duration of exposure indices of total exposure in both hours and hours weighted by subjective ordinal of "smokiness", Kreuzer *et al.* (1998) reported that risk increased significantly, particularly for nonsmoking women (versus estimates for both sexes combined). Among women categorized in the intermediate and high exposure groups (>29,000-61,000 total hours, >61,000 total hours), lung cancer risk increased significantly with increasing hours relative to the no/low exposure group (p for trend 0.01) [adjusted ORs 1.85 (95% CI 0.96-3.54) and 2.70 (95% CI 1.01-7.18), respectively]. Finally, the study of Nyberg *et al.* (1998a) also reported increasing risk estimates with total ETS years at work [<30 years: adjusted OR 1.40 (95% CI 0.76-2.56); ≥30 years: adjusted OR 2.21 (95% CI 1.08-4.52)] and total weight duration ("hour-years") [<30 HY: adjusted OR 1.27 (95% CI 0.69-2.34); ≥30 HY: adjusted OR 2.51 (95% CI 1.28-4.93)].

Two meta-analyses of lung cancer risk from workplace ETS that were published subsequent to the Cal/EPA review in 1997 yielded similar non-significantly elevated overall rate ratios. Tweedie *et al.* (1996), using innovative Bayesian meta-analysis methods, estimated the rate ratio to be 1.12 (95% CI 0.93-1.28), based on 10 epidemiological studies. Merletti *et al.* (1998) estimated the rate ratio to be 1.14, 95% CI 0.98-1.33, using traditional meta-analysis methods (Tweedie *et al.*, 1996; Boffetta *et al.*, 1998). There was considerable overlap in studies included in the two meta-analyses of workplace exposure.

As with earlier studies, indicators of workplace ETS exposure may have varied substantially across studies, with often limited information provided on the specific occupational data obtained (Cal/EPA, 1997). However, studies generally identified elevated, non-significant risks, increasing with estimates for cumulative years of occupational ETS exposure (Boffetta *et al.*, 1998; Nyberg *et al.*, 1998a; Kreuzer *et al.*, 2000; Johnson *et al.*, 2001). Some of the earlier non-positive meta-analyses were affected by exposure estimation inconsistencies and errors in reporting the underlying studies, or inappropriate weighting factors applied in the meta-analyses, as described in detail by Wells and Henley (1997) and Wells (1998b). Several published meta-analyses on workplace ETS and lung cancer have reported pooled risk estimates between 1.0 and 1.6, varying substantially by the inclusion criteria and extracted risk estimates utilized (summarized in Wells, 1998b). Previously OEHHA concluded that workplace ETS exposure also increases the risk of lung cancer (Cal/EPA, 1997). More recent primary studies also support this conclusion despite difficulties in obtaining estimates of lifetime occupational exposure.

Table 7.2D Studies on ETS exposure at the workplace and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Johnson *et al.* (2001)				OR
Case-control	Occupational	Never exposed	10/135	1.0 (Referent)
Canada	years[a]:	Residential only	23/253	1.21 (0.5-2.8)
Population		1-7	10/131	1.24 (0.5-3.3)
		8-19	14/125	1.71 (0.7-4.3)
		≥ 20	14/117	1.71 (0.7-4.3)
				OR[b]
	Occupational	Never exposed	10/135	1.0 (Referent)
	smoker-	Residential only	23/253	1.21 (0.5-2.8)
	years:	1-23	10/126	1.16 (0.4-3.1)
		24-47	14/120	1.98 (0.8-4.9)
		≥ 48	14/127	1.58 (0.6-4.0)
Wang *et al.* (1996a)				OR (Crude)[c]
Case-control, China	Passive smoking	Total	Not presented	1.90 (p<0.05)
Hospital Based	at work:	Male		2.10 (p>0.05)
Wang *et al.* (1996b)	Workplace exposure ETS			OR (Crude)[d]
Case-control, China	Non-smoking women		113/115	0.89 (0.45-1.77)
Hospital Based				
Zhong *et al.* (1999)				OR[e]
Case-control	Workplace ETS:	Adult only	22/24	1.9 (0.9-3.7)
China		Childhood and Adult	24/29	1.7 (0.9-3.4)
Population Non-smoking women.	Exposed at work:	No	474/368	1.0 (Referent)
		Yes	127/136	1.7 (1.3-2.3)
	Number hours per day:	1-2	48/30	1.0 (0.6-1.7)
		3-4	49/45	1.6 (1.0-2.5)
		> 4	30/61	2.9 (1.8-4.7)
				p trend<0.001
	Number of years	1-12	35/43	2.0 (1.2-3.3)
		13-24	49/48	1.4 (0.9-2.3)
		> 24	43/45	1.8 (1.1-2.8)
				p trend=0.50
	Number co-workers	1-2	56/37	1.0 (0.6-1.6)
	Smoked:	3-4	41/42	1.7 (1.1-2.8)
		> 4	30/57	3.0 (1.8-4.9)
				p trend<0.001

[a] ORs adjusted for age, province, education and total fruit/vegetable consumption. ORs are from Table III of Johnson *et al.* (2001).

[b] Sum over the subject's lifetime of occupational exposure (i.e. number of employees smoked regularly in immediate work multiplied by the number of years in that job. ORs from Table III of Johnson *et al.* (2001), adjusted for age, province, education and total fruit/vegetable consumption.

[c] Unadjusted OR from Table 2, Wang *et al.* (1996a).

[d] Unadjusted OR from Table 1, Wang *et al.* (1996b)

[e] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history lung cancer, high-risk occupations, and residential ETS, from Tables 2 and 5 Zhong *et al.* (1999).

Table 7.2D Studies on ETS exposure at the workplace and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Lee *et al* (2000)[f]	Workplace exposure			
Case-control	Co-workers:	Non-smoker	236/400	(Referent)
Taiwan, Hospital Based		Absence	12/24	0.7 (0.3-1.5)
		Presence	21/12	1.2 (0.5-2.4)
Boffetta *et al.* (1998)				OR[g]
Pooled Case-control	Workplace Ever:	No	276/687	1.00 (Referent)
Multiple Country		Yes	374/855	1.17 (0.94-1.45)
	Women Only:	No	240/535	1.00 (Referent)
		Yes	269/476	1.19 (0.94-1.51)
	Exposure duration (years):	1-29	278/634	1.15 (0.91-1.44)
		30-38	55/129	1.26 (0.85-1.85)
		≥ 39	39/91	1.19 (0.76-1.86)
				p trend=0.21
	Women Only:	1-29	211/399	1.14 (0.89-1.47)
		30-38	37/47	1.50 (0.93-2.43)
		≥ 39	20/29	1.24 (0.67-2.28)
				p trend=0.10
	Exposure duration (index level × hr/day × yrs)	0.1-46.1	196/525	0.97 (0.76-1.25)
		46.2-88.9	47/105	1.41 (0.93-2.12)
		≥ 89.0	48/71	2.07 (1.33-3.21)
				p trend<0.01
Nyberg *et al.* (1998a)				OR[h]
Case-control	Exposed at work:	Never	27/69	1.00 (Referent)
Sweden[*]		Ever	97/166	1.61 (0.91-2.85)
	Total duration ETS at work:	Unexposed	27/69	1.00 (Referent)
		< 30 years	66/130	1.40 (0.76-2.56)
		≥ 30 years	31/36	2.21 (1.08-4.52)
	Total weighted duration ETS at work("hour-years")	Unexposed	27/69	1.00 (Referent)
		< 30 HY	57/120	1.27 (0.69-2.34)
		≥ 30 HY	40/45	2.51 (1.28-4.93)
Zaridze *et al.* (1998)	Colleagues' smoking			OR[i]
Case-control	No		291/153	1.00 (Referent)
Russia	Yes		67/36	0.88 (0.55-1.41)

[f] Appears some case overlap with Ko *et al.* (1997); ORs from Table 3 Lee *et al.* (2000); adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor. Smoker in the presence of passive smokers were classified as "presence", otherwise reported as "absence", Lee *et al.* (2000).

[g] ORs adjusted for age and sex-study center interaction from Table 4 Boffetta *et al.* (1998).

[*] Included in Boffetta *et al.* (1998).

[h] Both genders combined, ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations Tables 2 and 3 Nyberg *et al.* (1998a).

[i] ORs adjusted for age and education Table 3 Zardize *et al.* (1998a).

Table 7.2D Studies on ETS exposure at the workplace and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Kreuzer *et al.* (2000;1998)				OR[k]
Case-control	Ever exposed:	No	131/491	1.00 (Referent)
Germany[*]		Yes	161/847	1.03 (0.78-1.36)
	Women only	No	111/258	1.00 (Referent)
		Yes	123/277	1.14 (0.83-1.57)
	Exposure duration (hours):	0-29,000	247/1,101	1.00 (Referent)
		> 29,000-61,000	26/127	1.57 (0.97-2.54)
		> 61,000	13/87	1.36 (0.71-2.61)
				p trend=0.10
	Women only	0-29,000	203/497	1.00 (Referent)
		> 29,000-61,000	17/26	1.85 (0.96-3.54)
		> 61,000	9/8	2.70 (1.01-7.18)
				p trend=0.01
	Weighted duration[kj]:	0-56,200	199/873	1.00 (Referent)
		> 56,200-100,600	11/77	1.09 (0.55-2.19)
		> 100,600	17/55	1.93 (1.04-3.58)
				p trend=0.06
	Women only	0-56,200	162/385	1.00 (Referent)
		> 56,200-100,600	6/15	1.09 (0.41-2.91)
		> 100,600	13/12	2.52 (1.12-5.71)
				p trend=0.04

[*] Included in Boffetta *et al.* (1998)

[j] Weighted duration of exposure (hours × level of smokiness)

[k] ORs adjusted for sex, age and region Table 2 Kreuzer *et al.* (1998).

7.2.5.4. ETS Exposure in Other Settings

Table 7.2E summarizes data on ETS exposure from multiple settings available from seven studies. Among these more recent studies, few estimated exposure and/or lung cancer from other settings, such as public transit or other social settings (Jockel *et al.*, 1998). However, two did combine residential and occupational exposure (Boffetta *et al.*, 1998; Johnson *et al.*, 2001) or also combined these with other sources (Jockel *et al.*, 1998; Kreuzer *et al.*, 1998). In the pooled analysis (Boffetta *et al.*, 1998), the simple binomial combined variable was not substantially different from the spousal estimate [adjusted OR 1.14 (95% CI 0.88-1.47)]. However, the exposure duration variable for spousal/workplace combined (in hours/day × years) gave evidence of a trend in increasing risk with increasing exposure (p=0.01). The Canadian case-control study observed a similar trend for residential plus occupational years or smokers-years (p=0.05) (Johnson *et al.*, 2001).

In Jockel *et al.* (1998), the risk estimate for other ETS sources, a combination of workplace, transit and other, increased with increasing exposure [no/low: OR 1.0 (referent); intermediate: adjusted OR 1.44 (95% CI 0.47-4.45); high: 3.10 (95% CI 0.89-5.89)]. A similar increase in risk with estimated ETS dose was also observed with total ETS exposure, including spousal and childhood [intermediate: adjusted OR 0.87 (95% CI 0.36-2.07); high: 3.24 (95% CI 1.44-7.32)]. Note that the OR for 'high' exposure is statistically significant. Kreuzer *et al.* (1998) found a significant dose response trend with weighted exposure or weighted duration among women only, with statistically significant adjusted ORs in the highest exposed women at 2.70 (95% CI 1.01-7.18) and 2.52 (95% CI 1.12-5.71), respectively.

Table 7.2E. Studies on ETS exposure in multiple settings and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Johnson *et al.* (2001)	Residential plus	Never exposed	10/135	1.0 (Referent)
Case-control	occupational yrs[a]:	1-24	18/206	1.46 (0.6-3.5)
Canada		25-45	21/213	1.40 (0.6-3.3)
Population		≥ 46	22/207	1.35 (0.6-3.2)
	Residential plus	1-36	12/205	0.83 (0.3-2.1)
	occupational	37-77	24/214	1.54 (0.7-3.5)
	smoker-yrs[b]:	≥ 78	25/207	1.82 (0.8-4.2)
				p value 0.05
Zhong *et al.* (1999)	ETS at work and home			OR[c]
Case-control, China		Adulthood only	33/36	1.9 (1.1-3.5)
Non-smoking women.		Childhood and adulthood	48/47	1.6 (0.9-2.7)
Lee *et al.* (2000)[d]	Adult life exposure[e]	None	97/227	1.0 (Referent)
Case-control		1-20	22/42	1.3 (0.7-2.5)
Taiwan		21-40	64/100	1.5 (0.9-2.4)
Hospital Based		> 40	85/76	2.6 (1.6-4.2)
				p trend=0.001
	Lifetime exposure [f]	None	79/196	1.0 (Referent)
		1-20	16/33	1.3 (0.6-2.6)
		21-40	54/90	1.6 (0.9-2.6)
		41-60	43/59	2.0 (1.2-3.5)
		> 60	76/67	2.8 (1.6-4.8)
				p trend=0.001
Boffetta *et al.* (1998)	Spousal and Workplace			OR[g]
Pooled Case-control	Total	No	122/339	1.00 (Referent)
Multiple Country		Yes	527/1201	1.14 (0.88-1.47)
	Women Only	No	88/198	1.00 (Referent)
		Yes	420/811	1.15 (0.86-1.55)
	Exposure duration	None	122/339	1.00 (Referent)
	(hrs/day x yrs)	0-165	289/749	0.91 (0.69-1.20)
		166-253	63/151	1.31 (0.88-1.94)
		> 254	57/101	1.46 (0.96-2.22)
				p trend=0.01

[a] ORs adjusted for age, province, education and total fruit/vegetable consumption.

[b] Sum over the subject's lifetime of residential exposure (i.e. number of regular residential smokers multiplied by the number of years in that home). ORs from Table III of Johnson *et al.* (2001), adjusted for age, province, education and total fruit/vegetable consumption.

[c] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history lung cancer, and high-risk occupations, from Tables 2 and 5 Zhong *et al.* (1999).

[d] Appears case overlap with Ko *et al.* (1997).

[e] Home and workplace adult exposure ORs from Table 4 Lee *et al.* (2000), adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor.

[f] As above but included childhood exposure.

[g] ORs adjusted for age and sex-study center interaction from Table 5 Boffetta *et al.* (1998).

Table 7.2E. Studies on ETS exposure in multiple settings and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Jockel *et al.* (1998)	All adult ETS exposure excluding			
Case-control	spousal (Workplace, transit, other):			OR[h]
Germany		No/low	131/41	1.00 (Referent)
		Intermediate	18/5	1.44 (0.47-4.45)
		High	11/9	3.10(1.12-8.60)
	Total exposure (child/adult,			
	spousal, work, other):	No/low	101/29	1.00 (Referent)
		Intermediate	38/9	0.87 (0.36-2.07)
		High	21/17	3.24 (1.44-7.32)
Kreuzer *et al.* (2000;1998)	ETS All Sources			OR[J]
Case-control	Exposure duration	0-29,000	247/1,101	1.00 (Referent)
Germany*	(hours):	> 29,000-61,000	26/127	1.57 (0.97-2.54)
		> 61,000	13/87	1.36 (0.71-2.61)
				p trend=0.10
	Women only:	0-29,000	203/497	1.00 (Referent)
		> 29,000-61,000	17/26	1.85 (0.96-3.54)
		> 61,000	9/8	2.70 (1.01-7.18)
				p trend=0.01
	Weighted duration[i]	0-56,200	199/873	1.00 (Referent)
		> 56,200-100,600	11/77	1.09 (0.55-2.19)
		> 100,600	17/55	1.93 (1.04-3.58)
				p trend=0.06
	Women only	0-56,200	162/385	1.00 (Referent)
		> 56,200-100,600	6/15	1.09 (0.41-2.91)
		> 100,600	13/12	2.52 (1.12-5.71)
				p trend=0.04
Enstrom and Kabat (2003)	Spousal smoking			RR[K] for death
United States	Men:	formerly smoking spouse		0.82 (0.29-2.26)
		currently smoking spouse		0.57 (0.26-1.26)
	Women:	formerly smoking spouse		1.04 (0.69-1.57)
		currently smoking spouse		0.88 (0.60-1.28)
		ever smoking spouse		0.94 (0.66-1.33)

[h] ORs adjusted for sex, age and region, Table 3 Jockel *et al.* (1998).
[i] Weighted duration of exposure (hours x level of smokiness).
[j] ORs adjusted for age, sex and region from Table 4 Kreuzer *et al.* (2000).
[k] Adjusted at baseline for age, race, education, exercise, BMI, urbanization, fruit or juice intake, health status.

7.2.6. Summary of ETS and Lung Cancer

Since the previous OEHHA review (Cal/EPA, 1997), numerous epidemiological studies and several meta-analyses (Mengersen, 1995; Law and Hackshaw, 1996; Rundle *et al.*, 2002; Hackshaw *et al.*, 1997; Hackshaw, 1998; Wells, 1998b; Boffetta *et al.*, 1998; Taylor *et al.*, 2001) have continued to examine the association between passive smoking and lung cancer. The rate ratio estimates from Taylor *et al* (2001) are presented in Figure 7.2.1. Unfortunately, only two additional U.S. based studies were available for review. In contrast to many earlier studies, the majority of recent primary studies, specifically the population-based studies on spousal ETS, addressed issues of small sample size, possible selection bias, misclassification biases, and inadequate adjustment for potential confounders, including adjustment for dietary factors.

Although arguments may still be made regarding the extent of the effect on cancer risk estimates due to the potential misclassification of smoking status (Hackshaw *et al.*, 1997; Hackshaw, 1998; Lee, 1998), in combination with studies described in the earlier OEHHA report (Cal/EPA, 1997), these recent studies provide additional evidence that ETS exposure is causally associated with lung cancer. They consistently report elevated and often significant risk estimates, particularly for women married to smokers. Results from the recent Canadian and European case-control studies are compatible not only with the previous pooled estimate of the U.S. EPA (1992c) report, summary RR of 1.19 (90% CI=1.04-1.35) for ever exposed to spousal ETS (for U.S. studies), but also with several recent meta-analyses, range RR 1.2-1.3 (Mengersen, 1995; Law and Hackshaw, 1996; Rundle *et al.*, 2002; Hackshaw *et al.*, 1997; Taylor *et al.*, 2001). In addition, several of the recent primary studies provided evidence of positive increasing trends in lung cancer risk in nonsmokers with increasing ETS exposure, with some but not all exposure indices of duration, daily amount, or cumulative dose, for both spousal and workplace exposures, as well as combined exposures.

Particularly in earlier studies, misclassification of exposure in the "unexposed" populations by not measuring lifetime exposure or exposure to sources other than spousal or residential would bias potential findings towards the null. Johnson *et al* (2001) developed a table of studies (Table IV, Johnson *et al.*, 2001) that evaluated lung cancer risk associated with spousal, occupational, and total passive smoking exposure in women who never smoked and included some form of quantitative adult lifetime residential and occupational assessment of ETS exposure. In Table 7.2F, we have taken the point estimates for the combined residential and occupational high exposure categories from these studies and created a weighting scheme by inverse variance (Rothman and Greenland, 1998). There was no difference in summary statistics found between a fixed or random effects models with both finding an OR of 1.8 (95% CI 1.5-2.2).

The conclusion that there is a causal association between ETS-exposure and lung cancer stated in the original OEHHA report (Cal EPA, 1997) is further strengthened by the new data.

Table 7.2F Lung cancer risk for high exposure categories, associated with total passive smoke exposure in never-smokers: Population-based studies that include quantitative adult lifetime residential and occupational assessment of ETS exposure.

Study	Weights fixed	Weights random	OR	Lower limit	Upper limit
Fontham *et al.*, 1994	20.72	20.02	1.74	1.14	2.65
Boffetta *et al.*, 1998	18.06	14.68	1.54	0.97	2.44
Nyberg *et al.*, 1998a	8.53	7.69	2.52	1.28	4.9
Jockel *et al.*, 1998	5.81	5.41	3.24	1.44	7.32
Zhong *et al.*, 1999	17.60	14.38	1.8	1.1	2.8
Kreuzer *et al.*, 2000	28.14	20.71	1.39	0.96	2.01
Lee *et al.*, 2000	12.73	10.95	2.8	1.6	4.8
Wang *et al.*, 2000	12.73	10.95	1.51	0.9	2.7
Johnson *et al.*, 2000	5.59	5.22	1.82	0.8	4.2
Summary fixed effects			1.79	1.49	2.16
Summary random effects			1.82	1.48	2.24

Test for heterogeneity: Q = 8.171 on 7 degrees of freedom (p = 0.318). Der Simonian and Laird estimate of between studies variance = 0.013. Summary estimates based on fixed and random effects models with 95% confidence intervals. Weighting by inverse variance. Based on table IV in Johnson *et al.* (2001)

7.2.6.1. Deaths and Incident Cases of Lung Cancer Attributable to ETS

The U.S. EPA (1992c) method of estimating attributable lung cancer deaths was applied to estimate lung cancer attributable risk using updated exposure and population-at-risk inputs. This method and the inputs to the model are described in Appendix B at the end of Chapter 7.

The calculation, based on the equations of U.S. EPA (1992c), apportions the overall number of lung cancer deaths into four categories: (1) deaths in mainstream smokers and former smokers, (2) ETS-attributable deaths in nonsmokers exposed to spousal smoking, (3) ETS-attributable deaths in non-smokers not exposed to spousal smoking, and (4) deaths not related to tobacco smoke.

The equations (described in Appendix B at the end of Chapter 7) use the assumption that risk is linear in dose, as specified in the NRC (1986f) model for relative risk in epidemiology studies:

$$R(d_E) = (1 + Z * ßd_N)/(1 + ßd_N)$$

where $R(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS). Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N. ß is the amount of increased risk per unit dose.

We estimate that for the nation in 2003, the number of ETS-attributable lung cancer deaths associated with spousal smoking for both genders combined is in the range of 3423 to 8866. In the summary table in the Executive Summary (Table ES-2), we only include the lower number as it is based on a relative risk estimate obtained in the best U.S. study which quantified exposure on the basis of cotinine levels (Fontham *et al*., 1994), and is also similar to the pooled estimate from the majority of the meta-analyses. The deaths among males are lower than among females reflecting the lower proportion of non-smoking males with spousal exposure. On the other hand, this analysis does not address ETS exposure at work or in other venues that may be generally higher for males than for females.

The number of ETS-attributable lung cancer deaths in Californian may be crudely estimated by taking California's population as 12% of the national population, and assuming the same rates of exposure to active and spousal smoking. This would result in estimates for females and males, respectively, of 307 and 104 deaths. The total ETS attributable lung cancer deaths in California would thus be expected to be in the range of 411-1064.

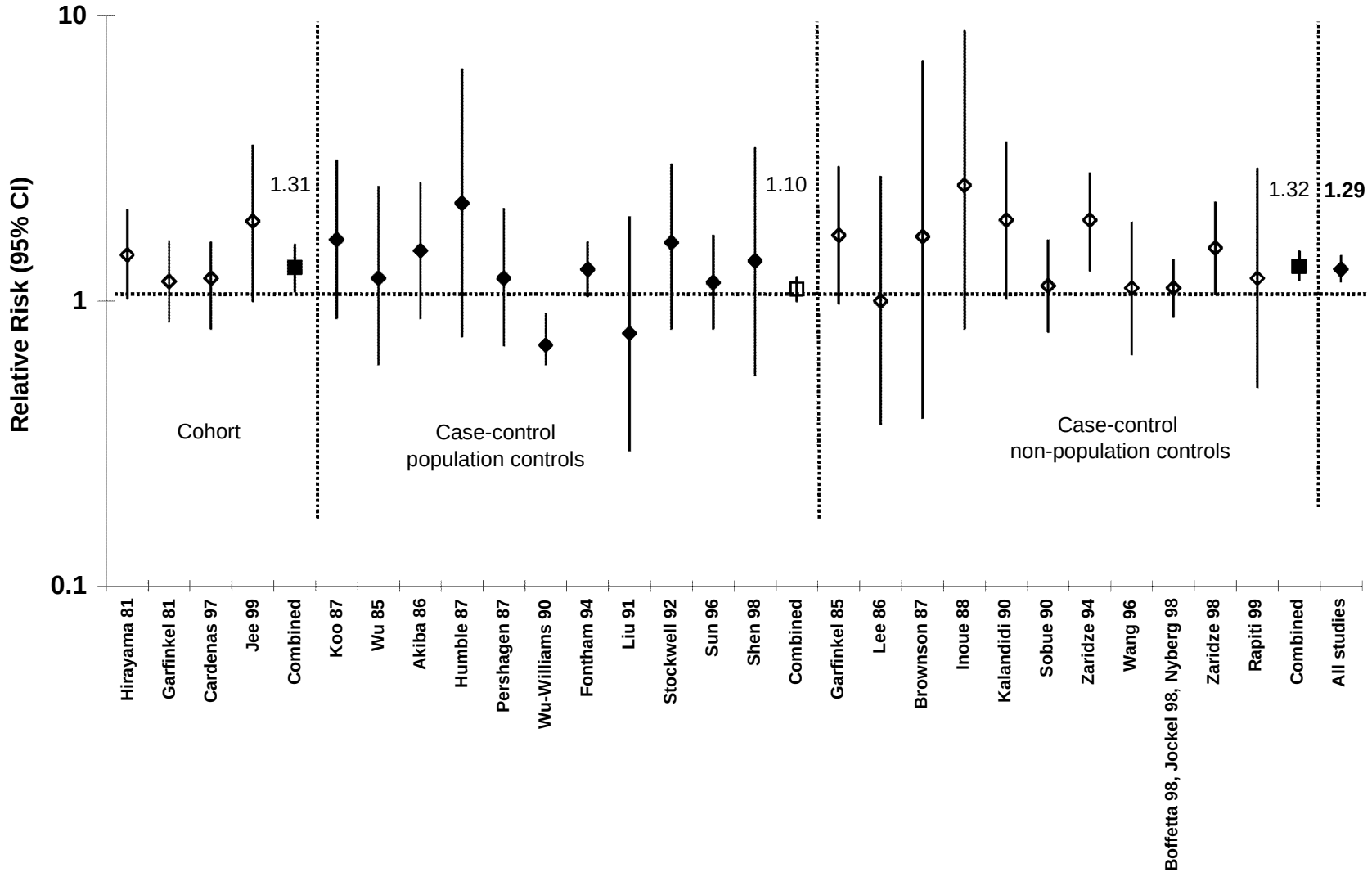


Figure 7.2.1. Lung Cancer Meta-analysis Based on Data from Taylor *et al.*, 2001

7.3. ETS and Cancer Sites Other than Lung that are Associated with Active Smoking: Nasal Sinus, Head and Neck, Cervical and Bladder

7.3.1. ETS and Head and Neck Cancer

7.3.1.1. ETS and All Cancers of the Head and Neck: Previous Studies

The Cal/EPA (1997) did not previously review any studies investigating the association between ETS exposure and cancers of the head and neck.

7.3.1.2. ETS and All Cancers of the Head and Neck: Recent Epidemiological Studies

As summarized in Table 7.3A, two hospital-based case control studies investigated the association between ETS exposure and the risk of malignancies of the head and neck (Tan *et al.*, 1997; Zhang *et al.*, 2000). Both studies included cases of squamous cell head and neck cancers (SCHNC) from a variety of anatomic sub-sites, including lip, tongue, gum, floor of the mouth, oropharynx, nasopharynx, hypopharynx, esophagus, and larynx.

Tan et al. (1997) identified 59 non-tobacco using cases and two sets of controls (853 cancer patients with squamous cell head and neck cancers (SCHNC) and 167 non-SCHNC, nonsmoking patients matched on age, race, sex and alcohol use). The risk estimates were elevated for spousal exposure to ETS [OR 2.80 ($p<0.006$)], workplace ETS [OR 10.16 ($p<0.001$)], or either [OR 5.34 ($p<0.001$)], comparing non-smoking SCHNC cases (all sites combined) to matched non-smoking controls (Table 7.3A). These relatively large risk estimates are impressive; however, the small study size, limited exposure assessment and lack of control for other potential confounders require additional study.

Zhang et al. (2000) included 173 pathologically confirmed cases of SCHNC and 176 cancer-free controls (identified blood bank). The risk of SCHNC was significantly associated with ETS exposure [crude OR 2.8 (95% CI 1.3-6.0)] declining to statistical non-significance after controlling for age, sex, race, education, alcohol, pack-years cigarette smoking and marijuana use [adjusted OR 2.4 (95% CI 0.9-6.8)]. Both adjusted and unadjusted ORs are consistent with Tan *et al.* (1997) noted above. Evidence of a dose-response was also observed [moderate: adjusted OR 2.1 (95% CI 0.7-6.1); heavy: adjusted OR 3.6 (95% CI 1.1-11.5)]. In the analysis restricted to non-active smokers elevated, but non-significant associations between ETS and SCHNC risk remained [crude OR 2.2 (95% CI 0.6-8.4)], again with some evidence of a dose-response [moderate: OR 1.8 (95% CI 0.5-7.3); heavy: OR 4.3 (95% CI 0.8-23.5), p for trend 0.008] (Table 7.3A). This study also is suggestive of a relationship between ETS exposure and SCHNC; however, the small number of nonsmokers and the residual influence of active smoking on the larger risk estimate decrease the study's utility.

Table 7.3A. Association between passive smoke exposure and risk of head and neck cancer in nonsmokers

Case Control Studies	Exposure to Passive Smoking (Cases/Controls)	Relative Risk OR (95% CI or p-value)		
Tan *et al.* (1997)		Total[a]	Male[a]	Female[a]
	Home (43/132)	2.80 (0.0006)	1.15 (0.79)	7.35 (<0.001)
	Workplace (38/128)	10.16 (<0.001)	11.63 (<0.001)	8.89 (0.002)
	Either (44/132)	5.34 (<0.001)	3.75 (0.015)	8.0 (<0.001)
Zhang *et al.* (2000)		Non-Smokers[a]	Adjusted ORs (Includes smokers and nonsmokers)[b]	
	ETS: Never[c]	1.0 (Referent)	1.0 (Referent)	
	Ever	2.2 (0.6-8.4)	2.4 (0.9-6.8)	
	Degree Never[c]	1.0 (Referent)	1.0 (Referent)	
	ETS: Moderate	1.8 (0.5-7.3)	2.1 (0.7-6.1)	
	Heavy[d]	4.3 (0.8-23.5)	3.6 (1.1-11.5)	
		p trend=0.0082	p trend=0.0249	
	ETS Never	1.0 (Referent)	1.0 (Referent)	
	Home: Occasionally	3.2 (1.0-10.4)	1.6 (0.8-3.3)	
	Regularly	1.5 (0.5-4.5)	1.7 (0.8-3.3)	
		p trend=0.4483	p trend=0.1574	
	ETS Never	1.0 (Referent)	1.0 (Referent)	
	Work: Occasionally	2.2 (0.7-6.9)	1.0 (0.5-2.1)	
	Regularly	1.5 (0.5-5.0)	1.0 (0.5-2.1)	
		p trend=0.4670	p trend=0.9240	
	Spousal No	1.0 (Referent)	1.0 (Referent)	
	Smoking: Yes	0.9 (0.2-5.2)	1.7 (0.8-3.7)	

[a]OR equals crude odds ratio
[b]Adjusted for age, race, education, heavy alcohol use, marijuana use, pack-years active smoking
[c]Never exposed to ETS at both home and work
[d]Regularly exposed to ETS at both home and work

7.3.1.3. Summary of ETS and All Cancers of the Head and Neck.

The evidence from these two hospital-based epidemiology studies of the association between ETS and malignancies of the head and neck, although suggestive, remains inconclusive. The two case-control studies found an elevated, but statistically non-significant increase for head and neck cancer risk associated with ETS exposure after adjustment for potential confounders. Both studies are limited by small case numbers, particularly by individual anatomic site and among non-smokers, meager exposure assessment, and selection bias in the hospital-based controls.

7.3.1.4. Nasal Sinus and Nasopharyngeal Cancer

7.3.1.4.1. Active Smoking and Nasal Sinus Cancer

Active, primary smoking is considered a significant causal factor for cancer of the nasal sinus cavity (IARC, 2004a), with highest risk estimates reported for heavy smoking, current tobacco use, and squamous cell carcinomas (Elwood, 1981; Strader *et al.*, 1988; Zheng *et al.*, 1992). For this update, no new primary studies were located.

7.3.1.4.2. ETS and Nasal Sinus Cancer: Previous Findings

Three studies, one cohort (mortality) and two case-control studies (one incidence, one mortality) were previously reviewed by OEHHA (Cal/EPA, 1997). One cohort reported a significant dose-dependent increasing risk of nasal sinus cancer deaths among nonsmoking women relative to husbands' smoking ($p<0.03$) (Hirayama, 1984). The two case-control studies reported elevated non-significant risk among nonsmoking spouses of smokers, both among women (Fukuda and Shibata, 1990) and men (Zheng *et al.*, 1993). These results led OEHHA to conclude that strong evidence exists that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults (Cal/EPA, 1997).

7.3.1.4.3. ETS and Nasal Sinus and Nasopharyngeal Cancers: recent data

No new studies were located that examined the association between ETS and nasal sinus cancer. Two recent case-control studies, one population-based and one hospital-based, reported a positive association between nasopharyngeal carcinoma (NPC) and ETS (Armstrong *et al.*, 2000; Yuan *et al.*, 2000). In contrast, two other case-control studies reported a null or negative association between ETS and NPC (Vaughan *et al.*, 1996; Cheng *et al.*, 1999).

Vaughan et al. (1996) conducted a population-based case-control study at five U.S. cancer registries. Of the 294 eligible cases diagnosed between 1987 and 1993, interviews were completed on 231 individuals, as well as 246 controls. Although strong positive dose-response between NPC and active cigarette smoking was reported, including an adjusted OR of 6.5 for current smokers at the highest dose level (60 pack-years), no association between NPC (differentiated squamous cell NPC) and exposures to ETS was identified in lifetime nonsmokers or former smokers. However, no data or results regarding ETS and NPC were presented in the published report.

Cheng et al. (1999) reported a Taiwanese hospital-based case-control study utilizing 375 histologically confirmed NPC cases and 327 community controls. In the case of active smoking, only slightly elevated but statistically non-significant adjusted risk estimates were reported for current smokers [OR 1.4 (95% CI 0.9-2.1)] or former smokers [OR 1.1 (95% CI 0.6-2.1)]. Among non-smokers, neither childhood nor adult ETS exposure was associated with an elevated risk of NPC [adjusted ORs 0.6 (95% CI 0.4-1.0) and 0.7 (95% CI 0.5-1.2), respectively] after adjustment for age, sex, race, education, and family history of NPC.

Armstrong et al. (2000) conducted a Malaysian-based hospital study (four radiotherapy centers) consisting of 282 of 530 eligible cases identified with histologically confirmed NPC between 1990 and 1992, in which cases consisted of both prevalent and incident cases. A large proportion of identified cases either died or were too ill to participate in the study (125; 24%). Smoking and other data were collected from cases and neighborhood controls via personal

interview. In non-smokers exposed to parental smoking during childhood, a significantly elevated NPC risk was identified [adjusted OR 2.28 (95% CI 1.21-4.28)] after adjustment for multiple dietary factors. However, ETS exposure due to spousal or other household smokers was not associated with elevated NPC risk (data not shown).

Yuan et al. 2000. This population-based case-control study in Shanghai, China consisted of 935 NPC cases and 1,032 community controls. A total of 1,110 histologically confirmed cases of NPC were reported to the Shanghai Cancer Registry between 1987 and 1991, with 935 (84%) participating in the final study. Smoking and other data were obtained during personal interview, with ETS exposure identified for childhood (≤ 18 years), residential adult and workplace exposure. In non-smokers, a significant increase in NPC risk was associated with lifetime ETS among women [adjusted OR 1.95 (95% CI 1.18-3.21)], but not men [adjusted OR 1.29 (95% CI 0.62-2.68)]. Additionally, in women, childhood ETS exposure was also significantly associated with elevated NPC risk, due to maternal smoking [adjusted OR 3.36 (95% CI 1.41-8.05)], paternal smoking [adjusted OR 2.95 (95% CI 1.41-6.19)], and other household smokers [adjusted OR 2.72 (95% CI 1.07-6.92)]. Evidence for a dose response between increasing NPC risk and number of cigarettes/day were observed for maternal (p=0.003) and paternal smoking (p=0.001). In adults, spousal and workplace ETS exposure was significantly associated with an elevated NPC risk among women [adjusted ORs 3.09 (95% CI 1.48-6.46; p=0.003) and 2.84 (95% CI 1.34-6.00; p=0.01), respectively], but not among men. Risk estimates were adjusted for age, sex, education, dietary factors, cooking smoke/fumes, occupational exposure to fumes, history of NPC and chronic ear/nose conditions.

7.3.1.4.4. Summary of ETS and Nasal Sinus and Nasopharyngeal Cancer

As previously determined by OEHHA, "the 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" (Cal/EPA, 1997). In the absence of newer studies on nasal sinus cancer, this conclusion remains unchanged. Regarding nasopharyngeal cancer, the results of the Yuan *et al.* (2000) study suggest a gender difference in cancer susceptibility in which females are more at risk for nasopharyngeal cancer after ETS exposure. For both males and females there is evidence of a dose-response for childhood exposure to both maternal and paternal smoking, although in males the confidence intervals included no effect. The study by Armstrong *et al.* (2000) did not find an association between nasopharyngeal cancer and ETS exposure in adulthood. However, there was a significant association between childhood exposure to parental smoking and subsequent nasopharyngeal cancer (OR 1.54; p = 0.04). This is consistent with the results of Yuan *et al.* for females and may indicate a developmental window of susceptibility. Thus the more recent studies are considered suggestive of a possible association between childhood ETS exposure and subsequent development of nasopharyngeal cancer.

7.3.2. Cervical Cancer

7.3.2.1. Active Smoking and Cervical Cancer

Epidemiological evidence for the association between active smoking and cervical cancer, both malignant, in situ and intraepithelial neoplasia (CIN), has been derived from a large number of studies (Winkelstein, 1990). Smokers have been found to have an approximately 2-fold

increased risk of cervical cancer. Other risk factors, particularly infection with human papilloma virus (HPV) or a surrogate of potential exposure to HPV (e.g., number of sexual partners or age at first intercourse), strongly influence risk estimates, requiring studies to adjust risk estimates accordingly (Cal/EPA, 1997).

Four additional primary studies were available for review, one cohort and three case-control (two nested in larger cohorts) (Engeland *et al.*, 1996; Deacon *et al.*, 2000; Hakama *et al.*, 2000; Kjellberg *et al.*, 2000). Two studies, Engeland *et al.* (1996) and Hakama *et al.* (2000), reported on active smoking and cervical cancer risk (invasive cancers), and the remaining two studies, Deacon *et al.* (2000) and Kjellberg *et al.* (2000), evaluated smoking exposure relative to risk for in situ cervical cancer (CIN 3), often considered a precursor of invasive cervical cancer. The three more recent studies accounted for other known risk factors, including sexual behavior and human papilloma virus infection (HPV).

Engeland et al. 1996. This Norwegian population-based cohort of 26,000 men and women was followed from 1966 to 1993 to investigate the relationship between smoking and multiple cancer sites. Smoking status was established by baseline questionnaire in 1964-1965. Cancer of the uterine cervix, 86 cases with 99% histologically confirmed, was significantly elevated among smokers compared to never smokers [RR 2.5 (95% CI 1.6-3.9)]; however, the study lacked data on HPV status and other potential confounders. No dose-response relationship was observed.

Deacon et al. 2000. This nested case-control study was conducted in the United Kingdom from a population-based cervical screening cohort. The study included 199 histologically confirmed cases of cervical neoplasia (CIN 3) in women known to be HPV positive (74% response), 181 other HPV positive women without CIN 3, and 203 HPV negative controls (66% response). Data on smoking, reproductive, sexual and other gynecological history were obtained via interview. Among HPV positive women, active smoking was significantly associated with an increased risk of CIN 3, with a significantly increasing trend ($p < 0.0001$) in risk with increasing smoking duration or amount (cigarettes per day, cpd) [1-10 cpd: 1.36 (95% CI 0.73-2.51); 11-16 cpd: 2.20 (95% CI 1.24-3.89); 17+ cpd: 3.06 (95% CI 1.77-5.31)]. No association was observed between smoking and HPV infection.

Hakama et al. (2000) conducted a nested case-control study from three cohorts of women (derived from serum banks) in Finland, Norway, and Sweden, with cancer cases identified through linkage with three population-based cancer registries. A total of 149 cases of squamous cell carcinoma (SCC) of the cervix and 442 controls were included in the analysis. HPV infection past or present was determined through serological analysis. Active smoking was measured via serum cotinine with smokers defined as those with a cotinine level 20 μg/mL or higher. The risk of squamous cell carcinoma was elevated among women seropositive for HPV, *Chlamydia trachomatis* and smoking. Among smokers, in the absence of either infectious agent, the OR for SCC was 1.8 (95% CI 1.1-3.0).

Kjellberg et al. (2000) reported on a population-based Swedish case-control study of 137 women with high-grade cervical neoplasia (CIN 2-3) and 253 matched controls. HPV infection was determined for both active infection (cervical brush samples) and past or present infections (seropositivity). Data on smoking, diet, health, sexual and reproductive history were collected via questionnaire. Active smoking was significantly associated with an elevated risk of CIN 2-3

[OR 2.6 (95% CI 1.7-4.0)]; additional adjustment for HPV status (whether current only or past/present) did not alter this association [ORs 2.5 (95% CI 1.3-4.9) and 3.0 (95% 1.9-4.7), respectively]. Evidence for a dose-response between increasing risk of cervical neoplasia and increasing levels of smoking was also reported (p for trend < 0.001).

7.3.2.2. ETS and Cervical Cancer: Previous Findings

In 1997, OEHHA reviewed one cohort (mortality) and three case-control studies, two of which were designed to investigate the role of smoking, active and passive, in the etiology of cervical cancer (Slattery *et al.*, 1989; Coker *et al.*, 1992). The two cervical cancer specific studies included incident cases and either population- or medical practice-based controls, however, only one included limited data on HPV infection status (surrogate measure as history of genital warts) (Coker *et al.*, 1992). The study lacking an estimate of HPV status (Slattery *et al.*, 1989) found significantly elevated adjusted risk estimates (age, education, number of sexual partners) for ETS exposure and cervical cancer risk. The second study found positive non-significant associations between ETS exposure and the risk of in situ cervical cancer for smoking by husbands [adjusted OR 1.5 (95% C.I. 0.9-6.2)] or others [adjusted OR 1.5 (95% C.I. 0.4-8.4)].

In combination with biochemical studies, the epidemiological evidence suggests the ETS exposure does potentially play a role in increasing cervical cancer risk; however, more studies specifically designed to look at recent/current exposures, exposures outside the home, as well as data on other etiological factors such as HPV infection, are required.

7.3.2.3. Recent Epidemiological Data on ETS and Cervical Cancer

Two new primary studies reporting on the relationship between ETS and cervical neoplasms were located. As part of their study on ETS and lung cancer, Jee *et al*. (1999) (described in Sections 7.2.3 and 7.4.1.5) reported no association between cervical cancer and the husband's smoking (RR 0.9, 95% CI 0.6-1.2). However, one U.S. population-based (large health maintenance organization) cross sectional study evaluated the role of cigarette smoking, both active and passive, on the occurrence of abnormal cervical cytology (Scholes *et al.* 1999). The study included women identified with Class 1 (with normal limits/benign changes) through Class 3 and 4 (mild or moderate dysplasia, CIN 1/2) cervical intraepithelial neoplasia (CIN); no severe dysplasia (CIN 3) or invasive cervical cancer cases were included. Smoking and other data were collected via telephone interview. ETS exposure was limited to spousal/partner smoking. A total of 4,053 women (71%) were interviewed, including 465 with Class 2 (19%) and 117 with Class 3-4 (5%) Pap results. After adjustment for lifetime number of sexual partners, age and age at first intercourse, non-smokers with spousal ETS exposure had an elevated risk of an abnormal (Class 2-4) Pap smear [adjusted OR 1.4 (95% CI 1.0-2.0)]. Similarly, current smokers also had an elevated risk of abnormal Pap smears [adjusted OR 1.4 (95% CI 1.1-1.8)].

Wu *et al*. (2003) investigated the association between ETS exposure and cervical intraepithelial neoplasms among nonsmoking women in Taiwan. The investigators used a community-based nested case-control design on the city of Chia-Yi in Taiwan. The study population consisted of women 19+ years of age participating in a Taiwanese government Pap smear screening program, which was free to participants. There were 420 women out of 32,466 who had newly diagnosed cervical intraepithelial neoplasia (CIN) that were category I or higher. Of 349 of these women

who were biopsied, 116 had definite lesions that exceeded the level II CIN. These women served as the cases. Two controls were assigned to each case, selected at random, and age-matched. Controls had negative pap smears within the same time period as cases and lived in the same area of Chia-Yi. Questionnaires were administered by public health nurses blinded to the hypothesis of the study (but not the case status of the subjects). Questionnaires asked about demographic characteristics, smoking status, history of ETS exposure, exposure to x-rays, hair dyes, sexual and reproductive history, history of cooking tasks and whether ventilated kitchens were used.

The authors defined active smokers as those who had smoked more than one cigarette per day for at least a year. Passive smokers were defined as subjects that had been exposed to the smoke of at least one cigarette per day for at least one year at home or at the workplace. ETS exposure was ascertained for childhood (< 20 yrs) and adulthood (>20 yrs of age). Questions were asked to determine the number of years of exposure, when exposure started or ended, and how many cigarettes were smoked in their presence each day. The investigators used the information to determine pack-years of ETS exposure. Multivariate conditional and unconditional logistic regression was used to explore the association between ETS and case or control status. The final model included controls for education, age at which intercourse first occurred, number of pregnancies, and cooking in unventilated kitchens. Active smokers were discarded from the analysis of ETS association leaving 89 case-control pairs of nonsmokers. ETS at home in adulthood was associated with cervical intraepithelial neoplasia (adjusted OR 2.73; 95% CI 1.31-5.67). There was an elevated but non-significant risk associated with ETS exposure in the workplace (adjusted OR 1.56; 95% CI 0.83-2.92). Childhood ETS exposure was not associated with the development of CIN. Risk was higher for less-educated women than for those with more than a high-school education. A dose-response trend was noted. The group who were exposed to 1-10 cigarettes/day had an OR of 2.13 (95% CI 0.96-4.73) and the OR for the group exposed to more than 10 cigarettes/day was 3.97 (95% CI 1.65-9.55) (p for trend = 0.002). Similarly, when measured as pack-years of ETS exposure, the OR for 1-20 pack-yr was 1.90 (95% CI 0.72-5.03), while the OR for >20 pack-yr was 2.99 (95% CI 1.10-8.09). One major limitation was a lack of information on HPV status. However, the authors note that Taiwanese women are much less sexually active prior to marriage than Western women as culturally virginity at marriage and fidelity in marriage are highly valued. In addition, there is evidence of a dose-response relationship for ETS; the HPV status would not necessarily track with extent of ETS exposure.

7.3.2.4. Biomarkers of Cervical ETS Exposure: Previous Studies

In 1997, OEHHA reviewed five cross-sectional clinical studies reporting the measurement of biological markers of exposure to tobacco smoke among non-smokers (Cal/EPA, 1997). Four studies reported on detectable levels of nicotine and cotinine in the cervical mucus of non-smokers (Sasson *et al.*, 1985; Hellberg *et al.*, 1988; Jones *et al.*, 1991; McCann *et al.*, 1992). Out of the three studies stratifying on the presence or absence of ETS, two reported no difference in levels among ETS exposed women (Hellberg *et al.*, 1988; McCann *et al.*, 1992), while the third reported higher levels of nicotine in women with ETS exposure (Jones *et al.*, 1991). Another, small study reported the presence of potentially tobacco-related DNA-adducts in the cervical epithelium of non-smoking women being surgically treated (hysterectomy or colposcopy) for benign disease (Simons *et al.*, 1993). However, no data on application of these methods to epidemiological investigations of ETS and cervical cancer were presented.

7.3.2.5. Biomarkers of Cervical ETS Exposure: Recent Studies

Two small recent studies measured the levels of carcinogen metabolites (Prokopczyk *et al.*, 1997) or adducts (Melikian *et al.*, 1999) in the cervical mucus or tissue; both studies compared levels between smokers and nonsmokers (see Table 7.3B). Melikian *et al.* (1999) characterized benzo[a]pyrene-related DNA adducts (BPDE) in the cervical tissue of 17 women (8 smokers, 9 nonsmokers). In epithelial tissue the mean adduct level was significantly higher in smokers relative to nonsmokers, with measured means of 3.5 versus 1.9 BPDE adducts/10^8 nucleotides, respectively (P=0.02). No difference in mean levels was observed in stromal tissue (mean 1.8 versus 1.4 adducts/10^8 nucleotides) among smokers and nonsmokers (p=0.48). Prokopczyk *et al.* (1997) compared the levels of a carcinogenic, tobacco-specific N-nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), in the cervical mucus of 14 smokers and 10 nonsmokers. NNK concentrations were significantly higher in smokers (mean 46.9 ng/g range 11.9-115.0 ng/g), relative to nonsmokers (13.0 ng/g, range 4.1-30.8 ng/g) (p=0.004). Although the number of subjects was limited, both studies further demonstrate the ability of tobacco-related metabolites and related-adducts to reach non-respiratory target sites, such as the cervix, indicating that such compounds could play a role in the etiology of cervical cancer.

Table 7.3B. Carcinogenic metabolites and adducts measured in the cervical mucus and cervical tissue of smokers and nonsmokers

Study	Measurement	Mean ± SD	
Melikian *et al.* (1999)	BPDE[a] adducts in cervical tissue	Epithelial tissue (adducts/10^8 nucleotides)	Stromal tissue (adducts/10^8 nucleotides)
Smokers (n = 8)		3.5 ± 1.06, p = 0.02[b]	1.8 ± 0.96, p = 0.48[b]
Nonsmokers (n = 9)		1.9 ± 1.27	1.4 ± 1.1
Prokopczyk *et al.* (1997)	NNK[a]	(ng/g)	
Smokers (n = 15)		46.9 ± 32.5, p = 0.004[b]	
Nonsmokers (n = 10)		13.0 ± 9.3	

[a] BPDE = 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-benzo[*a*]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
[b] Smokers vs. non-smokers.

7.3.2.6. Summary of ETS and Cervical Cancer

The current review agrees with the previous position that there is evidence suggestive of an association between ETS exposure and cervical cancer as stated by OEHHA in 1997 (Cal/EPA, 1997). Although no additional epidemiological studies on ETS exposure and cervical cancer were available for review, the studies on early cervical neoplasia (Scholes *et al.*, 1999; Wu *et al.*, 2003) indicate that, as with active smoking, ETS may have a role in the etiology of cervical cancer. Additional data on the timing of ETS exposure, the influence of confounding factors, particularly HPV infection, as well as utilization of biological markers of exposure and/or effect (e.g. cotinine or nicotine, bimolecular adducts), will be required to substantiate the magnitude of the potential cervical cancer risk due to ETS.

7.3.3. Bladder Cancer

7.3.3.1. Active Smoking and Bladder Cancer

Primary smoking has been well established as a significant cause of bladder cancer (IARC, 1986a). Relative risks for active smoking ranged between 2 to 10 across studies, with variation potentially due to difference in tobacco types and chemical content, as previously reviewed in the OEHHA report. Recent studies support that cigarette smoking significantly increases the risk of bladder cancer among both men and women (see below).

Several recently published case-control studies, including several large pooled European analyses (Brennan *et al.*, 2000, 2001; Fortuny *et al.*, 1999; Pitard *et al.*, 2001), one prospective cohort study (Zeegers *et al.*, 2002) and two U.S. population-based registry studies in Los Angeles (Castelao *et al.*, 2001) and in Iowa (Chiu *et al.*, 2001) further establish active tobacco smoking as a bladder carcinogen. The European pooled analyses reported risk estimates for smokers 2- to 6-fold higher compared to nonsmokers, with an increasing risk of bladder cancer by increasing duration (years) and amounts smoked among men (Brennan *et al.*, 2000; Pitard *et al.*, 2001) and women (Brennan *et al.*, 2001).

Castelao et al. 2001. In this Los Angeles case-control study, ever-active cigarette smokers had a statistically significant elevated risk of bladder cancer [OR 2.5 (95% CI 2.1-3.0)] with risk increasing among active smokers [OR 3.8 (95% CI 3.1-4.7)]. A significant dose-response relationship was observed between amount smoked daily and duration of smoking. Estimates increased substantially with estimation of joint effects of intensity (amount smoked per day) and duration (P interaction 0.016). For example, the bladder cancer risk associated with men smoking 20-39 cigarettes per day increased substantially with duration [<20 years: OR 1.52 (95% CI 1.05-2.21); 20-39 years: OR 2.72 (95% CI 2.10-3.52); ≥40 years: OR 4.87 (3.46-6.84)]. Similar results were observed among women [<20 years: OR 2.65 (95% CI 1.50-4.66); 20-39 years: OR 4.33 (95% CI 2.58-7.27); ≥40 years: OR 4.33 (95% CI 2.02-9.26)]. This study confirmed earlier reports that active smoking increases the risk of bladder cancer, and that the duration and intensity of cigarette smoking increase the risk of bladder cancer.

Chiu et al. 2001. In this Iowa case-control study, there were 1,406 bladder cancer cases and controls with available smoking data (obtained via mailed questionnaire). Individuals were classified as never-smokers if lifetime tobacco use did not exceed 6 months. Risk estimates for bladder cancer were adjusted for age, total dietary energy intake, occupation, vegetable intake, coffee intake, bladder infection and family history of bladder cancer. This study identified risk estimates for "ever" smoking of similar order as the Los Angeles study (Castelao *et al.*, 2001) [ORs 2.5 (95% 2.0-3.1) and 2.7 (95% CI 2.0-3.6), for men and women, respectively]. Bladder cancer risk among current smokers increased with cumulative dose (pack-years) among men [<20 years: adjusted OR 3.9 (95% CI 2.1-7.1); 20-39 years: adjusted OR 2.7 (95% CI 1.7-4.3); >40 years: adjusted OR 4.6 (95% CI 3.4-6.3)] and women [<20 years: adjusted OR 2.1 (95% CI 1.0-4.5); 20-39 years: adjusted OR 4.3 (95% CI 2.6-7.1); >40 years: adjusted OR 4.5 (95% CI 2.8-7.1)].

The strengths of this study, such as the population-based nature of this study, including population-based controls, the relatively high response rate (>85%), and the adjustment for

several potential confounders, provides substantial evidence for an association between active smoking and bladder cancer.

Zeegers et al., 2002. This study, investigating the association between active and passive smoking and bladder cancer, is based on a prospective cohort study of diet and cancer in the Netherlands. The authors employed a case-cohort approach in which the 619 incident cases of bladder cancer were derived from the entire cohort (n = 120,852) while a sub-cohort of 3,346 was followed from 1986 to 1992 for vital status information. At baseline, the study population of 55-69 year old men and women completed self-administered questionnaires on cancer risk factors. The data collected included age at first and last exposure to smoking, smoking frequency and duration, tobacco form (cigarette, pipe, cigar), and cigarette brand and type (filtered or not). ETS exposure was determined from questions on the smoking habits of parents and spouses, as well as from data regarding work and "private" exposures. Risks were estimated using exponentially distributed failure time regression models. A large number of potential confounders were considered but only those that altered the risk of bladder cancer by more than 10% were incorporated into the final model. For this reason, the RRs reported were adjusted only for age and gender.

As reflected in Table 7.3C, compared to never smoking, active smoking was significantly associated with bladder cancer incidence with significant dose-response trends measured either as cigarettes per day or duration of exposure. In addition, younger age at first exposure was associated with increased risk. There was also a significant trend of decreasing risk with increasing time since smoking cessation.

Table 7.3C. Active Smoking and Risk of Bladder Cancer

Smoking feature	Cases in cohort	Person-years	RR	95% CI
Never	55	7,276	1.0	
Ex-smoker	263	7,001	2.1	1.5-3.0
Current	282	5,664	3.3	2.4-4.0
Cigarettes/day				
< 5	30	1,488	1.8	1.1-2.9
5 -<10	59	1,826	2.4	1.6-3.7
10 -<15	87	2,463	2.2	1.5-3.3
15 -<20	93	1,780	3.4	2.3-5.0
20 -<25	120	2,329	3.2	2.2-4.7
≥25	115	1,900	3.7	1.5-5.4
		trend	p < 0.01	
Duration (yrs)				
<10	10	632	1.4	0.68-2.9
10-<20	39	1,592	1.8	1.1-2.8
20-<30	63	2,506	1.7	1.1-2.6
30-<40	125	3,213	2.7	1.9-3.9
40-<50	220	3,807	3.4	2.4-4.8
≥50	79	565	5.4	3.5-8.5
		trend	p <0.01	
Cessation (yrs)				
<1	295	5,821	3.4	2.5-4.7
1-<10	112	2,240	2.9	2.0-4.3
10-<20	71	2,324	1.7	1.1-2.5
20-<30	54	1,527	1.9	1.2-2.9
≥30	11	723	0.81	0.4-1.6
		trend	p <0.01	

7.3.3.2. ETS and Bladder Cancer: Previous Findings

In the previous OEHHA report (Cal/EPA, 1997) two case-control studies reporting on the association between ETS exposure and bladder cancer were reviewed (Kabat *et al.*, 1986; Burch *et al.*, 1989). Neither study demonstrated a significantly increased risk associated with ETS exposure. Both studies had limited power due to small sample sizes and poor ETS exposure measurements, leading to the conclusion that the epidemiological evidence for a relationship between ETS and bladder cancer remains inadequate.

7.3.3.3. ETS and Bladder Cancer: Recent Studies

Zeegers et al., 2002. This study was described in the previous section. Exposure to parental smoking or high levels of ETS at work elevated bladder cancer risk but not significantly (1.2, 95% CI 0.56-2.4 and 1.4, 95% CI 0.70-2.6, respectively). There was no evidence of an association between ETS exposure from an ex- or current smoking partner. This is in contrast to

the highly significant association this study found for the association between active smoking and bladder cancer. It is questionable, however, how unexposed the reference population is since the estimate for work exposure compares "high" versus "low" ETS rather than ETS exposure with no exposure. The estimates based on partner smoking status (never, ex, current) do not reflect other potential sources of ETS. A more complete evaluation of actual ETS exposure is needed to adequately address the question of the role of ETS exposure in bladder cancer.

7.3.3.4. Biomarkers of Bladder Carcinogens from ETS Exposure: Previous Findings

OEHHA previously described two cross sectional studies reporting concentrations of hemoglobin adducts of 4- and 3-aminobiphenyl (4- and 3-ABP), two indicators of exposure to tobacco smoke, among non-smokers (Bartsch *et al.*, 1990; Maclure *et al.*, 1989). Both studies demonstrated a positive association between reported ETS exposure and adduct concentrations (Cal/EPA, 1997).

7.3.3.5. Biomarkers of Bladder Carcinogens from ETS Exposure: Recent Data

No new primary studies were located.

7.3.3.6. Summary of ETS and Bladder Cancer

As stated in the previous OEHHA report (Cal/EPA, 1997), the evidence from the epidemiological studies of ETS and bladder cancer remains inconclusive. The two ETS specific case-control studies in the previous document and the cohort study cited here found no significant increased bladder cancer risk associated with exposure; serious limitations existed in these studies. However, the biochemical evidence from two biomarker studies was more suggestive of a potential association. Both studies identified higher levels of hemoglobin adducts of the bladder carcinogen 4-aminobiphenyl in nonsmokers 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 Previous Reviews Have Concluded that Evidence for the Role of Active Smoking is Supportive or Equivocal for Causation: Breast, Stomach, Brain, Leukemia, Lymphomas and Non-Hodgkin's Lymphomas, Other Rare Childhood Cancers

7.4.1. Breast Cancer

7.4.1.1. Active Smoking and Breast Cancer

7.4.1.1.1. Introduction and Previous Findings

Although a number of studies investigating the association between active smoking and breast cancer were available for review in the previous OEHHA report, the overall results were inconclusive, with the majority of studies finding no association or a weak usually statistically non-significant positive association (Cal/EPA, 1997).

As outlined in the previous report, the ability to reach a consistent conclusion is inhibited by various weaknesses found in many older studies. These include bias in the selection of cases and controls from either hospitals (potentially biasing risk downward since controls may have ETS related disease and therefore higher than background exposure) or breast cancer screening programs (potentially biasing risk upward since self selection for screening may select those with lower ETS exposure). Additionally, the older studies of active smoking and breast cancer risk often compare smoking women, whether ever or current smokers, with nonsmoking women regardless of exposure to ETS, and often lack adjustment for other known risk factors (i.e., menstrual and reproductive factors, family history, alcohol intake, social class). When only studies that utilize a never active/never passive exposed reference group are examined, a stronger association between both active and passive smoke exposure and breast cancer is evident (see discussion in Section 7.4.1.4. and 7.ApA.2). The only previously reviewed study that utilized a never active/never passive smoking definition of non-exposure was Morabia *et al.* (1996). Originally designed to investigate the association between ETS and breast cancer, this study reported a significantly elevated breast cancer risk for ever active or current smokers. The prospective study by Calle *et al*. (1994) found significant associations with breast cancer mortality and current smoking at baseline, number of cigarettes per day, years smoked, and age at initiation. Adjustment for known breast cancer risk factors did not change these relationships. In general, cancer mortality studies (such as Calle *et al*., 1994) understate the relationship between disease and exposure, particularly in a chronic disease with good survival such as breast cancer (at least at early diagnosis).

7.4.1.1.2. Recent Surgeon General and IARC Reports

The Surgeon General's 2004 report on active smoking (U.S. DHHS, 2004c) reviewed studies published from September 1992 through 1999 and a few additional up to 2001. The Surgeon General's (U.S. DHHS, 2004c) interpretation of the data on active smoking relies on essentially the same data set examined by OEHHA (1997) and in this report up to 1999, but considered few studies reported between 2000 and 2002. OEHHA considered 23 studies published between 2000 and 2005 whereas the Surgeon General report considered 5 of those studies. Similarly, IARC (2004a) evaluated mostly studies published prior to 1999 with 4 studies published between 2000 and 2002.

The Surgeon General's report concludes that "the epidemiological evidence provides no support for an overall relationship, neither causal nor protective, between active smoking and breast cancer" (U.S. DHHS, 2004c). The report states on page 307, "In conclusion, hypotheses that women with higher levels of exposure to cigarette smoking (i.e., heavy smokers and those who have been smoking since an early age) would have elevated risks of breast cancer have not been supported by data from large studies" and "This null relationship is consistent with the two hypothesized mechanisms, antiestrogenic effects and carcinogenic exposures, that imply countervailing consequences of smoking that both increase and decrease the risk for breast cancer."

The IARC report emphasized the Collaborative Group on Hormonal Factors in Breast Cancer Study (2002). The report concludes based on the overall results that most epidemiological studies have found no association with active smoking after control for confounders and note that the pooled analysis (Collaborative Study) found no effect. The report also notes that in the Collaborative Study no attention was paid to the reported associations with passive smoking, nor was information obtained on age of smoking initiation or the amount smoked.

7.4.1.1.3. Recent Epidemiological Data

Several recently reviewed studies on the association between active smoking and breast cancer demonstrate an increased risk (incidence or mortality). These elevations in breast cancer risk reached statistical significance in most of the recently reviewed studies overall or in some strata, in either active or former smokers after adjustment for multiple reproductive and other risk factors (Millikan *et al.*, 1998; Lash and Aschengrau, 1999; Jee *et al.*, 1999; Johnson *et al.*, 2000; Marcus *et al.*, 2000; Morabia *et al.*, 2000; Egan *et al.*, 2002; Reynolds *et al.,* 2004a; Hanaoka *et al*., 2005; Gram *et al*., 2005). Population based case-control studies found current smoking or former smoking was related to significantly increased breast cancer risk with estimates ranging up to 2.3, varying by age or menopausal status; however, studies were often limited in the number of premenopausal cases. Additionally, evidence for a dose response relationship between breast cancer risk and duration or amount of active smoking was noted in several studies (Millikan *et al.*, 1998; Johnson *et al.*, 2000; Terry *et al*., 2002; Band *et al*., 2002; Kropp and Chang-Claude, 2002; Reynolds *et al*., 2004a; Gram *et al*., 2005).

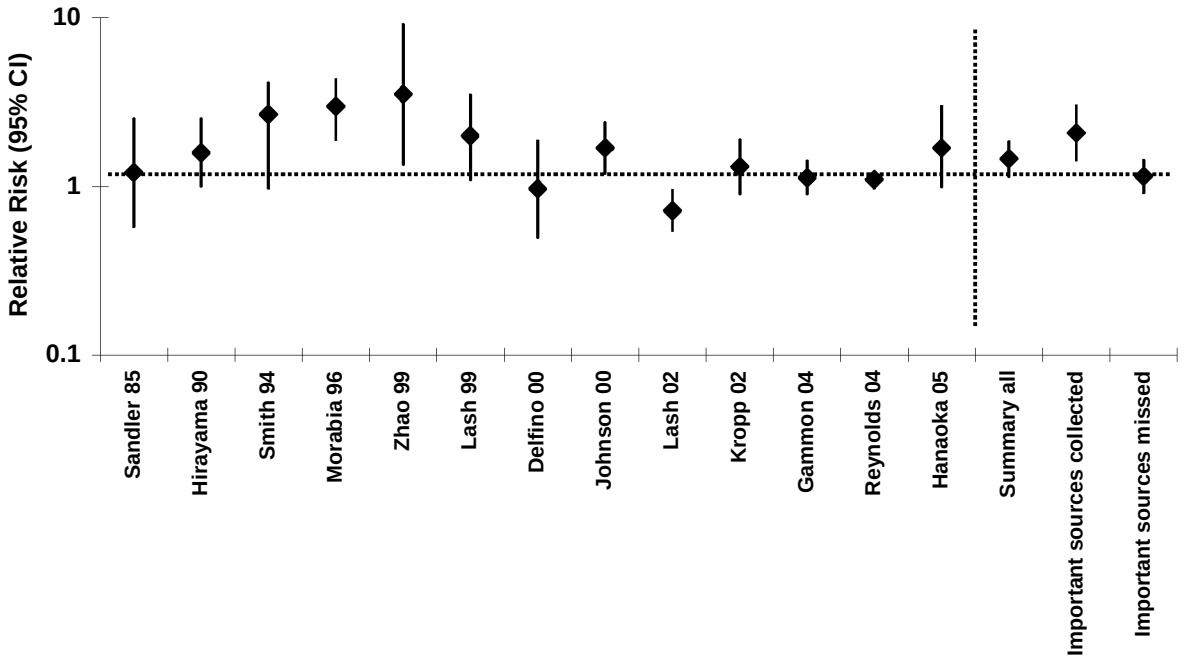
The more recent epidemiological studies are described in Appendix 7A at the end of Chapter 7. The following conclusions are based on those studies.

7.4.1.1.4. Active Smoking: Discussion and Conclusion

While there continues to be some heterogeneity in study results, overall, the studies presented in Appendix 7A in this update provide evidence of a role for active smoking in causation of breast cancer, and include evidence of dose-response. In 11 of 13 studies examining breast cancer risk from active smoking compared to a referent of never smoking women not exposed to ETS (Figure 7.4.1 below), point estimates were greater than 1 (many of them significantly so). Of the six studies considered by OEHHA as "most informative" based on best exposure assessment and design (see Section 7.4.1.4) (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Hanaoka *et al*., 2005), all have point estimates above unity (Figure 7.4.1 and Figure 7.ApA.1). There are now studies providing some evidence for gene-environment interactions, as well as studies demonstrating susceptible subpopulations with highly significantly increased breast cancer risk associated with active smoking (e.g., those

with familial high risks in Couch *et al*., 2001). Furthermore, some studies demonstrate significant risks related to the hormonal receptor status of the tumor (Manjer *et al*., 2001; Morabia *et al*., 1998). Finally, six recent prospective cohort studies (supported by similar findings in case control studies) found statistically significant elevated breast cancer risk associated with active smoking for at least some of the metrics of exposure (Egan *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*. 2004a, Hanaoka, 2005; Zhang *et al*., 2004; Gram *et al*., 2005). A number of studies (Table 7.ApA.5) found statistically significant elevated breast cancer risk for current or ever active smokers (Lash and Aschengrau, 1999; Johnson *et al*., 2000; Terry *et al*., 2002; Morabia *et al*., 2000, Reynolds *et al*., 2004a; Zhang *et al*., 2004; Hanaoka *et al*., 2005).

Figure 7.4.1 Summary Breast Cancer Risk Estimates for Active Smoking Compared to Never Smoking Women who were Never Regularly Exposed to ETS (Based on Johnson, 2005, table 5)



Long duration of exposure or higher pack-years (Table 7.ApA.6) was associated with significantly elevated breast cancer risks in a number of studies (Millikan *et al*., 1998; Lash and Aschengrau, 1999; Johnson *et al*., 2000; Band *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*., 2004a; Gram *et al*., 2005). A meta-analysis conducted by Johnson (2005) examined 13 studies of active smokers (controlling for passive smoking) and found a significantly elevated risk, OR 1.48 (95% CI 1.17-1.86). In those studies with a more complete passive exposure assessment, and thus cleaner referent groups, the breast cancer risk from active smoking was estimated at 2.08 (95% CI 1.44-3.01).

Morabia *et al*. (1996), Lash and Ashengrau (1999), Kropp and Chang-Claude (2002), and Johnson *et al*. (2000) all reported that the risk estimate for breast cancer in active smokers increased when ETS-exposed women were excluded from the non-exposed referent group. In a case-control study, Johnson *et al*. (2000) demonstrated statistically significant elevated risks

when comparing smokers to never-active never-passive nonsmokers (OR 2.3; 95% CI 1.2-4.5) after accounting for a number of confounders including reproductive health, SES, and alcohol consumption. When childhood exposures were included, risks increased.

Timing of smoking initiation was also investigated in various studies, with several finding that earlier age of smoking onset or initiating active smoking prior to first childbirth strengthened the reported association (Lash and Aschengrau, 1999; Marcus *et al.*, 2000: Egan *et al*., 2002; Band *et al.,* 2002; Reynolds *et al*., 2004a; Gram *et al*., 2005). Johnson *et al*. (2003), Band *et al*. (2002), and Lash and Aschengrau (1999) found increased risks which reached statistical significance in parous women related to number of years of smoking before a first full-term pregnancy.

Considering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and elevated breast cancer risk.

7.4.1.2. ETS and Breast Cancer

7.4.1.2.1. Introduction and Previous Findings.

Previously, OEHHA examined the association between ETS exposure and breast cancer in four analytical epidemiology studies (one cohort and three case controls studies) (Hirayama, 1984; Sandler *et al.*, 1985a; Smith *et al.*, 1994; Morabia *et al.*, 1996), only one of which was initially designed to investigate the role of ETS in breast cancer (Morabia *et al.*, 1996). Although all four studies were suggestive of an association between ETS exposures and increased risk of breast cancer, risk estimates were modestly elevated and usually not statistically significant. Elevated risk estimates were also not consistent across subsets of women. Some studies found no association with active smoking, but an association with passive smoking. Additionally, no indication of increasing risk of breast cancer with increasing dose or exposure intensity was observed. Overall, the results were considered inconclusive by OEHHA (Cal/EPA, 1997).

Since only brief mention was made of the above studies in the Cal/EPA (1997) document, and since they are used in the development of the summary statistics presented in the conclusion of this chapter, they are summarized below. In addition, the description of an older study by Hirose *et al*. (1995) is also included here since it was not reviewed in the 1997 report.

Hirayama (1984) examined mortality in a prospective cohort of 91,540 nonsmoking wives in Japan during 16 years beginning in 1965. Participants were interviewed in 1965 and tracked by establishing a record linkage system between the risk factor records and death certificates. In his original study he did not report on breast cancer risk other than to mention that it was possibly associated. However, Judson Wells has published more detailed breast cancer mortality data provided to him by Dr. Hirayama in letters to the editor in the American Journal of Epidemiology (Wells, 1991; 1998b). The overall adjusted relative risk in nonsmoking wives exposed to spousal ETS was 1.32 (95% C.I. 0.83-2.09).

Sandler et al. (1985a) examined cancer risk associated with passive exposure to spousal smoking. In this case-control study, cases (n = 518) were 15-59 years of age from the tumor registry of the North Carolina Memorial Hospital diagnosed with cancer in 1979-1981. Controls (n = 518) were matched by sex, age and race. Data collected by mailed questionnaire included

age, race, gender, marital status, occupation, education, and personal and spousal smoking histories. Passive smoke exposure was estimated from the number of years of marriage during which the spouse smoked.

After adjustment for age and education, the risk of cancer among smokers and nonsmokers combined for all sites was 1.6 (95% CI 1.2; 2.1), and for breast cancer specifically, 1.8 (95% CI 1.0; 3.7). Among nonsmokers separately, the risk for breast cancer was 2.0 (95%CI 0.9; 4.3) compared to 2.8 (95% CI 1.0; 7.6) for smokers. While these numbers may suggest an elevated risk for breast cancer from ETS, the number of cases was small (n = 32) and the confidence interval included no effect. For the purpose of developing a summary statistic at the end of this chapter, a summary overall risk estimate was calculated by Wells using data obtained from Dr. Sandler. The overall RR of breast cancer in passively exposed women was 1.62 (95% CI 0.76; 3.44) (Wells, 1998a). A similar statistic was calculated for premenopausal breast cancer by Wells (1991) based on case and control data from Dr. Sandler (personal communication). The calculated OR was 7.1 (95% CI 1.6; 31.3).

Interviews of 649 relatives of subjects showed good agreement between subjects' and relatives' responses regardless of case/control status, suggesting minimal recall bias. There were no estimates of the intensity of ETS exposure, nor exposure from sources other than the spouse. The non-exposed referent likely included individuals exposed to ETS from other sources such as work. Confounders such as diet, health and other lifestyle characteristics were apparently also not adjusted for in the analysis.

Smith et al., 1994. This case-control study examined the relation between breast cancer risk and alcohol consumption, active and passive smoking, and caffeine among women in the UK. It included women diagnosed with breast cancer between 1982 and 1985 before the age of 36. For the analysis of passive smoking, information was obtained by self-administered questionnaire on 170 matched case-control pairs regarding passive smoke exposure in childhood (< age 16), and in adulthood from cohabitants, work and other sources.

In an unmatched analysis of the entire group, there were elevated breast cancer risks associated with ETS exposure during childhood only (RR 1.32, 95% CI 0.16; 10.80) and adulthood only (RR 3.13, 95% CI 0.73; 13.31), but neither was statistically significant. Also non-statistically significant risks were noted for the combined exposure, RR 2.63 (95% CI 0.73; 9.44), and for total lifetime exposures of 1-200 cig-yrs, RR 2.82 (95% CI 1.00; 7.93); > 200 cig-yrs, RR 2.24 (95% CI 0.75; 6.58). For the purpose of developing a summary statistic at the end of this chapter, a summary overall risk estimate was calculated using component risks and confidence intervals reported in the paper for non-smokers (1-200, >200 cig-yrs, Table 5 of Smith *et al*., 1994). We derived crude cell counts from data provided in Smith *et al*. (1994) and if necessary used methods described in Greenland and Longnecker (1992) to obtain missing cell information. From cell counts we calculated a risk estimate that combined all exposure groups. Using a search technique within Microsoft Excel software (Solver tool), adjusted cell counts were calculated from the adjusted RRs. Confidence intervals from these adjusted cell counts were obtained using the Woolf method described in Schlesselman (1982). The RR for breast cancer was 2.53 (95% CI 1.12; 5.71); note that all these women were premenopausal at diagnosis. These values were adjusted for age, region, age at menarche, nulliparity, age at first full-term

pregnancy, breastfeeding, oral contraceptive use, family history of breast cancer, own smoking, biopsy for benign breast disease, and alcohol use.

Information on passive smoke exposure was obtained via a self-completed questionnaire returned by mail, thus minimizing interviewer bias, but the possibility of recall bias remained.

Hirose et al. (1995) conducted a case-control study of the risk factors for breast cancer in relation to menopausal status. Self-administered questionnaires were given to first-visit outpatients at the Aichi Cancer Center Hospital in Japan from 1988 to 1992. Data on occupation, medical history, anthropometrics, marital status, family history of breast cancer, dietary, smoking and drinking habits, reproductive history, and exercise were collected from 36,944 women prior to disease diagnosis. For the study, 1,052 histologically-confirmed breast cancer cases (607 premenopausal, 445 postmenopausal) were compared with 23,163 non-cancer outpatient controls.

From unconditional logistic regression analyses adjusted for age and year of first visit, passive smoking represented a significant risk for postmenopausal (OR 1.39, 95% CI 1.04; 1.85), but not for premenopausal women (OR 1.15, 95% CI 0.91; 1.46). Unfortunately, passive smoking was not subjected to multivariate analysis to control for potential confounding. Additional concern is raised due to the use of non-cancer outpatient controls. Thus the apparent link between ETS exposure and breast cancer must be interpreted with caution since the analysis was not adjusted for potential confounders nor did it take into account potential sources of ETS exposure other than spousal smoking.

Morabia et al. (1996) examined the relationship of breast cancer with active and passive smoking among Swiss women in a population-based case control study. Cases (n = 244) were women <75 years old with a first diagnosis of invasive breast cancer in 1992-1993, while population controls (n = 1,032) were 30-74 years of age. Data were collected by interview with questions covering the major known or postulated risk factors for breast cancer as well as smoking history. Smoke exposure data were recorded year by year from age ten to the date of the interview, and included both passive and active exposures, duration of exposures (hours per day) and intensities (cigarettes per day). In this study, passive exposure was defined as having been exposed to ETS for at least one hour per day for at least 12 consecutive months. Multivariate analyses were adjusted for age, education, BMI, age at menarche, age at first live birth, oral contraceptive use, history of familial breast cancer and cancer biopsy. Dietary data were available for 150 cases and 336 controls, and were used to adjust the multivariate analyses of the whole group (n = 1,276) for alcohol and saturated fat intake.

Passive smoke exposure was associated with an elevated breast cancer risk [OR 2.3 (95% CI 1.5-3.7)] which increased after adjustment for dietary intake [OR 3.2 (95% CI 1.7-5.9)]. Breast cancer risk was also estimated for premenopausal women resulting in a multivariate OR of 3.6 (95% CI 1.6; 8.2) for ever passive exposure.

A strength of this study's design was its ability to quantify potential selection, recall and detection biases. Selection bias was assessed by collecting smoking status on non-participants; the authors indicated there was some *"slightly conservative selection bias* (that) *may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their*

true smoking status." Interviewers were blind to the interviewees' case-control status. No evidence for differential recall between controls and cases was found based on questions regarding attitudes towards ETS exposure. This study thus supports an association of both passive and active smoking with breast cancer.

7.4.1.2.2. ETS and Breast Cancer: Recent Epidemiological Data.

Tables 7.4.1I through 7.4.1M summarize results from published primary studies investigating the association between ETS exposure and breast cancer risk. Several cohort and case-control studies have reported on breast cancer risk and exposure to ETS (Millikan *et al.*, 1998; Jee *et al.*, 1999; Lash and Aschengrau, 1999; Zhao *et al.*, 1999; Delfino *et al.*, 2000; Johnson *et al.*, 2000; Liu *et al.*, 2000; Marcus *et al.*, 2000; Wartenberg *et al.*, 2000; Egan *et al.*, 2002; Kropp and Change-Claude, 2002; Reynolds *et al*., 2004a; Shrubsole *et al*., 2004; Gammon *et al*., 2004). In contrast to previously reviewed studies (Cal/EPA, 1997), many of these more recent reports accounted for a number of covariates that affect breast cancer risk and diagnosis, and utilized never-smoking and not exposed to ETS as the referent exposure definition. The majority of studies presented risk estimates for ETS related to spousal or residential exposure, including spousal only (Jee *et al.*, 1999) or spousal and other smokers in the home (Millikan *et al.*, 1998; Lash and Aschengrau, 1999; Johnson *et al.*, 2000; Marcus *et al.*, 2000; Wartenberg *et al.*, 2000; Egan *et al.*, 2002, Reynolds *et al*., 2004a). A few studies assessed breast cancer risk associated with ETS exposure at work (Johnson *et al.*, 2000; Wartenberg *et al.*, 2000; Egan *et al.*, 2002; Shrubsole *et al*., 2004). Some studies evaluated breast cancer risk in relation to age or menopausal status (Millikan *et al.*, 1998; Morabia *et al.*, 1998; Delfino *et al.*, 2000; Johnson *et al.*, 2000; Morabia *et al.*, 2000; Hanaoka *et al*., 2005). It should be noted that the age or menopausal status in the case-control studies is obtained at diagnosis, but in the cohort studies this information was obtained at enrollment. Although the authors report results by age or menopausal status in some of the cohort studies, the actual age or menopausal status at diagnosis is not identified. This likely misclassifies as premenopausal many who are actually postmenopausal at diagnosis. Some studies evaluated breast cancer risk modification due to genotypic variation in metabolic enzymes, and tumor hormone receptor status (Millikan *et al.*, 1998; Morabia *et al.*, 1998, 2000). As discussed in the conclusions section, overall, the weight of evidence (including toxicology of smoke constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS and breast cancer in younger primarily premenopausal women. Individual studies are discussed below.

7.4.1.2.2.1. Description of More Recent Studies

Millikan et al., 1998. An analysis based on an on-going population-based case-control study, the Carolina Breast Cancer Study (CNCS), examined the effects of active smoking and genetic variation of N-acetylation metabolism (NAT). This report analyzed data from 498 cases and 473 controls with risk estimates adjusted for age, race, reproductive factors, alcohol, and family history of breast cancer. Data were presented for breast cancer risk and ETS exposure (restricted to women never-active smokers with residential exposure after age 18). A small, statistically non-significant, elevated risk of breast cancer associated with residential ETS exposure was reported for all women combined [adjusted OR 1.3 (95% CI 0.9-1.9)], being slightly higher in pre- compared to postmenopausal women [premenopausal adjusted OR 1.5 (95% CI 0.8-2.8); post menopausal adjusted OR 1.2 (95% CI 0.7-2.2)] (Table 7.4.1I). As with active smoking, the effect of NAT1*10 allele or NAT2-rapid/slow acetylation on modifying breast cancer risk with passive smoking was limited (Table 7.4.1K). In premenopausal women, the association of

passive smoke (again compared with never-active smokers/no ETS exposed women) with breast cancer was associated with an elevated, but non-significant risk [adjusted OR 1.7 (95% CI 0.7-4.3)] among women with the NAT1*10 allele which appears stronger than the OR for women with the NAT1-non*10 allele [OR 1.3 (95% CI 0.5-3.2)]. No difference was observed among postmenopausal women. A limitation of this study is the use of a referent population in which adult exposure to ETS was determined by a single question (have you lived with a housemate since the age of 18 years who smoked?). This would result in a referent group containing ETS exposed (e.g., those exposed at work or other settings), biasing results towards the null. A strength of the study is its restriction of the study population to never active smokers, which prevents potential confounding from active smoking.

Jee et al., 1999. This Korean prospective cohort study reported the effects of spousal smoking on the incidence of cancer in women ages 40 and over. A total of 158,927 of 260,359 (61%) eligible non-smoking wives completed an annual examination and questionnaire in 1992 through a Korean health insurance provider. Data was collected from both spouses. Though no data on other sources of ETS were presented, Jee notes that 1.1% of his wives were current smokers, and 0.6% were ex-smokers. Women in Korea do not frequently meet socially with men other than their husbands so their tobacco smoke exposure comes mostly from their husband or an occasional father-in-law. Childhood exposure was not addressed. The incidence of breast cancer was slightly elevated, but not statistically significant, among women married to ex-smokers [adjusted RR 1.2 (95% 0.8-1.8)] and current smokers [adjusted RR 1.3 (95% CI 0.9-1.8] after adjustment for age, socioeconomic status, residency, husband's vegetable intake, and husband's occupation (Table 7.4.1L). Although the limited number of breast cancer cases (n=138) inhibits the ability to stratify by exposure duration with sufficient statistical power, the risk of breast cancer was highest among wives married to current smokers for greater than 30 years [RR 1.7 (95% CI 1.0-2.8)] (no trend data shown). The brief follow-up, only through December 1997 (3.5 years), and restriction of case identification to hospital discharge summaries, may have limited the measurement of cancer burden in this population. Another limitation of this study was lack of consideration of time-since-first-exposure when examining risk by years of passive smoke exposure. Since cancer risk generally goes up with time-since-first-exposure (effect modification), the increased risk seen after 30 years of passive smoking may have been due to increased time-since-first-exposure.

Lash and Aschengrau, 1999. This U.S. case-control study identified 334 incident cases of breast cancer from 1983 to 1986 among residents of five Massachusetts communities. Odds ratios were adjusted for age, parity, family history of breast cancer, body mass index, history of benign breast disease or other breast cancer diagnosis, and history of radiation therapy. Ever active, passive only or nonsmoker (no active or passive) status was determined via interview; the assessment of passive smoking only considered residential exposure. Age of first exposure and total duration of exposure to ETS were evaluated. Odds ratios were adjusted for age, parity, family history of breast cancer, body mass index, history of benign breast disease or other breast cancer diagnosis, and history of radiation therapy. Some odds ratios were additionally adjusted for alcohol consumption.

Passive only smokers had a statistically significantly elevated risk of breast cancer after further adjustment for alcohol [adjusted OR 2.0 (95% CI 1.1-3.7)], when using a never-active, never-passive definition of non-exposure, approximately equal to the risk found in this same study for

ever-active smokers (Table 7.ApA.5). Odds of breast cancer varied inversely with duration of exposure to passive smoke [≤20 yrs: OR 3.2 (95% CI 1.5-7.1); >20 yrs: OR 2.1 (95% 1.0-4.1)] (Table 7.4.1J). In contrast to results for active smoking, passive smoking breast cancer risk was not dependent on, or varied substantially by, exposure prior to versus after first pregnancy. Age of first exposure to passive smoking influenced the risk of developing breast cancer (Table 7.4.1J). Risk of breast cancer increased in women with exposure at younger ages [< 12 yrs old: OR 4.5 (95% CI 1.2-16); 12-20 yrs old: OR 3.8 (95% CI 1.1-13); ≥ 21 yrs old: OR 2.4 (95% CI 0.9-6.1)]. In ever-active smoking women, breast cancer risk was elevated with exposure to passive smoke at younger ages (e.g., living with another active smoker)[< 12 yrs old: OR 7.5 (95% CI 1.6-36); 12-20 yrs old: OR 3.9 (95% CI 0.8-20); ≥ 21 yrs old: OR 4.7 (95% CI 1.6-14)].

This was a retrospective study so some recall bias may be expected. The authors note: *"However, the substantial associations that were found were within the strata defined by time periods calculated from a series of responses. We do not expect these derived exposures to be susceptible to recall bias."* While SES was not measured directly, several potential surrogates such as educational level were added to the regression analysis and found to not significantly affect the results.

Zhao et al., 1999. This case control study was undertaken to identify risk factors for breast cancer among 265 cases in Chengdu, China. Women with breast cancer confirmed by surgery or biopsy were matched to controls by age, living area, profession and education. Data collected by questionnaire included demographics, menstruation history, pregnancies, history of breast disease, breast feeding, oral contraceptive use, active and passive smoking history, alcohol and tea consumption, and other dietary factors. Conditional logistic multivariable regression analysis was based on single factor analysis.

Based on the data provided, the crude risk (OR) of breast cancer among never-smokers exposed to ETS was 2.38 (95% CI 1.66; 3.40). In premenopausal women, the OR was 2.56 (95% CI 1.63-4.01) and in postmenopausal women, 2.38 (95% CI 1.17-3.76) (personal communication between Kenneth Johnson and Zhao, May 2001). This study found elevated risks for breast cancer with passive smoking, as well as for a history of benign breast disease, time from menarche to menopause of ≥ 35 years, oral contraceptive use, and the consumption of bee extract. Risk reduction was associated with alcohol and tea consumption, breast-feeding, and the consumption of fish, vegetables and bean products. However, the analyses were unadjusted for these factors. This and the small size of this study were limitations.

Delfino et al., 2000. This U.S. case-control study recruited women (113 cases, 278 controls with benign breast disease) with suspicious breast masses detected either clinically or by mammography. Smoking status, active and passive, was collected via questionnaire prior to biopsy diagnosis. Passive exposure was considered high if one had lived with a smoker in their home, either usually or some of the time. It was labeled low if this rarely or never occurred. No consideration was made of other possible sources of smoke exposure. Overall, an elevated non-significant effect of passive smoking on breast cancer risk was observed [OR 1.32 (95% CI 0.69-2.52)] compared to never exposed (active or passive) women (all control group), but the analysis did not account for active smoking by the subjects (Table 7.4.1I) or ETS exposure at the workplace. However, when the study population was restricted to never active smokers, the OR for high adult ETS exposure utilizing low-risk controls was 1.86 (95% CI 0.81-4.27). In another

analysis of never active smokers, passive smoking was positively, but not statistically significantly (small sample size, 21 cases) associated with breast cancer risk, among premenopausal women [OR 2.69 (95% CI 0.91-8.00)], but not among postmenopausal women [OR 1.01 (95% CI 0.45-2.27)]. Additionally, no interaction between NAT2 genotype and passive smoking was found. However, the study lacked sufficient power to detect small influences of NAT2 genotype alone on breast cancer risk. This study may have included women with significant non-residential ETS exposure among the never exposed referent group. Limitations of the study include lack of control in some analyses for active smoking by the subjects and an apparent lack of adjustment for alcohol consumption. Prior to biopsy, women took self-administered questionnaires on risk factors. The study included only subjects whose questionnaires were returned by mail prior to receiving diagnosis. Eligible patients, participants and interviewers were all blind to case/control status. Interviewer and reporting bias were thus minimized. Participation rates were similar between those with and those without a diagnosis of cancer.

Johnson et al., 2000. This population-based case-control study utilized data from the Canadian National Enhanced Cancer Surveillance System including 805 premenopausal and 1,512 postmenopausal women with incident primary breast cancer cases. ORs were adjusted for alcohol, education, age, age at first childbirth, adult height, age at menarche, BMI, parity, physical activity and residence. Among never-active smokers the adjusted ORs for breast cancer risk and ETS exposure were 2.3 (95% CI 1.2-4.6) and 1.2 (95% CI 0.8-1.8) for premenopausal and postmenopausal women, respectively (compared to never exposed women, Table 7.4.1I). For all never smokers exposed to ETS, the OR is 1.48 (95% CI 1.06-2.07) (Johnson, 2005). Adjusted premenopausal risk estimates associated with childhood ETS exposure in never-active smokers were 1.6 (95% CI 0.6- 4.4) for childhood only exposure and 2.6 (95% CI 1.2-5.5) for child and adult passive exposure. In this study, childhood included ages 0-19 years. In contrast, no statistically significant elevation in risk was observed for childhood ETS exposure among never-active smoking postmenopausal women [ORs 0.9 (95% CI 0.4-2.0) and 1.3 (95% CI 0.8-2.0), childhood only and childhood/adult combined ETS exposure, respectively].

Additionally, a dose-response relationship between exposure to passive smoking, residential and/or occupational, and breast cancer risk was observed among never-active smokers in premenopausal women [1-6 yrs: OR 1.2 (95% CI 0.4-3.4); 7-16 yrs: OR 1.8 (95% CI 0.7-4.9); 17-21 yrs: OR 2.0 (95% CI 0.8-5.0); 22-35 yrs: OR 3.3 (95% CI 1.5-7.5); 35+ yrs: OR 2.9 (95% CI 1.3-6.6), p for trend 0.0007]. This was not observed in postmenopausal women. This dose-response relationship between total residential and occupational years of ETS exposure and breast cancer risk strengthens the findings for an association (Table 7.4.1J).

In this study, questionnaires were mailed, thereby eliminating interviewer bias. ETS questions were among many others on breast cancer (BC) risk factors. Data from subjects with one of 18 other cancers, including a large sample of lung cancer cases, were also collected in the same data collection (the National Enhanced Cancer Surveillance System). Possible recall or response bias was examined by comparing 71 never smoking women with lung cancer and 714 never smoking women controls, the same pool of controls used for the breast cancer analysis. They found an age-adjusted OR of 1.2 (95%CI 0.7; 7.1) for the association between lung cancer and years of home ETS, similar to estimates found in recent meta-analysis. The authors use the lung cancer results to suggest that bias is likely not seriously affecting the breast cancer risk estimate.

Furthermore when Johnson *et al*. examined the risk of active smoking in the traditional way (ignoring ETS exposure) the observed breast cancer risk was 1.0 for premenopausal women and 1.2 for postmenopausal women, consistent with other studies using contaminated referent populations in the literature. Strengths of the study included adjustment for known risk factors such as alcohol and education, and restriction of the population to never active smokers to avoid confounding from active smoking. A limitation of the study was lack of consideration of time-since-first-exposure in the dose-response analyses where dose was length of ETS exposure.

Rookus et al. (2000) described in an abstract their analysis of a Dutch population-based case-control study (n = 918) of breast cancer and oral contraceptives, in which lifetime histories of active and passive smoking were collected by interview. Passive smokers were defined as lifetime non-smokers with at least 20 years daily domestic or occupational exposure to ETS, or if someone smoked daily in their bedroom for more than one year. ORs were adjusted for lifetime physical activity level and other potential confounders. When passive smokers were included in the reference group of never smokers, the ORs for current and ex-smokers were 1.0 (95% CI: 0.8-1.3) and 1.3 (95% CI: 1.0-1.6), respectively. When passive smokers were excluded from the reference group, the risk of breast cancer among passive smokers was increased (OR: 1.2, 95% CI: 0.8-1.7). This risk was comparable to the risks of current smokers and ex-smokers relative to non-exposed controls (OR: 1.2, 95% CI: 0.8-1.6 and 1.4, 95% CI: 1.0-2.0, respectively). Differential effects of passive exposure before first pregnancy or on P53 over-expression were not detected. This study is of interest in that ETS exposure from both domestic and occupational situations was measured, and it directly addresses the concern that many studies may miss the effect of active smoking if passive smoking is inadequately measured and controlled for. The authors state: "In conclusion: passive smoking seems to slightly increase the risk of breast cancer comparable to the risk increase following active smoking. Therefore, in studies on active smoking and breast cancer risk, the risk estimates will be biased to zero if passive smokers are included in the reference group."

Woo et al. (2000) described a population-based, nested case-control study in Washington County, MD. In 1975, the smoking status of adult household members was determined by census. Incident breast cancer cases (n = 706) during the subsequent 17 years were identified among women census participants through the Washington County Cancer Registry, along with age matched controls (n = 1,426). For all never active smokers, passive smoke exposure was not associated with breast cancer overall (OR 1.04, 95% CI 0.83-1.33). This was also true for postmenopausal never smokers (OR 0.91, 95% CI 0.71-1.18). (Postmenopausal was defined as age $\geq$ 50 years; it is assumed that this refers to age at diagnosis although the report does not state this explicitly.) However, there was a significantly elevated risk of breast cancer in premenopausal never-smoking women exposed to ETS, relative to those not exposed (OR = 2.78, 95% CI 1.37 - 5.63). Determination of ETS exposure status appears from the limited report to have been on the basis of cohabitation with a smoker at the time of the census. As noted elsewhere, this ignores other ETS exposure situations (e.g., occupational) that are significant for many study populations, and also does not provide information on age or parity at the time of exposure. No efforts to control for confounding factors are described. In spite of these limitations of the study, the authors note an association between ETS exposure and premenopausal breast cancer, although the overall result for all cases (pre- and postmenopausal) is nonpositive. This is consistent with several other studies reporting increased risk of premenopausal breast cancer.

Liu et al. (2000) conducted a case-control study from 1994-1996 in China, to investigate the roles of ETS exposure and other early life factors in the etiology of breast cancer. The study included 186 cases of histologically confirmed breast cancer in women, 24 to 55 years of age, who were diagnosed in a university teaching hospital. Controls, matched for age at diagnosis, date of diagnosis, and marital and never-smoking status, were selected from cancer-free women visiting the same facility. A standardized questionnaire was used in interviews to collect historical information about ETS exposure during childhood (<10 years of age), youth (10-16 years of age) and adulthood. For the two early periods, data regarding passive smoke exposure, body weight and height, history of diseases leading to hospitalization, life stress, and family economic situation were collected. For adulthood, information was also collected on passive smoke exposure at work. In the final multiple logistic regression analyses, ORs were calculated for each of the following factors after controlling for the other listed factors: passive smoking at home in childhood, passive smoking at home in adulthood, passive smoking in the workplace in adulthood, age at menarche, low body weight in childhood, overweight in adulthood, family economic situation in youth, history of hospitalized diseases in childhood and youth, history of benign breast disease, and history of life stress.

ETS was significantly associated with an increased risk for breast cancer following exposure at home in childhood (OR 1.24, 95% CI 1.07; 1.43), at home in adulthood (OR 4.07, 95% CI 2.21; 7.50), and in the workplace (OR 1.27, 95% CI 1.04; 1.55). Of the listed factors, only age at menarche was not associated with increased risk. The above mentioned statistics are striking in light of this study being relatively small, thus limiting its ability to detect robust associations. The study population was hospital-based and may not be representative of the general population. Recall bias is a concern regarding the early-life exposures and conditions. We were unable to obtain the raw data or other clarifying information from the author and thus consider that these statistics must be evaluated with caution.

Marcus et al., 2000. This population-based case-control study, the Carolina Breast Cancer Study, analyzed data from 864 incident breast cancer cases (diagnosed between May 1993 and May 1996) and 790 controls, to evaluate the relationship between adolescent exposure to ETS and breast cancer risk. Overall response was 77% cases and 68% controls. Residential exposure to ETS prior to age 18 (in a combined grouping of ever and never active smokers) was not associated with an increased risk of breast cancer [adjusted OR 1.1 (95% CI 0.9-1.3)] after adjustment for race and age at diagnosis/selection. Results did not differ by years of exposure or early/late age at diagnosis (< 50 years vs. $\geq$ 50 years). Exclusion of active smokers from the analysis of passive smokers for exposure before age 18 reduced the risk estimate to below unity [adjusted OR 0.8 (95% CI 0.6-1.1)] (Table 7.4.1I). The data in this paper are of limited usefulness in evaluation of breast cancer risk from passive smoking in non-smokers, since the only assessment of risk to nonsmokers looked solely at residential passive smoke exposure before age 18 and not for any other time period or source (i.e., occupational).

The authors suggest that differential recall between cases and controls regarding adolescent smoke exposure was unlikely since an association between adolescent smoke exposure and breast cancer is not generally perceived. On the other hand, the authors acknowledge that misclassification is likely regarding the timing of thelarche vis-à-vis smoke exposure but they suspect it would be non-differential.

Morabia et al., 2000, 1998. This population-based case-control study in Geneva, Switzerland investigated the association of breast cancer with passive and active smoking (Morabia *et al.*, 1996, described in Cal/EPA, 1997). Two hundred and forty-four cases were enrolled (71 percent of eligible cases) in an earlier study (Morabia *et al.*, 1996); however, biological samples were obtained from 170 of the possible 205 eligible cases still alive and residing in Geneva (Morabia *et al.*, 2000). In the more recent analysis by these investigators, the additional influence on risk of slow and fast acetylation, based on genotypic variation in N-acetyltransferase 2 (NAT2), was also determined (Morabia *et al.*, 2000). In never active smoking women, pooling premenopausal and postmenopausal women, the adjusted OR of breast cancer was 3.1 (95% CI 1.5-6.0) for ever passive smokers (adjusted for age, education, and family history of breast cancer) compared to never-exposed women (no active or passive smoking exposure). After stratification by NAT2 status, breast cancer risk with ever passive smoking increased for high acetylators (all women). In premenopausal women, the NAT2 genotype did not influence the adjusted OR 3.2 (95% CI 1.2-8.7). However, among postmenopausal women, a statistically significant association with breast cancer was found in fast acetylators with ever passive smoking [adjusted OR 11.6 (95% CI 2.2-62.2)], with no effect observed in slow acetylators [adjusted OR 1.1 (95% CI 0.3-4.3)] (Table 7.4.K).

Passive tobacco smoking was a risk factor for both estrogen receptor positive (ER+) and negative (ER-) tumors among both pre- and postmenopausal women (Morabia *et al.*, 1998). For all women combined (pre- and postmenopausal), passive smoking risk for ER- tumors was similar to the risk for active smoking [age-adjusted OR 3.8 (95% CI 1.5-10.0)]. ER+ breast cancer risk among passive smokers was lower [age-adjusted OR 1.8 (95% CI 1.1-3.0)].

Wartenberg et al., 2000. This large cohort study examined the association between breast cancer mortality and ETS exposure from spousal smoking. As part of an American Cancer Society prospective cohort (CPS-II), a cohort of 146,488 never smoking, single-marriage women was derived from a total female enrollment of 676,306 in 1982. Breast cancer death rates among women with husbands that smoked were compared with women married to nonsmokers. The CPS-II is a convenience sample (volunteer recruitment and enrollment) across the United States and Puerto Rico. Data on a variety of demographic and personal risk factors were identified via questionnaire. After 12 years of follow-up (through December 1994), 669 breast cancer-related deaths occurred. Overall, no association between ETS exposure (as defined by a smoking spouse) and death from breast cancer was observed [RR 1.0 (95% CI 0.8-1.2)] (Table 7.4.1L). Breast cancer death rates did not vary between never-smoking women married to nonsmokers, former smokers, or current smokers (age adjusted and multivariate-adjusted rates). Additionally, breast cancer mortality rates did not show a statistically significant increase with spousal smoking intensity (packs per day), spousal duration (years of smoking), or spousal cumulative exposure (pack-years). A statistically insignificant elevation in risk of death due to breast cancer was observed in women married before age 20 to current smokers [RR 1.2 (95% CI 0.8-1.8). Relative risk estimates were adjusted for multiple factors including age at entry into the study (in 1982), race, education, history of breast cancer in primary relative, multiple reproductive factors, alcohol, body mass index, multiple dietary factors, and occupation. For the purpose of developing a summary statistic at the end of this chapter, a summary risk estimate was calculated for premenopausal women using component risks and confidence intervals reported in the paper for non-smokers (combining risk ratios for current and former smoking spouses for age < 50 years; table 6). We derived cell counts from data provided in Wartenberg *et al*. (2000) using

methods described in Greenland and Longnecker (1992) to obtain missing cell information. From cell counts we calculated a risk estimate comparing the combined exposure groups to the referent. Confidence intervals were obtained using the Woolf method described in Schlesselman (1982). Thus, for premenopausal women the derived RR is 1.15 (95% CI 0.82-1.60).

Although, the study's large size and prospective design lend strength to investigating the association between breast cancer death and spousal ETS exposure, breast cancer mortality (as opposed to incidence) is a more limited outcome for identifying overall risk of breast cancer. Death due to breast cancer depends on many factors, particularly stage at initial diagnosis, and access to and quality of treatment, which influence survival. As an overall outcome measure, breast cancer mortality remains imprecise, and may severely underreport the total breast cancer burden in a study population. Concerns have been raised that the lack of measure of nonspousal ETS exposure diluted this study's ability to identify an association between breast cancer risk and passive smoking (Johnson, 2001; Wells, 2001). In response, Wartenberg *et al.* (2001) reiterated that no association was observed between breast cancer risk and self-reported exposure either at work [RR 0.8 (95% CI 0.6-1.0)], at other locations [RR 0.9 (95% CI 0.7-1.2)], or when all sources were combined and examined according to daily hours of exposure (data available on 128,295 women) (Wartenberg *et al.*, 2000). Nevertheless, since the ETS exposures other than from spouse were included in the questionnaire only at one time, namely, at enrollment, the potential for substantial historic exposure misclassification exists (Johnson, 2001). Another limitation was lack of consideration of time-since-first-exposure in the dose-response analyses.

Nishino et al. (2001) investigated the effects of spousal smoking among a cohort of 9,675 lifetime non-smoking women completing mailed self-administered questionnaires in 1984 (total response rate of 96% for men and women). Individuals were followed for 9 years with cancer cases identified through record linkage with a population cancer registry. ETS exposure was based on spousal smoking at time of initial survey.

The adjusted relative risk for breast cancer associated with having a smoking husband was not elevated [RR 0.58 (95% CI 0.32-1.1) Table 7.4.1L]. No change to this inverse relationship to breast cancer risk was reported after additional adjustment for alcohol, dietary factors, and residential area.

Although the study adjusted for several potentially important confounding factors, including dietary intake of vegetables, it was limited by a single ETS measurement at baseline and by not including sources of ETS exposure other than husband (other residential, occupational, or childhood). Also, according to the authors, "In this study, women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoking exposure…." Thus, the authors conclude, this study must be interpreted with caution with respect to the association between passive smoking and breast cancer.

Egan et al. (2002) used the U.S. Nurses' Health Study cohort to analyze the influence of active and passive smoking on the incidence of invasive breast cancer. Although the Nurses' Health Study was established in 1976, this analysis includes 78,206 women followed prospectively from 1982 until June 1996, reporting 3,140 cases of invasive breast cancer. The relative risks of

breast cancer for passive smoking among never-active smokers remained near unity for several exposures including maternal smoking [adjusted RR 0.98 (95% CI 0.70-1.38)], or smoking by both parents [adjusted RR 0.92 (95% CI 0.76-1.13)]. Paternal smoking alone had a slightly elevated but non-significant positive association with breast cancer [adjusted RR 1.12 (95% CI 0.99-1.27)] (Table 7.4.1L). Current passive smoking (as reported in 1982 questionnaire) was also unrelated to breast cancer risk, either at home or work [adjusted RR 1.00 (95% CI 0.83-1.20)], or both settings combined [adjusted RR 0.90 (95% CI 0.67-1.22)]. The risk associated with cohabitating with an active smoker for 30 or more years was not elevated [adjusted RR 1.03 (95% CI 0.86-1.24)] (Table 7.4.1M). For the purpose of developing a summary statistic at the end of this chapter (Section 7.4.1.3), a summary risk estimate was calculated for women using component risks and confidence intervals reported in the paper for non-smokers (combining risk ratios for currently exposed at work or home in table 1 of the paper using methods previously described for Smith *et al*., 1994). The resulting RR for all women ever exposed to ETS is 1.06 (95% CI 0.90-1.25).

This large, prospective study fails to find an association between passive smoking and breast cancer risk. However, the passive smoking analyses reported for this study did not exclude all women with regular passive smoking exposure (childhood or adult) from the referent exposure category. This potential misclassification of passive-smoking status may significantly inhibit the ability to observe an association. Additionally, occupational exposure to ETS was based on one historical time point, in 1982, limiting the ability to establish lifetime workplace exposure. Since over one half of the entire cohort was reported to be active smokers and most reported initiation of smoking by 22 years of age, a large percentage of the "never active smokers" would have likely had significant exposure to ETS in nursing school and hospital training during a susceptible time period (prior to first pregnancy). These factors could lead to misclassification of ETS exposed nonsmokers as non-exposed, thereby reducing apparent risk. While there was no direct control for SES in this study it is assumed that since this is a cohort based on occupation and education level, the socioeconomic status is relatively homogeneous.

Kropp and Chang-Claude, 2002. This case-control study examined the association between active and passive smoke exposure and breast cancer risk in women up to 50 years of age in two regions of southern Germany. It was based on a population-based study of breast cancer conducted from 1992-1995. Cases (among never active smokers) were defined as having incident in situ or invasive breast cancer diagnosed under the age of 51 (n = 197), and were matched by age and study region to 459 randomly selected controls. Data on demographics, anthropometrics and potential risk factors were collected by self-administered questionnaire. Detailed smoking histories were obtained in 1999 from surviving patients during a followup telephone interview, and included information on age at start of smoking, amount and frequency of tobacco use, intensity of inhalation and date of changes in smoking habits. Passive smoke exposure was assessed for the childhood household, the adult household and for work. Ever passive smokers had an average ETS exposure of more than 1 hour per day for at least a year in either childhood or adulthood. The referent exposure category included only never smokers who had no residential or occupational ETS exposure. Multivariate analyses were adjusted for number of months of breastfeeding, BMI, education, family history, menopausal status and alcohol intake. Number of pregnancies, use of oral contraceptives, age at menarche and at first pregnancy, were found not to influence estimates and were not included in the statistical models. There was no control for diet or other medical conditions. After stratification for age (in 5-year

increments), ever passive exposure was associated with an adjusted OR for breast cancer of 1.59 (95% CI 1.06; 2.39) (Table 7.4.1I). The timing of ETS exposure in relation to breast cancer was also examined. ETS exposure only during childhood was not significantly associated with increased risk [OR 1.11 (95% CI 0.55; 2.27)]. However, significant risks were associated with exposure as an adult [OR 1.86 (95% CI 1.16; 2.98)] or during both childhood and adulthood [OR 1.63 (95% CI 1.03; 2.57)]. Regardless of its intensity (low or high), passive smoke exposure elevated the risk of breast cancer among nonactive smokers.

Because of its case-control design, this study may be susceptible to recall bias especially with respect to childhood exposure. However, the results of the telephone interview, conducted in 1999, were consistent with those of the questionnaires in the 1992-1995 study upon which the current study was based, thus increasing confidence in the more recent responses. The authors note that there was "*no great change in recall for active smoking between the first questionnaire and the follow-up interview even though smoking was only a minor aspect of the initial questionnaire. Taking into account the good quality of the other assessed factors, it seems unlikely that the reporting of active or passive smoking should be greatly biased by case/control status*."

Chang-Claude et al. (2002) examined the role of polymorphisms in the N-acetyltransferase 2 (NAT2) gene in the effects of active and passive smoke exposure on breast cancer risk. The current study, conducted in 1999-2000, was based on a population-based case-control study of 706 breast cancer patients and 1,381 controls conducted in Germany in 1992-1995. Data, including active smoking, were collected by self-administered questionnaire. Questions about childhood, adult and workplace smoke exposures were included. The reference group contained neither ever-active smokers (>100 cigarettes in their lifetimes) nor ever-passive smokers (> 1 hr ETS per day for at least 1 year).

Smoke exposure was associated with increased risks of breast cancer that were similar in passive (OR 1.5, 95% CI 1.0; 2.2) and active (OR 1.4, 95% CI 0.9; 2.2) smokers. ETS exposure in childhood was not associated with increased risk. However, among adult rapid acetylators with long-term ETS exposure, there was a significantly elevated risk (OR 2.91, 95% CI 1.12; 7.59) that was not seen among slow acetylators.

This study was limited by its small size and recall bias was possible. However, as noted in the related study above, it was unlikely that reporting of active or passive smoking would be biased by case/control status.

Lash and Aschengrau, 2002. This case-control study of the association between active or passive smoking and breast cancer was conducted in a manner similar to their earlier study on this same topic (Lash and Aschengrau, 1999), but in a different population. The 666 cases were diagnosed with invasive breast cancer between 1987 and 1993 and, along with 615 controls, were drawn from residents of eight Massachusetts towns on Cape Cod. Smoking status was determined as ever active, ever passive only, and never active never passive. Odds ratios were adjusted for a history of radiation therapy, BMI, family history of breast cancer, histories of breast cancer and/or benign breast disease, alcohol consumption, age at first birth and parity.

In contrast to their previous study (Lash and Aschengrau, 1999), for passive only smoking no association with the risk of breast cancer was found based on duration of exposure (0-20, 20-40, >40 yrs) or age at first residence with a smoker. When the first pregnancy was used to demarcate ETS exposure, there was a slight but not statistically significant risk associated with ETS only exposure prior to the first pregnancy (OR 1.1, 95% CI 0.64-1.9). Passive exposures before and after, or exclusively after the first pregnancy were associated with even lower ORs (0.85, 95% CI 0.56-1.3 and 0.55, 95% CI 0.31-0.96, respectively).

The cases in this study were matched to controls by age and vital status but no information was provided on either the age distribution or the menopausal status of the participants, both of which may be important in the interpretation of the reported null result. The only information in the paper regarding potential bias is: *"Given that smoking history and history of residential passive smoke exposure should be well recalled, and given that an earlier investigation using a similar survey and population yielded causal results, we doubt that non-differential misclassification of exposure status accounts for the null results reported here."*

These results are in apparent conflict with the authors' earlier study. The present study was published as a brief communication and a more detailed report addressing these issues may be forthcoming.

Shrubsole et al. (2004) analyzed data from the population-based Shanghai Breast Cancer Study (SBCS) to investigate the association between ETS exposure and the risk of breast cancer in women 25-64 years of age. Interviews of 1,459 women with breast cancer and 1,556 controls, frequency matched for age, provided data on demography, menstrual and reproductive history, diet, cancer and other disease history, weight, and physical activity. Questions about passive smoke exposure were added seven months after the initiation of the study, and collected data on exposures both at home (spousal) and at work from 1,119 cases and 1,231 controls. The analyses specifically excluded women with past or current histories of active smoking. Unconditional logistic regression was used to obtain risk estimates after controlling for breast cancer in a first-degree relative, history of fibroadenoma, ages at menarche, first live birth and menopause, BMI, physical activity, age, education, and menopausal status.

There was not a significant association between workplace ETS exposure and breast cancer among postmenopausal women. However, among premenopausal women (OR 1.6; 95% CI 1.0-2.5) and all women combined (OR 1.6; 95% CI 1.0-2.4), the association approached significance at the highest exposure levels with a significant dose-response trend (P for trend =0.02, 0.03, respectively; Table 7.4.1J). There was no apparent association of breast cancer with spousal smoking. While the combination of spousal exposure and high exposure at work resulted in elevated risk, these results were not statistically significant. For the summary risk estimates presented in Section 7.4.1.3, an ever-exposed grouping was created (as described for Smith *et al.*, 1994) by combining workplace only (OR 1.1; 95% CI 0.8-1.5), husband only (OR 0.9; 95% CI 0.7-1.2), and husband and workplace (OR 1.1; 95% CI 0.8-1.4) categories yielding an OR 1.02 (95% CI 0.81-1.29). A similar procedure was performed for evaluating premenopausal women yielding an OR 1.10 (95% C I 0.83-1.46).

Strengths of this study include its large size, population-based design and high participation rate. It is limited by having no exposure data on household ETS sources other than the husband, or on

passive smoke exposure during childhood. As a result, there may have been some exposure misclassification that contributed to the observed results. Interviews were conducted in person and may have been subject to interviewer bias. Assessment of workplace ETS exposure was limited to the preceding five years but assumed to reflect longer-term exposure. However, this assumption was not verified. Selection bias is thought to have been limited by the population-based design and the high participation rate (91.1%). The data in general are suggestive of increased risk for breast cancer among premenopausal women exposed to ETS at work.

Reynolds et al. (2004a) conducted a prospective analysis of breast cancer risk associated with passive and active smoking in the California Teacher Study (CTS), a large cohort of professional school employees. Of the 329,000 eligible women, 35% (116,544) were included in the study and followed from 1995 to 2000. A survey at baseline collected information on smoking history among active and former smokers, as well as on passive exposure among never-smokers. Never-smokers were categorized as passively exposed if they reported ever having lived with a smoker. This group was subdivided based on the period of ETS exposure: during childhood only, only as an adult, or with exposure during both periods. No other sources of ETS exposure were included. Other risk factors included in multivariate analyses were age, ethnicity, family history of breast cancer, alcohol consumption, age at menarche, pregnancy history, physical activity, BMI, menopausal status, and estrogen hormone therapy. While socioeconomic status was not explicitly addressed in this analysis, the nature of the cohort likely limits disparity in this variable. Among the 116,544 women in the cohort, 2,005 breast cancer cases were identified. The subset of never-smoking women (n = 76,189) included 1,150 breast cancer cases. Hazard ratios (HR) were estimated based on Cox proportional hazard regression models.

This study found no association between passive smoke exposure and breast cancer among never-smokers regardless of exposure period (childhood, adult, both), or menopausal status (Table 7.4.1L). It should be noted, however, that in this study premenopausal status is actually women who were pre- or perimenopausal at enrollment. A significant percentage of these would have become postmenopausal during the 10 year study and some cases termed "premenopausal" would have actually been postmenopausal at diagnosis. While this study has the advantages of being large, prospective, and designed specifically to examine breast cancer, the current analysis is limited in its assessment of ETS exposure. Characterizing exposure solely based on living with someone who smokes gives no information on intensity or duration of exposure and may miss significant exposures from other sources. Indeed, the authors note that beginning in the 1980s, the major exposure source was non-residential rather than residential for this cohort (Reynolds 2004b). This could lead to nondifferential exposure misclassification that could significantly dilute the apparent risk. In addition, since the exposure assessment was only made at baseline, there is no information regarding possible changes in smoke exposure or in other risk factors. In this context, the lack of association between ETS and breast cancer is difficult to interpret.

Gammon et al. (2004) utilized data collected for the Long Island Breast Cancer Study Project to evaluate the effects of both active and passive tobacco smoke exposure on breast cancer incidence. Cases were women residents of Nassau and Suffolk Counties on Long Island of any age or race newly diagnosed with in situ or invasive breast cancer between August 1, 1996 and July 31, 1997. The racial distribution indicated study participants were primarily Caucasian, and subject education levels were high. Information on active and passive smoke exposure (in the

home only), alcohol use, menstrual history, hormone use, demographics, physical activity, pregnancy history, occupational history, residency history, pesticide use, and a number of other factors were obtained by interviewer-administered questionnaire. Breast cancer risk was evaluated in relation to active smoking, passive exposure only, active and passive exposure or neither, using unconditional logistic regression and accounting for a large number of covariates. These covariates included parity, age at menarche, number of live births, lactational history, oral contraceptive use, hormone replacement therapy, body mass index, family history of breast cancer, dietary intake of fruits and vegetables, and several other factors. Work exposure and other exposure to ETS were not evaluated in this study.

For all women, there was no statistically significant elevation in odds ratio compared to never exposed for passive smoking only (residential exposure), active smoking, or both active and passive smoking (Table 7.4.1.J). Risk appears to be elevated slightly for active plus passive smokers, although not significantly. The authors note that the OR increases slightly to 1.22 (95%CI 0.90-1.66) for ETS exposure when exposure is of long duration (>361 months).

The analyses of smoke exposure (active, passive or otherwise) did not indicate elevated risks for childhood exposure (prior to age 18), exposure before first full-term pregnancy, by menopausal status, body mass index, alcohol intake, use of oral contraceptive, or use of hormone replacement therapy. In those with a family history of breast cancer, exposure to passive smoke only is associated with elevated risk (OR 1.49), but with broad confidence interval including no effect (95%CI 0.79-2.82).

When data for ever passively exposed to spousal smoking (as opposed to any residential exposure) were examined, significantly elevated risks were noted for exposure for 1-181 months (OR1.50; 95%CI 1.05-2.14) or for 326 months or longer (OR2.10; 95%CI 1.47-3.02) (Table 7.4.1J); risks for exposures to spousal smoking for 182-325 months were not elevated (although they had the fewest cases in this category). These data thus provide some evidence of an association between long-term exposure to passive smoking from the spouse and elevated risk of breast cancer.

This study's strengths include: accounting for a large number of confounders, an overall large sample of cases and controls, a lifetime assessment of residential passive smoke exposure and active smoking history, and a referent group that excluded active smokers. However, similar to many ETS studies, data on sources of exposure other than that in the home are lacking. Thus there may be nonsmokers in the non ETS-exposed category that were exposed to ETS at work. This type of misclassification biases towards the null.

Hanaoka et al., (2005) investigated the role of tobacco smoke exposure in the etiology of breast cancer in a prospective cohort study of middle-aged Japanese women. In 1990, a self-administered questionnaire collected baseline data on personal and family medical histories, smoking habits, alcohol use, dietary habits and other lifestyle factors. Passive smoking was defined as a history of exposure to residential ETS or routine exposure to ETS in any work and/or public setting. The age at onset (before or after 20 years of age) for residential exposure and frequency of exposure (for current occupational/outside home exposure) were also determined. Cancer incidence and mortality data were collected during follow-up through the end of 1999. Of the 21,805 women participating in the study, 180 developed breast cancer.

Relative risks were estimated by the Cox proportional hazards model with adjustment for age, area, education, employment status, BMI, family history of breast cancer, benign breast disease, age at menarche, parity, menopausal status, and hormone and alcohol use. Fruit and vegetable consumption were not included as they had little effect on the estimates. No data were available on breast-feeding.

There was a significantly elevated risk of breast cancer among premenopausal never-smoking women with ETS exposure (RR 2.6, 95% CI 1.3; 5.2) (Table 7.4.1L). However, after menopause, no elevated risk was evident. Among all women (pre- and postmenopausal), active smoking was associated with an elevated risk of breast cancer that was of borderline statistical significance (RR 1.7, 95% CI 1.0; 3.1), while the risk for passive exposure in never smokers (RR 1.10; 95% CI 0.80-1.60) was not significant.

In pre-, but not postmenopausal women, ETS exposure in occupational and/or public settings was associated with an elevated breast cancer risk (RR 2.3, 95% CI 1.4; 3.8). Also in these settings, a significant exposure-response trend was observed [almost none, RR 1.0; 1-3 days/month, RR 0.6 (95%CI 0.4; 2.4); >1 day/week RR 2.2 (95% CI 1.4; 3.7); p for trend 0.002] (Table 7.4.1M).

This prospective population-based study has the advantages of general applicability and limited recall or selection bias. This is the first prospective cohort study to utilize a referent population that excluded both ETS exposure in childhood and from adult residential and occupational sources. Smoking habits and passive exposures were assessed in more than one environment, and thus better capture the subjects' actual exposures than studies based on marriage to a smoking spouse. However, no biochemical determination of exposures was done and exposure was only assessed at baseline for occupational/outside home sources. Cessation of smoke exposure during the 10-year follow-up could result in some misclassification that might bias the results towards the null. Some strata in the analysis are only sparsely populated thus limiting the study's power to detect an effect in those strata. Nevertheless, this study provides clear evidence that both passive and active smoking significantly increase the risks of breast cancer among premenopausal women, and that there is significant exposure-response for passive smoking. In this study, postmenopausal women were not found to be at higher risk from passive smoke exposure.

7.4.1.2.3. Meta-analysis

Three meta-analyses have appeared in the recent literature, one as a published paper (Khuder and Simon, 2000), one in a book chapter (Morabia *et al*., 2001), and another in a published letter (Wells, 1998a). In addition, OEHHA presents a meta-analysis below.

Khuder and Simon (2000) conducted a meta-analysis of eleven studies published between 1984 and 2000 that examined the association between ETS and breast cancer. The bulk of these studies, comprising three cohort and eight case-control studies, have been reviewed in this and the previous OEHHA document (Cal/EPA, 1997). Due to heterogeneity among the studies, a random-effects model was employed that gave a combined risk estimate (OR) of 1.41 (95% CI 1.14-1.75). This estimate was based on both published and unpublished studies. The estimate from the seven published studies was similar (OR 1.43; 95% CI 1.10-1.85). Among seven studies that stratified by level of passive exposure, the ORs for the lowest level of exposure

ranged from 0.80 to 3.10, and for the highest levels, from 1.10 to 3.20. A positive dose-response relationship was reported in all seven studies, with a significant test for trend in two cases. All studies in this analysis found elevated risks, seven of which were statistically significant, thus supporting an association of ETS exposure with breast cancer.

Morabia *et al*. (2001) conducted a meta-analysis of six studies of breast cancer and passive smoking, including 5 case-control and one prospective study, and provide a pooled risk estimate for these studies indicating significant associations between ETS exposure and breast cancer (OR1.7; 95% CI 1.3-2.3). Four of these studies were evaluated by Wells (1998a), who derived a pooled estimate of 1.71 (95% CI 1.30-2.25).

Thus, meta-analytic studies provide, statistically significant point estimates for breast cancer which indicate a modest association with ETS exposure. Our own meta-analysis discussed below also provides positive statistically significant effect estimates for breast cancer risk [OR 1.25 (95% CI 1.08-1.44) overall for 19 studies; 1.68 (95% CI 1.31; 2.15) for premenopausal women in 14 studies).

7.4.1.3. OEHHA Summary Risk Estimates

OEHHA worked with Dr. Kenneth Johnson (Health Canada) to review published studies reporting on breast cancer risk associated with passive smoking among women who report never having smoked, and to conduct meta-analysis of those studies. The studies were then classified by their ability to identify a measure of lifetime exposure to ETS (Table 7.4.1A below). Studies of passive smoking and breast cancer from 1984 through January 2005 were identified through a literature search, reviews of the literature, and data call-in (as discussed in Chapter 1). Minimum criteria for inclusion in the meta-analysis were: 1) the study was published in the peer reviewed literature; 2) the study utilized established epidemiologic design (case-control or cohort study); 3) a quantitative measure of exposure to passive smoke was reported; 4) the study allowed examination of the effect of passive smoking among never-smoking women. Several studies abstracted in this section failed to meet these criteria and were not included in the meta-analysis because they were published only as abstracts (Rookus *et al*., 2000; Woo *et al*., 2000), did not present separate data for never smokers (Marcus *et al*., 2000), or had data that appeared inconsistent and that could not be verified by contacting the author (Liu *et al*., 2000). As noted in Chapter 1, the overall meta-analysis uses risk estimates from individual studies that are based on the least stratification in order to represent the "overall exposed" versus referent group. Thus, the pooled estimates are biased towards the null as the analysis does not incorporate elevated risk estimates for higher exposure groups, or other susceptible populations. We also conducted meta-analysis of data for women who were premenopausal or younger than age 50 at diagnosis in the case-control studies or at baseline in the cohort studies. A version of this analysis, authored by Dr. Johnson, has been published (Johnson, 2005).

7.4.1.3.1. Overall Risk in Women of All Ages

Nineteen studies were utilized for a meta-analysis, which yielded a summary risk estimate of 1.25(CI 1.08-1.44) for breast cancer overall in all exposed women (see Table 7.4.1B and Figure 7.4.2 below). However, the risk estimates were heterogeneous ($p<0.001$). OEHHA separately evaluated studies which included all major sources of lifetime passive smoke exposure (combined childhood residential, adult residential and occupational as defined in Table 7.4.1A

below). When the summary was limited to the five studies which satisfied this exposure assessment criteria (all were case-control studies), the summary risk estimate was 1.91 (95% CI 1.53 - 2.39) and statistical tests were consistent with homogeneity (p= 0.235). This is consistent with the analyses by Wells (1998a), Morabia *et al*. (2001), and Khuder and Simon (2000) cited above. Using just the studies that did not include all major sources of lifetime passive smoke exposure, the estimated summary risk was 1.06 (95% CI 0.96-1.17). Among these studies, the cohort studies and the case-control studies yielded summary estimates of 1.02 and 1.14 respectively. These results support the assertion that poor exposure assessment biases the results towards the null.

7.4.1.3.2. Risk in Younger (Primarily Premenopausal) Women

Analysis of the 14 studies where passive smoking-premenopausal breast cancer risk estimates could be established yielded a summary risk estimate of 1.68 (95% CI 1.31 - 2.15). (See Table 7.4.1C and Figure 7.4.3 below.) Here as well, the estimates were heterogeneous. Ten studies had individual risk estimates of 1.5 or higher for younger, primarily premenopausal women. In the five studies which adequately assessed major sources of lifetime passive smoke exposure, the summary risk estimate for premenopausal breast cancer was 2.20 (95% CI 1.69-2.87). For these five studies the statistical test for heterogeneity was consistent with homogeneity (p= 0.354). Combining the studies in which important passive sources were missed yields a pooled risk estimate of 1.33 (95% CI 1.04 – 1.70). Breast cancer is a common disease and ETS is a widespread and frequent exposure; an effect estimate of even 1.25 implies a large number of women will be impacted by ETS exposure. More importantly, the effect estimate for younger, primarily premenopausal women derived from studies with the best exposure assessment indicates a strong (>2) and consistent association.

Table 7.4.1A. Quality of Exposure Assessment in Studies of ETS and Breast Cancer Risk.

	Environmental Tobacco Smoke Exposure Assessment					
Study	**Summary of Exposure Measures**	**Childhood Exposure**	**Adult Residential Exposure**	**Occupational Exposure**	**Other Exposure**	**Important Exposure Missed?**
Hirayama, 1984	husband's smoking history	No	husband's smoking history	No		likely
Sandler *et al.,* 1985b	childhood and husband's history	Years smoked by parents and others in household	husband's smoking history	No		likely
Smith *et al.,* 1994	lifetime residential and occupational	detailed history	detailed history	detailed history		unlikely
Morabia *et al.,* 1996	lifetime residential and occupational and social	detailed history	detailed history	detailed history	social	unlikely
Millikan *et al.,* 1998	adult residential	No	housemate's smoking	No	No	likely
Lash and Aschengrau, 1999	lifetime residential	Yes	Yes	No		likely
Zhao *et al.,* 1999	lifetime passive smoking history	Yes	Yes	Yes	Yes	unlikely
Jee *et al.,* 1999	husband's smoking history	No	husband's smoking history	No		likely
Delfino *et al.,* 2000	adult residential	No	adult residential	No	No	likely
Johnson *et al.,* 2000	lifetime residential and occupational	# of smokers in each residence	# of smokers in each residence	For each job: # of smokers who smoked regularly in immediate work area		unlikely
Wartenberg *et al.,* 2000	husband's smoking history	No	husband's smoking history	No*		likely

* Current occupational exposure in 1982 collected, but only husband's smoking history used for main analysis and husband's history not used in analysis of 1982 cross-sectional exposure.

Table 7.4.1A. Quality of Exposure Assessment in Studies of ETS and Breast Cancer Risk.

	Environmental Tobacco Smoke Exposure Assessment					
Study	**Summary of Exposure Measures**	**Childhood Exposure**	**Adult Residential Exposure**	**Occupational Exposure**	**Other Exposure**	**Important Exposure Missed?**
Liu *et al.,* 2000	Childhood, youth, adult, home work, #cpd	Yes	Yes	Yes	No	unlikely
Nishino *et al*., 2001	Currently living with smoker(s) in 1984	No	Husband, wife, parents, children or others living in household who smoke (currently in 1984)	No	No	likely
Egan *et al*., 2002	Parental, years lived as adult with a smoker, current (1982) home and work.	Mother, father or both parents smoked	Years lived with smoker, current 1982	Current, in 1982 only	No	likely
Lash & Aschengrau, 2002	Lifetime residential	Yes	Yes	No	No	likely
Kropp & Chang-Claude, 2002	Years exposed to age 50	Years exposed	Years exposed	Years exposed	No	unlikely
Gammon *et al.,* 2004	Adult residential	No	Yes	No	No	likely
Reynolds *et al*., 2004a	Lifetime residential	Yes	Yes	No	No	likely
Shrubsole *et al*., 2004	Husband and workplace	No	Husband's smoking	During prior 5 years	No	likely
Hanaoka *et al*., 2005	lifetime residential, outside home cross section at baseline	Yes	Ever lived with regular smoker	Current 1990 only	Current 1990	likely

Table 7.4.1B. Summary estimates for passive smoking and overall breast cancer risk when compared to women who reported no active smoking and no regular ETS exposure

Study	Study Design[a]	Important ETS Exposure Missed	Relative Risk[b]	95% Confidence Interval Lower	Upper	Statistical Weight (Random Effects)
Hirayama 1984	cohort	likely	1.32	0.83	2.09	9.03
Sandler *et al.* 1985b	cc	likely	1.62	0.76	3.44	4.91
Smith *et al*., 1996.	cc	unlikely	2.53	1.12	5.71	4.39
Morabia *et al.* 1996	cc	unlikely	2.30	1.50	3.70	9.24
Millikan *et al.*1998	cc	likely	1.30	0.90	1.90	10.93
Lash & Aschengrau, 1999	cc	likely	2.00	1.10	3.70	6.63
Delfino *et al*, 2000	cc	likely	1.86	0.81	4.27	4.26
Zhao *et al* 1999	cc	unlikely	2.38	1.66	3.40	11.28
Jee *et al.*1999	cohort	likely	1.30	0.90	1.80	11.57
Johnson *et al.* 2000	cc	unlikely	1.48	1.06	2.07	11.86
Wartenberg *et al.* 2000	cohort	likely	1.00	0.80	1.20	15.18
Nishino *et al.*2001	cohort	likely	0.58	0.32	1.10	6.48
Kropp & Chang-. 2002	cc	unlikely	1.59	1.06	2.39	10.18
Lash & Aschengrau, 2002	cc	likely	0.85	0.63	1.10	13.26
Egan *et al.* 2002	cohort	likely	1.06	0.90	1.25	16.08
Reynolds *et al*., 2004a	cohort	likely	0.94	0.82	1.07	16.73
Shrubsole *et al*., 2004	cc	likely	1.02	0.81	1.29	14.44
Gammon *et al*., 2004	cc	likely	1.04	0.81	1.35	13.86
Hanaoka *et al*., 2005	cohort	likely	1.10	0.80	1.60	11.57
Meta-analysis Results						**Test for heterogeneity**
Summary RR[c] all studies			1.25 (1.11)[d]	1.08 (1.04)	1.44 (1.19)	p<0.001
Summary RR - important ETS sources collected			1.91 (1.89)	1.53 (1.57)	2.39 (2.27)	p=0.235
Summary RR - important ETS sources missed			1.06 (1.03)	0.96 (0.96)	1.17 (1.11)	p=0.106
Cohort studies - important ETS sources missed			1.02 (1.01)	0.92 (0.93)	1.14(1.10)	p=0.229
Case-control studies - ETS sources missed			1.14 (1.08)	0.94 (0.95)	1.38 (1.23)	p=0.094

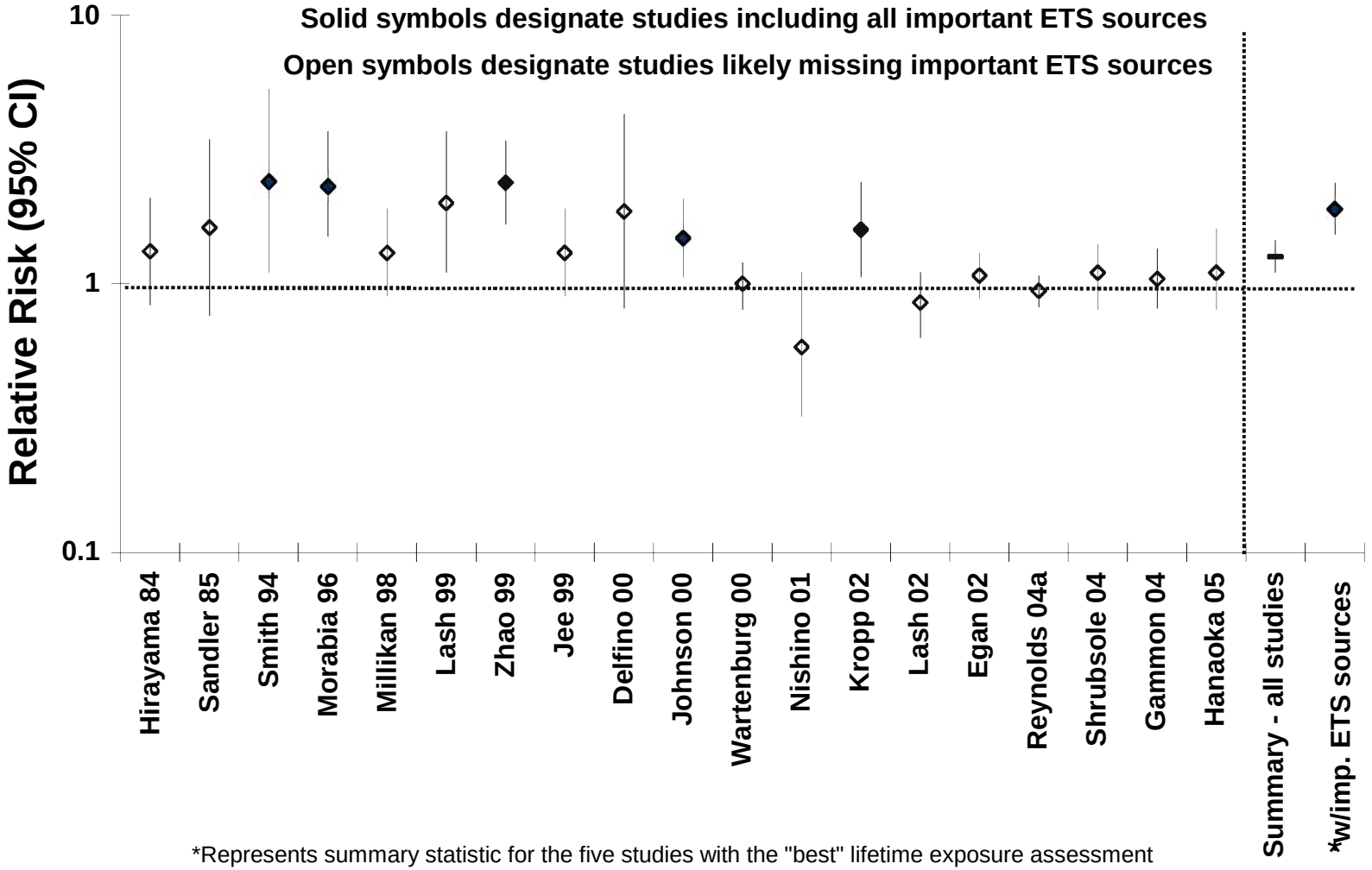
[a] cc = Case-Control.

[b] Odds ratios assumed to be a reasonable approximation for the relative risk in case-control studies. Weighting reported is for full model.

[c] Summary RR estimates were calculated using the method of DerSimonian and Laird.
Note: For several studies, summary overall risk estimates had to be calculated using component risks and confidence intervals reported in the paper and combined using methods described under Smith *et al*. (1994) and other individual study reviews. For several of the earlier studies, risk estimates for the desired comparisons were published in letters by Wells (1991, 1992a, 1998a) after personal communication with the authors. Combined estimates: Hirayama 1984, Wells letter (1998a). For Smith *et al.* (1994), estimated overall passive smoking risk calculated by summarizing the adjusted lifetime exposure categories (1-200, > 200 cigarette-years); Zhao *et al*. (1999) estimates from personal communication from author (to K. Johnson) correcting misprint in original paper; Johnson *et al*. (2000) combined estimates for pre- and postmenopausal risks; Egan *et al*. (2002) combined currently exposed at work and home; Shrubsole *et al.* (2004) combined husband or workplace only and husband and workplace exposure. Smith *et al*. (1994) and Kropp and Chang Claude (2002) studies only include younger women.

[d] Parentheses in summary RRs denote fixed effects model.

Fig. 7.4.2 OEHHA summary estimates for passive smoking and overall breast cancer risk when compared to women who reported no active smoking and no regular ETS exposure.



*Represents summary statistic for the five studies with the "best" lifetime exposure assessment

Table 7.4.1C Summary risk estimates for ETS and breast cancer in premenopausal women when compared to women who reported no active smoking and no regular ETS exposure

Study	Study Design[a]	Important ETS Exposure Missed	Relative Risk	95% Confidence Interval Lower	Upper	Statistical Weight (Random Effects)
Hirayama 1984[b]	cohort	likely	1.50	0.50	4.20	2.39
Sandler 1985[c]	cc	likely	7.10	1.60	31.3	1.43
Smith 1994[d]	cc	unlikely	2.53	1.12	5.71	3.38
Morabia 1996	cc	unlikely	3.60	1.60	8.20	3.37
Millikan 1998	cc	likely	1.50	0.80	2.80	4.44
Delfino 2000	cc	likely	2.69	0.91	8.00	2.32
Zhao 1999[e]	cc	unlikely	2.56	1.63	4.01	5.69
Johnson 2000	cc	unlikely	2.30	1.20	4.60	4.16
Wartenberg 2000[f]	cohort	likely	1.15	0.82	1.60	6.58
Kropp 2002	cc	unlikely	1.59	1.06	2.39	6.03
Shrubsole 2004[g]	cc	likely	1.10	0.83	1.46	6.96
Gammon 2004	cc	likely	1.21	0.78	1.90	5.73
Hanaoka 2005	cohort	likely	2.60	1.30	5.20	4.03
Reynolds 2004a	cohort	likely	0.93	0.71	1.22	7.04
Meta-analysis Results						**Test for heterogeneity**
Summary RR [h] all studies			1.68 (1.38)[i]	1.31 (1.21)	2.15 (1.56)	$p < 0.001$
Summary RR - important ETS sources collected			2.20 (2.18)	1.69 (1.70)	2.87 (2.79)	$p = 0.354$
Summary RR - important ETS sources missed			1.33 (1.17)	1.04 (1.01)	1.70 (1.36)	$p = 0.032$
Cohort studies - important ETS sources missed			1.27 (1.11)	0.86 (0.91)	1.86 (1.35)	$p = 0.051$
Case-control studies - important ETS sources missed			1.47 (1.26)	1.00 (1.01)	2.16 (1.56)	$p = 0.082$

[a] cc = Case-Control.

[b] Based on estimates published in letters by Wells (1991,1992a,1998a) after personal communication with the authors. Premenopausal estimate obtained by using husband age category of 40-49 years (Wells, 1991).

[c] Based on estimates published in letters by Wells (1991,1992a,1998a)

[d] Smith *et al*. (1994), estimated overall passive smoking risk calculated by summarizing the adjusted lifetime exposure categories (1-200, > 200 cigarette-years)

[e] Zhao *et al.* (1999), premenopausal data from personal communication (K. Johnson) with author, based on menopausal status at time of diagnosis.

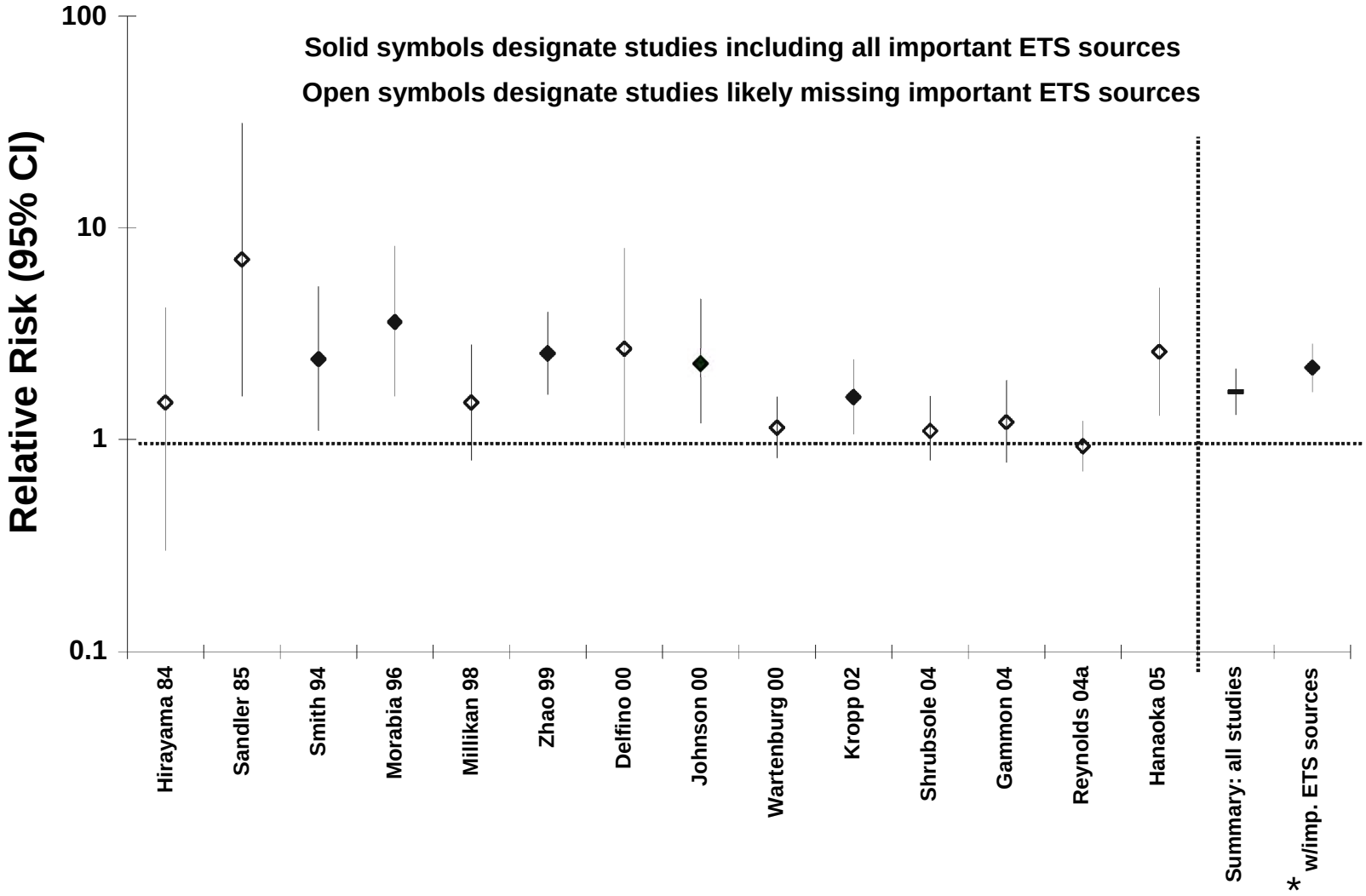
[f] Wartenberg *et al.* (2000), combined data for current and former spousal smoking age < 50 at baseline table 6.

[g] Shrubsole *et al*. (2004) combined husband or workplace only and husband and workplace exposure

[h] Summary RR estimates were calculated using the method of DerSimonian and Laird.

[i] Parentheses in summary RRs denote fixed effects model.

Fig. 7.4.3 Summary risk estimates for ETS and breast cancer in premenopausal women



*Represents summary statistic for the five studies with the "best" lifetime exposure assessment.

7.4.1.4. Discussion of ETS and Breast Cancer

Many population-based case-control studies (as well as three cohort studies), controlling for several important reproductive, dietary and other potential confounding factors, have identified elevated breast cancer risks for residential and occupational exposure overall or in individual strata. Higher risks were noted in several studies for breast cancer diagnosed in women under age fifty (primarily premenopausal), or with long duration or high intensity exposure. The toxicological data on carcinogenicity of tobacco smoke constituents (see Table 7.4.1E) strongly support that the risk associated with ETS exposure is highly plausible.

Several population-based case-control studies reported evidence of a positive dose-response relationship with passive smoking, particularly among premenopausal women (Morabia *et al*., 1996; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Shrubsole *et al*., 2004). Adjusted ORs were around 3.0 in the highest exposure categories (Johnson *et al.*, 2000). Breast cancer risk appears stronger for certain subgroups of women based on menopausal status or age, timing of exposure (childhood or prior to first pregnancy).

7.4.1.4.1. Criteria for Determining Most Informative Studies

Studies that were the best methodologically, especially with respect to exposure assessment, were emphasized by OEHHA in our weight-of-evidence evaluation. Several characteristics of study design and analysis in the individual studies reviewed affect their utility in determining whether there is a relationship between ETS exposure and breast cancer. While in general these factors (e.g., adequate exposure assessment and minimized exposure misclassification) are important for all epidemiologic studies, they are of particular importance in establishing the framework for evaluating the quality of these studies and have not been met by the majority of them. These factors are above and beyond the usual considerations such as study design, sample size, and adequacy of approach to bias and confounding (as discussed in chapter 1). These study characteristics include:

1) Exposure assessment - Factors deemed to enhance study quality include an historical determination of lifetime exposure to tobacco smoke including estimation of childhood and adult exposures, and both residential and occupational and other non-residential exposures. Exposure assessments that specifically attempt to ascertain exposures during multiple time periods are preferable to those relying upon a single point in time (e.g., current or at baseline).

2) Referent population – Studies which utilize an "unexposed" referent population that attempts to limit or eliminate those with ETS exposure are considered superior. In other words, the exposed group should be compared to those with no (or at least limited) ETS exposure from all sources and time periods. Those studies which failed to collect the desirable information delineated in #1 above are unable to satisfy this criterion.

3) Potential windows of susceptibility and timing of diagnosis – Studies which include examination of peri-pubertal adolescent and prepregnancy/nulliparous exposures are preferable. Reporting pre- and postmenopausal status ideally at the time of diagnosis, or at a minimum at baseline (as was done in many of the existing cohort studies) is desirable, particularly with adequate sample size.

4) Given that all of the criteria above relating to sources, quantity, and timing of exposure are satisfied, a prospective study is considered of higher quality than an equally strong case-control study.

Utilizing the above quality framework, six studies examining the association between ETS exposure and breast cancer are considered to meet these criteria (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Hanaoka *et al*., 2005) and are considered to be the best studies methodologically and, therefore, most informative (see Table 7.4.1A). Hanaoka's exposure measures are more limited than the others (occupational exposure was measured only for current exposure at enrollment), and so Hanaoka *et al*., (2005) was excluded from the stratified meta-analysis of best exposure assessment studies. However, it was the best of the prospective cohort studies reviewed and included the minimum characteristics noted above. Thus, OEHHA included Hanaoka *et al*., (2005) in our group of most informative studies. Previous cohort studies were problematic due to limited exposure ascertainment. In particular, the referent groups contained individuals exposed to ETS from workplace or other sources and/or during childhood. The discussion below will highlight the findings of these studies as well as include discussion of the overall weight of evidence from all epidemiologic studies and other supporting evidence.

The importance of the effect of exposure misclassification by having passive smokers in the referent group has been demonstrated in active smoking studies (Morabia *et al.*, 1996; Lash and Aschengrau, 1999; Johnson *et al.*, 2000; Kropp and Chang-Claude, 2002). Morabia *et al*. (1996) and Kropp and Chang-Claude (2002) each evaluated the influence on estimated breast cancer risk of the referent group by comparing smokers to all non-smokers (commonly utilized in studies) and smokers to a referent group of non-smokers having no spousal, residential or workplace ETS exposure. The risk estimates were higher when comparison was made to a never passive, never active group (see Table 7.4.1D). Johnson *et al.* (2000) demonstrated that comparison of smokers' breast cancer risks to never passively exposed non-smokers moved the breast cancer risk estimate upwards, and the estimate became statistically significant. This demonstrates the problem of limited exposure assessment. In most of the passive smoking studies of ETS, poor exposure assessment results in a referent population contaminated with ETS-exposed individuals, thus biasing results towards the null.

Table 7.4.1D. Utilizing Unexposed Referent Raises Risk Estimate (within study comparison, Morabia *et al*., 1996)

Exposure	Smokers vs non-smokers with no ETS	Smokers vs non-smokers (includes ETS exposed)
Active 1-9 cpd	2.2 (1.0; 4.4)	1.2 (0.8; 2.0)
10-19 cpd	2.7 (1.4; 5.4)	1.7 (1.1; 2.5)
≥ 20 cpd	4.6 (2.2; 9.7)	1.9 (1.2; 2.9)
Ever passive	3.2 (1.7; 5.9)	

(There were similar within-study findings in Johnson *et al*., 2000, Lash and Aschengrau, 1999, and Kropp and Chang Claude, 2002)

7.4.1.4.2. Evidence of Causality

7.4.1.4.2.1. Biological Plausibility

There are extensive data showing carcinogenesis in animals at a number of relevant sites by individual chemical components of tobacco smoke. These included some components that are actually more abundant in sidestream or environmental tobacco smoke than in mainstream smoke. The occurrence of these established carcinogens in tobacco smoke is important evidence of biological plausibility of the hypothesized causal association (see discussion of causal criteria in Chapter 1). This argument may be re-examined with specific reference to the question of whether exposure to tobacco smoke (by active or passive smoking) is plausibly associated with breast cancer in humans. Table 7.4.1E lists 20 chemicals identified in tobacco smoke that are listed as carcinogens by IARC, and which induce mammary tumors. The table provides the IARC classification: 1 carcinogenic to humans; 2A probably carcinogenic to humans; 2B possibly carcinogenic to humans. The table is not by any means an exhaustive list of the tobacco smoke components that may be carcinogenic to the mammary gland. The limitations on the extent to which tobacco smoke constituents have been adequately tested for carcinogenesis at any site were noted in the discussion at the beginning of this chapter. This applies to an even greater degree to mammary carcinogenesis, since this site has been examined in screening assays considerably less often than sites such as the skin or the lung.

It is assumed in this discussion that there is concordance between animal and human susceptibility to carcinogenesis, with regard both to active chemicals and site of action. This is a reasonable, if not infallible, assumption. Indeed it may if anything understate the number of potential human mammary carcinogens since this appears to be a relatively susceptible site in humans. Some rodent strains show high sensitivity to mammary carcinogenesis, whereas others do not. (No assumption is necessarily being made about the relative potency of any of these mammary carcinogens in animals *vs*. humans, although the probability of observing an effect in a relatively small-scale animal bioassay is greater for a potent carcinogen.)

Several polycyclic aromatic hydrocarbons that occur in tobacco smoke are known mammary carcinogens in laboratory animals. Cavalieri *et al.* (1989) identified dibenzo[a,l]pyrene as an extremely potent carcinogen in both skin and mammary tissue of the mouse. Arif *et al.* (1999) described this compound as “one of the most potent animal carcinogens and mutagens”. They showed formation of persistent DNA adducts in rat mammary tissue following injection of dibenzo[a,l]pyrene. These adducts were of the diol-epoxide type identified as the reactive intermediate in carcinogenesis by many other polycyclic aromatic hydrocarbons.

Table 7.4.1E. Mammary Carcinogens Found in Tobacco Smoke.

Compound	Cigarette main-stream smoke (amount per cigarette) [a]	Cigarette side-stream smoke (amount per cigarette) [b]	Cigarette smoke-polluted environments [c]	Cigar (C) or Pipe (P) smoke (µg/100 g) [d]	IARC Classific-ation[e]	Mammary gland tumors: Affected Species [f]
Aromatic hydrocarbons						
Benzene	28 - 106 µg	71 - 134 µg	5 - 22 µg/m^3	P: 34400 C: 9200-24600	1	Mouse
Benzo[a]pyrene	5.6 - 41.5 ng	52 - 95 ng	0 - 3.6 ng/m^3	C: 1.8-5.1 P: 8.4	2A	Rat
Dibenz[a,h]anthracene	4 ng	[g]			2A	Mouse [h]
Dibenzo[a,e]pyrene	Present				2B	Rat[i]
Dibenzo[a,h]pyrene	Present				2B	Rat[i]
Dibenzo[a,i]pyrene	1.7 - 3.2 ng				2B	Rat[i]
Dibenzo[a,l]pyrene	Present				2B	Rat[i]
Nitrosamines						
N-nitrosodiethylamine	0 - 25 ng		Up to 8.6 ng/m^3		2A	Rat
N-Nitrosodi-*n*-butylamine	0 - 3.0 ng				2B	Mouse
Aliphatic compounds						
Acrylamide	Present				2A	Rat
Acrylonitrile	8 - 39 µg	24 - 44 µg			2B	Rat
1,3-Butadiene	24 - 123 µg	81 - 135 µg	19 µg/m^3		2A	Mouse, rat
Isoprene	288 - 1193 µg	743 - 1163 µg	83 - 150 µg/m^3	C: 24500-63300	2B	Rat
Nitromethane	0.5 - 0.6 µg				2B	Rat[j]
Propylene oxide	0 - 100 ng				2B	Rat[k]
Urethane	20 - 38 ng				2B	Mouse, hamster
Vinyl chloride	11 - 15 ng			C: 0.14-0.27	1	Rat, mouse, hamster

Table 7.4.1E. Mammary Carcinogens Found in Tobacco Smoke.

Arylamines and nitroarenes						
4-Aminobiphenyl	2 - 8 ng	21 – 32 ng			1	Rats
Nitrobenzene	25 µg				2B	Mice[l]
ortho-Toluidine	30 - 200 ng				2A	Rats

Footnotes:

[a] IARC (2004a) citing preferentially Table 1.10 (the 1999 Massachusetts Benchmark Study), or else Table 1.14.
[b] IARC (2004a), citing Table 1.3 (the 1999 Massachusetts Benchmark Study)
[c] IARC (2004a), citing mainly Jenkins *et al*., 2000
[d] IARC (1986a) and IARC (2004a).
[e] IARC classification 1 = carcinogenic to humans; 2A = probably carcinogenic to humans; 2B = possibly carcinogenic to humans.
[f] NTP: 10th Annual Report on Carcinogens (2002) unless otherwise indicated
[g] Blank cell = no data available
[h] IARC (1973b).
[i] Cavalieri *et al*. (1989; 1991).
[j] IARC (2000).
[k] IARC (1994b).
[l] IARC (1996a).

A number of investigators have shown that human breast tissue is susceptible to formation of DNA adducts and oncogene mutations as a result of exposure to polycyclic aromatic hydrocarbons, including exposures as a result of smoking (Li *et al.,* 1999; Perera *et al.,* 1995; Conway *et al.*, 2002; Santella *et al.,* 2000; Rundle *et al.,* 2000; Li *et al.,* 2002). Metabolites and DNA adducts in urine and placenta have also been observed in humans exposed to polycyclic aromatic hydrocarbons from environmental sources including environmental tobacco smoke (Anderson *et al.,* 2001; Whyatt *et al.,* 1998a).

It is clear that mammary epithelium is capable of metabolic activation of carcinogens (reviewed by Phillips *et al*., 2001). Firozi *et al*. (2002) and Li *et al*. (1996) measured aromatic DNA adducts in breast tissue from cancer patients and controls. They found higher levels of DNA adducts in smokers than in non-smokers, and in non-cancerous tissue adjacent to a tumor than in tissue from the actual tumor. Dependence of adduct levels on polymorphisms of Cyp1A1 and NAT2 (genes specifying enzymes important in PAH metabolism) was also noted in smokers but not in non-smokers. Gene-gene interaction was noted in smokers with certain CYP1A1 and GSTM1 null polymorphisms combined having much higher levels of DNA adducts than either individually. Their findings suggest that polymorphisms of CYP1A1, GSTM1, and NAT2 significantly affect either the frequency or the level of DNA adducts in normal breast tissues of women with breast cancer, especially in smokers. Similarly, Faraglia *et al.* (2003) examined both normal and cancerous breast tissues from breast cancer patients for adducts related to 4-aminobiphenyl, a known carcinogen and tobacco smoke constituent. For normal tissues of current smokers, former smokers and non-smokers, a significant linear trend ($p = 0.04$) was observed between DNA adducts and smoking status. Consideration of both active and passive status (never either, ever passive only, ever active only, ever both) also showed a linear trend in the level of DNA adducts in normal tissue with smoking status ($p = 0.03$). An increase in adduct levels in normal tissue with passive smoking status alone (never, former, current) was seen but the trend was not statistically significant ($p = 0.14$). A significant limitation of the data set examined in this study was the small number of cases reporting neither active nor passive smoking. These studies provide evidence that carcinogens in cigarette smoke reach mammary tissue and form DNA-adducts.

The evidence with regard to plausibility of a causal association between environmental exposure to tobacco smoke and breast cancer thus includes the occurrence of identified carcinogens as components of ETS, demonstration of carcinogen-DNA adduct formation in breast tissue, demonstration of metabolic capability of mammary epithelium to biotransform carcinogens such as PAHs to the active metabolite, and demonstration that these compounds do, in fact, reach and damage human mammary tissue as a result of direct smoking or environmental exposures. This chain of evidence indicates that a causal association is highly plausible, both for active (Hecht, 2002) and passive smoking.

7.4.1.4.2.2. Consistency

A number of studies examining the association of ETS exposure with risk of breast cancer have identified elevated risks for younger, primarily premenopausal women. 13 of 14 of these studies found risks greater than one and 7 of these were statistically significant. These findings are evident across study design and geographical regions (see Figure 7.4.4 below). Several studies showed evidence of dose-response. The majority of studies: 1) adjusted for major risk factors, including reproductive history 2) attempted to assess risk for ETS exposure beyond the home

(Johnson *et al.*, 2000; Wartenberg *et al.*, 2000; Kropp and Chang-Claude, 2002; Shrubsole *et al.*, 2004; Hanaoka *et al.,* 2005); and 3) assessed risk based on timing of exposure, either during childhood (Morabia *et al*., 1996;Johnson *et al.*, 2000; Reynolds *et al*., 2004a), or relative to first pregnancy (Morabia *et al*., 1996,; Kropp and Chang-Claude, 2002; Gammon *et al*., 2004).

In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause risk estimates cluster around a null association (see Figure 7.4.4).

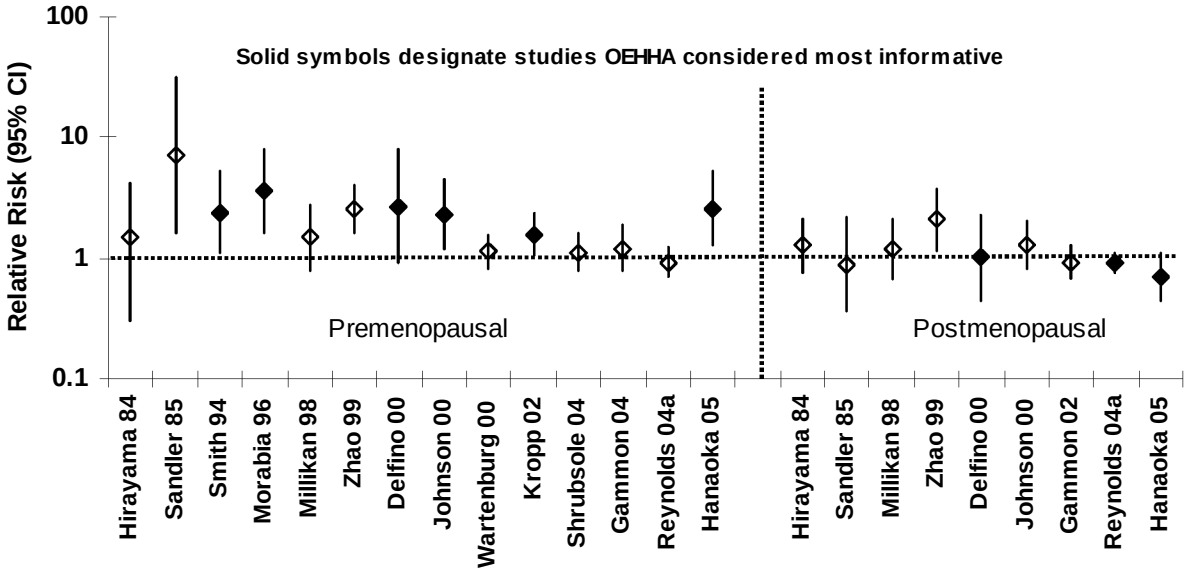


Figure 7.4.4. Comparison of studies examining ETS and breast cancer risk in pre- and postmenopausal women

7.4.1.4.2.3. Strength of Association

7.4.1.4.2.3.1. Younger Primarily Premenopausal Women

In the 14 studies that evaluated younger, primarily premenopausal women, there is a strong association between ETS exposure and breast cancer risk. All but one of these studies found risk estimates between 1.10 and 7.10 of which seven were statistically significant (Table 7.4.1C). All of the six studies considered by OEHHA to be most informative, as described in Section 7.4.1.4.1, found risk estimates of 1.59 or greater and were statistically significant (Table 7.4.1G). A summary risk estimate of 1.68 (95% CI 1.31-2.15) for breast cancer diagnosed in younger primarily premenopausal women was obtained in our meta-analysis of 14 studies. The meta-analysis of the 5 better exposure studies for premenopausal women results in a pooled risk estimate of 2.2 (95% CI 1.69-2.87).

7.4.1.4.2.3.2. Overall (Women of All Ages)

Of the 19 studies presenting summary estimates for passive smoking comparing non-smoking women with ETS exposure to those who reported no active smoking and no regular exposure to ETS reviewed for this document, 15 reported point estimates greater than one and six of these had 95% confidence intervals that excluded unity. OEHHA's meta-analysis obtained a pooled risk estimate of 1.25 (95% CI 1.08-1.44) for these 19 studies. The pooled risk estimate for the 5 studies (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002) that were considered unlikely to have missed assessing other important sources of ETS exposure was 1.91 (95% CI 1.53-2.39). Of the six studies considered by OEHHA to be most informative (the above five plus Hanaoka *et al*., 2005; see Section 7.4.1.4.1) in this assessment, all had positive risks ranging from 1.10-2.53 (Table 7.4.1F), and in all but Hanaoka *et al*., (2005) the 95% confidence intervals excluded unity.

Table 7.4.1F Breast Cancer risk with passive smoking for women of all ages (OEHHA most informative studies)

Study	Relative Risk	95% Confidence Interval	
		Lower	Upper
Smith *et al*., 1994	2.53	1.12	5.71
Morabia *et al*., 1996	2.30	1.66	3.66
Zhao *et al*., 1999	2.38	1.66	3.40
Johnson *et al*., 2000	1.48	1.06	2.07
Kropp and Chang-Claude, 2002	1.59	1.06	2.39
Hanaoka *et al*., 2005	1.10	0.80	1.60

Table 7.4.1G Breast Cancer risk with passive smoking for premenopausal women (OEHHA most informative studies)

Study	Relative Risk	95% Confidence Interval	
		Lower	Upper
Smith *et al*., 1994	2.53	1.12	5.71
Morabia *et al*., 1996	3.60	1.59	8.15
Zhao *et al*., 1999	2.56	1.63	4.01
Johnson *et al*., 2000	2.30	1.28	4.15
Kropp and Chang-Claude, 2002	1.59	1.06	2.39
Hanaoka *et al*., 2005	2.60	1.30	5.20

7.4.1.4.2.3.3. Confounding

Residual confounding is a concern when the estimated size of the association is low, as is the case for some of the breast cancer studies and for the pooled overall risk estimate. However, most of these studies adjusted for known major risk factors for breast cancer. In addition, several of the risk estimates from individual studies are above 2. It is unlikely an unknown confounding factor, which would have to be associated with both breast cancer and second-hand smoke exposure, would account for these risk estimates in younger (mostly premenopausal) women. In

most studies examined, adjusting for known confounders had little impact on the level of association between ETS and breast cancer. All of the six studies considered by OEHHA as most informative considered, and adjusted in the final model when appropriate, measures of reproductive factors (parity, age at first childbirth, age at menarche, etc.), alcohol consumption, and oral contraceptive use. Four or five of six studies also controlled for BMI, SES (or surrogates), breastfeeding, and family history. As noted above (Section 7.4.1.4.2.2), there are consistent findings of a positive association between ETS and breast cancer in women diagnosed at younger age (primarily premenopausal). Within the same group of studies there are several which present separate analysis for diagnosis post-menopause (older age). These results are generally null. It is unlikely that bias or confounding would produce an association in younger (mostly premenopausal) but not older (postmenopausal) women within the same studies.

7.4.1.4.2.4. Dose-Response Gradient

Several studies examining ETS exposure and breast cancer present evidence of a dose response (Hirayama, 1984; Jee *et al*., 1999: Johnson *et al*., 2000; Kropp and Chang-Claude, 2002: Shrubsole *et al.,* 2004; Hanaoka *et al*., 2005) (Table 7.4.1H). Hanaoka *et al*. found a relative risk for breast cancer of 2.3 (95% CI 1.4-3.8) in women who were premenopausal at cohort baseline and exposed to ETS in occupational and/or public settings. A significant exposure-response trend was observed (p = 0.002; see Table 7.4.1 G). Shrubsole *et al*. (2004) found adjusted ORs of 0.9, 1.0, 1.1, and 1.6, respectively (p for trend 0.03) for breast cancer in premenopausal women from workplace exposures of 1-59, 60-179, 180-299, and 300+ minutes/day,. Kropp and Chang-Claude (2002) report an OR of 1.42 for lifetime exposure of 1-50 hours/day-years, and an OR of 1.83 for > 50 hours/day-years (p for trend 0.009) in premenopausal women. Johnson *et al.* (2000) observed a dose-response gradient for premenopausal women for increasing levels of passive smoke exposure (residential plus occupational) in smoker-years (p=0.03). Jee *et al*. (1999) reported relative risks of 1.2 (95% CI 0.8-1.8), 1.3 (95% CI 0.9-1.8), and 1.7 (95% CI 1.0-2.8) for wives of ex-smokers, current smokers, and current smokers who smoked ≥ 30 years, respectively. Morabia *et al*. (1996) evaluated exposures of cases and controls starting at age 10 years in hrs/day - years. They reported ORs of 2.2 (95% CI 1.3-3.7) and 2.5 (95% CI 1.5-4.2) for ever passive exposures of 1-50 hr/day-yrs and >50 hr/day-yrs, respectively. The overall relative risk for ETS exposure in Hirayama's study was 1.32 but for never smoking women ages 50-59 whose spouses smoked more than 20 cigarettes/day the RR was 2.68 (95% CI 1.24-5.43) (Hirayama, 1984,1992).

While six new cohort studies (five incidence and one mortality) reviewed for this update provided inconsistent evidence of a dose response association between ETS exposure and breast cancer risk (Jee *et al.*, 1999; Wartenberg *et al.*, 2000; Nishino *et al.*, 2001; Egan *et al.*, 2002, Reynolds *et al*., 2004a; Hanaoka *et al*., 2005), ETS exposure assessment was limited, often to a single cross-sectional (baseline) assessment, thus limiting the studies' ability to find evidence of a dose-response gradient. As noted above, Hanaoka *et al.*, (2005), Jee *et al.*, (1999), and Hirayama (1984) provide evidence of a dose response.

Table 7.4.1H Evidence for a Dose Response in Passive Smoking Studies

Study	Setting	Findings OR or RR (95% CI)
Hanaoka *et al.* 2005	Premenopausal Occupational or public settings (d/mo)	Almost none 1.0 1-3 d/mo 0.6 (0.4-2.4) > 1 d/wk 2.2 (1.4-3.7) p trend 0.002
Shrubsole *et a,* 2004*l*	Premenopausal Workplace passive exposure minutes per day (mpd)	1-59 mpd 0.9 (0.6-1.4) 60-179 mpd 1.0 (0.7-1.6) 180-229 mpd 1.1 (0.7-1.7) 300+ mpd 1.6 (1.0-2.5) p trend = 0.03
Kropp & Chang-Claude, 2002	Lifetime ETS Hours/day-years (h/d-y)	1-50 h/d-y 1.42 (0.90-2.26) > 50 h/d-y 1.83 (1.16-2.87) p trend 0.009
Johnson *et al,* 2000.	Premenopausal Lifetime residential and occupational exposure in smoker-years (s-yr)	1-13 s-yr 1.5 (0.5-4.4) 14-32 s-yr 2.0 (0.9-4.5) 33-70 s-yr 2.9 (1.3-6.6) >70 s-yr 3.0 (1.3-6.6) p trend 0.03
Jee *et al,* 1999.	Husband's smoking status	Ex-smoker 1.2 (08-1.8) Current smoker 1.3 (0.9-1.8) ≥ 30 yrs smoking 1.7 (1.0-2.8)
Morabia *et al*., 1996	Ever Passive exposure	1-50 hrs/day-yrs 2.2 (1.3-3.7) >50 hrs/day-yrs 2.5 (1.5-4.2)
Hirayama, 1984/1992	Husband's smoking cigarettes/day (age 50-59)	1-19 cigarettes/day 1.3 (0.59-2.86) > 20 cigarettes/day 2.68 (1.24-5.43)

7.4.1.4.3. Limitations of Studies

Limitations of studies are described in the summaries of the individual epidemiological studies. The majority of studies controlled for alcohol consumption. A number controlled for SES, race and education, education and income, or education only. As well, the adjusted and the crude or age-adjusted results for the studies examined rarely differ substantially. Theoretically, since breast cancer is associated with higher SES, and higher SES is associated with lower likelihood of passive smoke exposure (Reynolds, 2004c), the odds ratios for breast cancer in passive smokers may have been biased to be too low in the absence of control for SES. Not controlling for SES or alcohol could impact the results strongly only if these factors were strong risk factors for breast cancer and they were highly correlated with passive smoking exposure.

Increasing alcohol consumption has been correlated with higher likelihood of ETS exposure (Reynolds *et al*., 2004c) as well as increasing hours per week of exposure (Friedman *et al*., 1983). The association between alcohol consumption and breast cancer is a relatively weak effect. Johnson *et al*. (2000) found ORs of 1.0, 1.2, and 1.1 for < 0.5, 0.5-3.5, and > 3.5 drinks/week. The Collaborative Group's analysis of 53 studies (2002) found no increased risk with up to 14 grams/day of alcohol consumption. At 15-24 grams/day the RR was 1.19. Relatively few women drink more than that; Reynold's *et al*. (2004b) found that amongst the California Teacher's Cohort, only 8% consumed more than 20 grams/day of alcohol. A

relatively infrequent behavior which is associated with only a small increase in relative risk such as this could not substantially alter the breast cancer risk estimates found in younger/premenopausal women. It should be noted that in most studies that examine alcohol, controlling for this risk factor has little impact on the risk estimates.

While SES may not be directly adjusted for in many studies, in general, the greater rates of breast cancer (between 1.1 and 2.0) found in women of higher SES are thought to largely reflect differing reproductive patterns such as parity, age at first birth, and age at menarche (Kelsey and Horn-Ross, 1993). These, along with other surrogates of SES such as education are routinely included in the multivariate analyses and inclusion of an additional variable for SES would not significantly alter the model. In addition, while Reynolds (2004b) found a significant positive correlation between a summary SES metric and former active smoking they found a non-significant negative correlation with passive smoke exposure.

Another limitation in several studies examining dose-response was lack of consideration of time-since-first-exposure in the dose-response analyses. Increased years of smoking may have been associated with longer time-since-first-exposure, and cancer risk generally goes up with time-since-first-exposure (effect modification), thus the dose–response results may have been influenced by time-since-first-exposure. As well, increased time-since-quitting may have been associated with longer time-since-first-exposure. The odds ratios in the shorter time-since-quitting periods may have been biased to be too low compared to longer time.

7.4.1.4.4. Bias in Case-Control Studies

Exposure reporting bias in case-control studies can occur if interviewers probe more deeply with cases (not a problem with self-administered questionnaires) or when cases remember past exposure better than controls (recall bias). These biases are more apt to occur if interviewers or subjects are not blinded to the main hypothesis(es) of the study. Fortunately, such bias is unlikely here since a possible link of smoking or ETS to breast cancer is not commonly known to the public nor previously accepted by the scientific community.

Two of the better quality studies (Johnson *et al*., 2000 and Morabia *et al*., 1996) examined potential bias within their studies. Morabia found that the perception of passive smoking did not change by case/control status. Johnson's multi-cancer study found that lung cancer risk assessed using the same target control group observed risks consistent with the previous literature. Both of these findings were interpreted as suggesting that recall bias was not a likely explanation for the study findings. OEHHA believes that most studies considered in this review adequately addressed potential for exposure reporting bias and those that did not were given less weight.

Both case-control and cohort studies may suffer from interviewer or recall bias since the subjects of the latter are typically adults at entry and are asked to report about ETS during earlier periods of life where exposure may be critical.

7.4.1.4.5. Controversies Regarding Relative Potency of Active and Passive Smoking

In the previous document (Cal/EPA, 1997) and elsewhere, the inconsistent results of studies available at that time examining active smoking and breast cancer were felt to undermine any determination of an association between passive smoking and breast cancer. The Surgeon-General's report (U.S. DHHS, 2004c) on active smoking concluded that there is no effect of

active smoking on breast cancer risk and, therefore, did not consider the effects of ETS in any detail. However, the only study cited as a source of information on passive smoking in the Surgeon General's 2004 report is Morabia *et al.* (1996). This contrasts with the analysis by OEHHA of four studies of ETS exposure and breast cancer noted in the earlier report (Cal/EPA, 1997), including Morabia *et al.* (1996), and twenty two studies which have appeared since 1997. Similarly, the recent IARC report (2004a) on carcinogenicity of tobacco smoke argues that "the lack of an association between active smoking and breast cancer weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer". Neither the Surgeon General's report (U.S. DHHS, 2004c) nor IARC (2004a) provide detailed analysis of the passive smoking literature on breast cancer. Nonetheless, it is important to acknowledge a wide distribution of opinion on whether ETS exposure is associated with breast cancer in non-smoking women, and the widespread perception that active smoking is not associated with breast cancer, so there could not be an association with passive smoking.

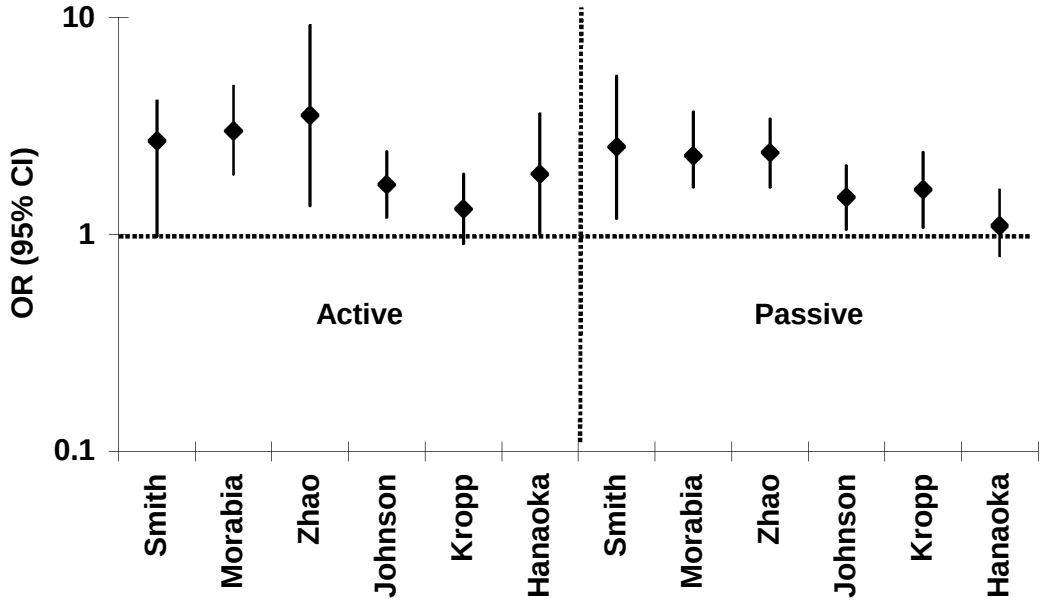
While there continues to be some heterogeneity in study results, overall, the studies presented in this update (along with in vitro and animal data on carcinogenesis) provide some evidence of a role for active smoking in causation of breast cancer. There are now studies providing evidence for gene-environment interactions and susceptible subpopulations with highly significant increased breast cancer risk associated with active smoking (e.g., those with familial high risks in Couch *et al*., 2001). Furthermore, there are studies demonstrating significant risks related to the hormonal receptor status of the tumor (Manjer *et al*., 2001; Morabia *et al*., 1998). Finally, six recent prospective cohort studies found statistically significant elevated breast cancer risk associated with active smoking for at least some of the metrics of exposure (Egan *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*. 2004a, Hanaoka *et al.*, 2005; Zhang *et al*., 2004; Gram *et al*., 2005). Thus, newer data provides evidence supportive of a causal association between breast cancer and active smoking (see Chapter 7, Appendix A). Nearly all studies that utilize a non-active/non-passive smoking referent population in which an attempt has been made to quantify the estimate of ETS exposure from numerous sources (not just spousal) find significant associations with breast cancer in at least some age or susceptibility groupings for both active and passive smoking (see figure 7.4.5 below).

Now that the association with active smoking has become considerably strengthened, and in our view provides evidence supportive of a causal association between active smoking and breast cancer, the emphasis of the argument that ETS does not cause breast cancer has shifted to the relative potency of active and passive smoking. Reasons given for concluding that the active smoking data undermine associations seen in the passive data included:

- The size of the association seen in active smokers is comparable to those noted in passive smoking: e.g., no dose response gradient between active and passive smokers is evident in the data.
- Active smokers are also passive smokers.

Several hypotheses have been suggested as explanations for the apparently flat dose-response for breast cancer between active and passive smoking. These hypotheses have been examined in various studies and reviews (Lash and Aschengrau, 1999, 2002; Morabia, 2002; Russo and Russo, 1994; Terry and Rohan, 2002; Band *et al*., 2002). Some discussion of these hypotheses, and newer data on active smoking and breast cancer risk follows.

Figure 7.4.5. Comparison of breast cancer risk from active and passive smoke exposure in studies considered most informative by OEHHA (see section 7.4.1.5).



7.4.1.4.5.1. Anti-estrogenicity of Active and Passive Smoking

Causal preventive effects from the anti-estrogenic activity of current active smoking may obscure any overall association between active smoking and breast cancer. Active smoking results in earlier age at menopause, increased risk of osteoporosis, and decreased effectiveness of hormone replacement therapy for osteoporosis (Baron *et al*., 1990; Jensen and Christiansen, 1988; Terry and Rohan, 2002) compared to nonsmokers (which would include passive smokers). These effects are evidence of the anti-estrogenicity of active smoking. The Surgeon General's report (U.S. DHHS, 2004c) on active smoking notes the potential competing effects between anti-estrogenicity and carcinogenicity on breast tissue in active smokers. Terry and Rohan (2002) note in their review of cigarette smoking and breast cancer that there is evidence to suggest active smoking influences the metabolism of estrogens resulting in more of the 2-hydroxy estradiol, which is a much less active estrogen, and less of the 16-hydroxy estradiol metabolite, which is a much more active estrogen. Several studies found statistically significant elevated breast cancer risks for ex-smokers even when current smoker's risks were not statistically significantly elevated (Millikan *et al*., 1998; Manjer *et al*., 2001; Egan *et al*., 2002). This is consistent with an anti-estrogenic effect of active tobacco smoking which is theorized to partly counter the carcinogenic effects of smoke constituents in the breast. The investigation by Band *et al*. (2002) (described in Appendix 7A) provides strong support for the competing effects of active smoking on breast cancer due to anti-estrogenic effects and presence of mammary carcinogens. The competing effect of anti-estrogenicity from active smoking is also supported by the finding of elevated risks of ER- and PR- tumors which are not estrogen-dependent, but not ER+ and PR+ tumors which depend on estrogen for growth, in premenopausal women associated with current or former active smoking (Manjer *et al*., 2001), an effect seen in some but not all

studies that evaluated this. Thus, the competing effects of antiestrogenicity and carcinogen exposure affect the breast cancer risk in active smokers. Even though active smokers are also passive smokers and likely experience higher carcinogen exposure than passive smokers, the anti-estrogenic effects of active smoking would to some extent mitigate the breast cancer risk.

The anti-estrogenic effects noted in the studies above are comparing smokers to nonsmokers (a group containing those passively exposed). Thus, the findings reflect, at least in part, the comparative effects of active to passive smoking. Few studies have looked directly at the effects of passive smoking relative to non-smokers not passively exposed. One new study of age at menopause and ETS exposure reviewed in chapter 5 of this document (Cooper, 1999) failed to find a lower age at menopause in women exposed to ETS from living with a smoker. These results are not in agreement with those of Everson *et al.* (1986), who found a decrease of 2 years in age at menopause among nonsmoking women whose spouses smoked compared to those whose spouses did not smoke. Neither paper recorded cigarettes smoked per day by the spouses or workplace exposure to ETS. Overall, there is limited data on the effect of ETS exposure on measures related to estrogenicity but the existing data suggest that active smoking may be more anti-estrogenic than passive exposure. More studies are needed to confirm this difference.

7.4.1.4.5.2. Exposure Misclassification

Because the magnitude of effect of passive smoking is similar to that of active smoking, studies should not have women exposed to ETS in the unexposed referent group. The studies of active and passive smoking reviewed here have fairly consistently indicated an underestimation of risks when exposure history was limited. Studies with more complete exposure ascertainment that limited ETS-exposed women in the "non-exposed" referent group consistently demonstrated higher breast cancer risks in both active and passive smoking studies. This was also seen in analyses within studies (Morabia *et al*., 1996; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002). Studies utilizing a limited evaluation of exposure, such as a single question about spousal smoking at baseline, have also been shown to underestimate risk of lung cancer (Johnson *et al*., 2001) and cardiovascular disease (Whincup *et al*., 2004). In addition, Whincup *et al*. (2004) evaluated cotinine at baseline in their prospective study as the measure of exposure, and showed that the risk of CHD was more strongly associated with cotinine levels in their analysis in the earlier years of follow-up than in the later years, as the exposure measure was further removed in time. This is an important exposure assessment problem in cohort studies that only evaluate exposure at baseline. Thus for many of the active and passive smoking studies, contamination of the referent group with individuals exposed to ETS biases the risk estimates downwards.

7.4.1.4.5.3. Windows of Susceptibility

Human breast tissue may be more vulnerable to exposure to tobacco smoke during certain critical time periods, for example, between menarche and first pregnancy, as is the case with ionizing radiation. Epidemiologic studies that do not evaluate ETS exposure peripubertally or prior to first pregnancy may misclassify the biologically relevant exposure and thus fail to detect a real association. The concept of windows of susceptibility around puberty and before the first pregnancy is biologically plausible in consideration of the development of breast tissue. Developmental periods include embryonic stages of nipple epithelium, puberty, pregnancy and lactation (Russo and Russo, 1994) during which the cells of the lobules and ductules divide and differentiate. Subsequent pregnancies promote differentiation of those cells which remain undifferentiated after the first pregnancy. A series of studies using a rodent model of mammary

carcinogenesis (reviewed by Russo and Russo, 1994) demonstrated that the mammary carcinogen dimethylbenzanthracene binds more readily *in vitro* to those cells that are not yet differentiated In addition, early stage cells present primarily prior to puberty in mammary tissue are more readily transformed *in vivo* by chemical carcinogens than those present after puberty, which in turn are more sensitive to transformation than those cells present following pregnancy and lactation. Studies of girls treated for Hodgkins lymphoma by radiation (Bhatia *et al*., 1996; Aisenberg *et al*., 1997), girls evaluated for scoliosis (Doody *et al*., 2000), and studies of Japanese bomb survivors (NRC, 1990; Tokanuga *et al*., 1994) clearly indicate that peripubertal radiation exposure greatly increases the risk of early-onset breast cancer. In addition, epidemiological studies show early age at first pregnancy as well as multiple pregnancies protect against breast cancer. Thus epidemiological data also support the concept of windows of susceptibility to exposure to carcinogens for breast tissue.

ETS exposure can occur before and during puberty from parental smoking while actual mainstream smoke exposure generally starts well into puberty to post-puberty and continues on into adulthood. Thus, there may be different patterns of exposure of infants and children relative to older children and adults to ETS versus mainstream smoke. The interaction of differing exposure patterns by age and type of smoke (mainstream versus ETS) may contribute to the apparent similarity of risk from ETS and active smoking with respect to breast cancer.

7.4.1.4.5.4. Similar Risks Observed in Active and Passive Smoking Studies.

The elevated risks of breast cancer from both active and passive smoking are similar; thus, the dose-response "curve" for passive and active smoking is non-monotonic. This may be due to a number of factors including a competing anti-estrogenic effect of active smoking discussed above, or saturation of some important process in carcinogenesis (e.g., metabolism of the carcinogen). The explanatory hypothesis of a non-monotonic dose response for the mammary carcinogenic effect of tobacco smoke, especially toward the higher dose ranges associated with active smoking, succeeds in unifying to a substantial degree all of the observed epidemiological results, without having to resort to any extraordinary deconstruction of the relevant studies. The converse hypothesis, that there is no such carcinogenic effect of environmental tobacco smoke, requires detailed, and individually different, dismissals of a substantial number of studies by assuming unproven statistical imbalances, unidentified confounders, and failure of recognized methods for dealing with confounding and covariance. In order to explain the null results of Wartenberg *et al*. (2000), and other large prospective studies where tobacco smoke exposure in the referent group was inadequately determined, it is necessary only that the risk for active smokers be reduced to approximately that experienced by passive smokers, not to zero.

7.4.1.5. Conclusions – ETS and Breast Cancer

7.4.1.5.1. Breast Cancer in Younger, Primarily Premenopausal Women

In the 14 studies that evaluated younger, primarily premenopausal women, there is a strong and consistent association found between ETS exposure and breast cancer risk. Thirteen of these studies found risk estimates between 1.10 and 7.10 of which seven were statistically significant (Table 7.4.1C). All of the six studies considered by OEHHA to be most informative found risk estimates of 1.59 or greater and were statistically significant (Table 7.4.1G). The meta-analysis of breast cancer risk for younger women obtained a risk estimate of 1.68 (95% CI 1.31-2.15),

and the meta-analysis of the better exposure studies for premenopausal women results in a pooled risk estimate of 2.2 (95% CI 1.69-2.87).

Overall, the weight of evidence (including toxicology of tobacco smoke constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women (see Figure 7.4.4). It must be noted here that the cohort studies which evaluated menopausal status or age as a surrogate did so at enrollment, not at diagnosis (or death, as in Wartenberg *et al.* 2000*).* Thus, when these studies report breast cancer risk in "premenopausal" women, they really are referring to women who were premenopausal or younger than age 50 (versus postmenopausal or older than 50) at enrollment. The case-control studies generally considered either age or actual menopausal status at diagnosis for the cases. Thus, it is more accurate to indicate that risks were higher in women whose breast cancer was diagnosed either premenopausally or at younger ages (less than 50 years).

If younger, primarily premenopausal women are the most at risk for breast cancer from ETS exposure, then the cohort studies determining menopausal status at baseline introduce a systematic bias towards the null. This results from incorporating into the "premenopausal" group women diagnosed with breast cancer post-menopause. This misclassification of age or menopausal status may be another reason that many cohort studies overall have shown less of an effect of passive smoking on breast cancer than the case control studies.

ETS appears to present a substantial breast cancer risk relative to other environmental exposures, as much as they are known.

7.4.1.5.2. Breast Cancer in Older PostMenopausal Women

The evidence of an association between ETS exposure and elevated breast cancer risk is more persuasive for those diagnosed at younger ages (mostly premenopausal) than for women diagnosed at older (postmenopausal) age. There were nine studies from which we could extract breast cancer risk estimates for postmenopausal women. In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause risk estimates cluster around a null association (see Figure 7.4.4). There are, however, elevated risk estimates in some studies for postmenopausal women either overall or in specific strata. In addition, it should be noted that there are many studies that show statistically significant elevated risks for breast cancer in postmenopausal active smokers (see Appendix A, Tables 7.ApA1-4). The evidence to date for older/postmenopausal women is, therefore, considered inconclusive. Further research indicating a positive association would be necessary prior to altering this finding.

Table 7.4.1l. Passive smoking and breast cancer risk: case-control studies

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Sandler *et al*. (1985b)[a]	All ages	Spousal	19/76	1.94	0.9-4.2	A, E, R
United States, 1979-1981	Premenopausal	Spousal	6/27	7.1	1.6-31.3	
Case Source = tumor registry	Postmenopausal	Spousal	13/49	0.9	0.4-2.2	
Controls = population	Non-smokers	Spousal	32/177	1.62	0.76-3.44	
Smith *et al*. (1994)	Diagnosis < 36 yrs.	No ETS	48/63	--	Ref	A, AF, AL, AM, BF, FH, HB,
United Kingdom, 1982-1985	Adult only	Partner only	46/37	1.58	0.81-3.10	OC
Case Source = regional registry	Adult only	All sources	16/14	3.13*	0.73-13.31	
Controls = regional registry	Child or adult[b]	Total lifetime	204/199	2.53	1.12-5.71	
Morabia *et al*. (1996)	Never active	No ETS	23/241	--	Ref	A, AF, AM, BMI, E, FH, OC
Switzerland, 1992-1993		All sources	98/379	2.3*	1.5-3.7	
Case Source = Clinic/Breast lab						
Controls = population						
Millikan *et al.* (1998)	Never active	No ETS	89/88	--	Ref	A, AF, AL, AM, FH, HB, P, R
Carolina Breast Cancer Study	Total study	ETS after age 18	158/165	1.3	0.9-1.9	
United States, 1993-1996	Premenopausal	No ETS	52/49	1.0	Ref	A, AF, AL, AM, FH, HB, P, R
		ETS after age 18	71/61	1.5	0.8-2.8	
Case Source = population registry	Postmenopausal	No ETS	37/39	1.0	Ref	A, AF, AL, AM, FH, HB, P, R
Controls = population		ETS after age 18	87/104	1.2	0.7-2.2	
Lash and Aschengrau (1999)	Never active	Never passive	40/139	--	Ref	A, AL, BMI, EC, FH, HB, HR,
United States, 1983-1986		Passive only	80/267	2.0	1.1-3.7	P
Case Source = general population	Relative to 1st	Only Before	6/15	2.8	0.8-9.9	A, BMI, EC, FH, HB, HR, P
Controls = population	Pregnancy	Only After	35/102	2.4	1.2-5.1	
		Both Before/After	21/63	2.2	1.1-4.7	

[a] From Wells (1998a) letter, Am J Epidemiol 147; 991-2. Low = no/rare residential ETS; High = usual/sometimes residential ETS

[b] Derived from Smith *et al.* (1994) Table 4 all non-smokers by combining total lifetime exposure categories as described in our review of study.

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age at menopause; BF = months breast feeding; BMI = Body mass index; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; FP = Fertility problems; HB = History benign breast disease; HR = History radiation; I = Income; M = Menopausal status; OC = Oral contraceptive use; P = Parity; PH = Physical Activity; PSH = passive smoking from husband; R = Race; RE = Residence; W = weight;; WH = waist to hip ratio.

Table 7.4.1l. Passive smoking and breast cancer risk: case-control studies

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Zhao *et al.* (1999)	Premenopausal	Passive only		2.56	1.63-4.01	Unadjusted
China (time not specified)		Overall risk	265/265	2.38	1.66-3.40	
Delfino *et al.* (2000)	No active	No passive	33/96	--	Ref	A, FH, M
United States (time not specified)		Passive only	16/44	1.78	0.77-4.11	*Estimates w/ low-risk controls
Case Source = Clinic/Breast Centers	Never smokers, Adult Exposure*	Low	33/96	1.00	Ref	A, FH, M
		High	31/51	1.50	0.79-2.87	
Controls = Clinic/Breast Centers	Premenopausal		21/DNS	2.69	0.91-8.00	A, FH, M
	Postmenopausal		DNS	1.01	0.45-2.27	
		Overall risk		1.86	0.81-4.27	
Johnson *et al.* (2000)	Premenopausal	No active/passive	14/35	--	Ref	A, AF, AH, AL, AM, BMI, E, P,
Canada, 1994-1997		Passive only	208/194	2.3	1.2-4.6	PH, RE
Case Source = Population Registry	Exposure Timing	Child only ETS	15/24	1.6	0.6-4.4	
Controls = Population		Adult ETS only	50/43	2.6	1.1-6.0	
		Child & Adult ETS	143/124	2.6	1.2-5.5	
	Postmenopausal	No active/passive	52/92	1.0	Ref	A, AF, AH, AL, AM, BMI, E, P,
		Passive only	334/406	1.2	0.8-1.8	PH, RE
	Exposure Timing	No active/passive	52/92	--	Ref	A, AF, AH, AL, AM, BMI, E, P,
		Child only ETS	15/31	0.9	0.4-2.0	PH, RE
		Adult ETS only	83/109	1.1	0.6-1.8	
		Child & Adult ETS	234/266	1.3	0.8-2.0	
		Overall risk		1.48	1.06-2.07	
Marcus *et al.* (2000)	ETS prior to age 18	No ETS exposure	257/248	--	Ref	A, R, includes ever active
United States, 1993-1996		Exposure	603/603	1.1	0.9-1.3	smokers in
Carolina Breast Cancer Study		No ETS/No Active	99/119	--	Ref	Exposed groups
		Exposure	603/542	0.8	0.6-1.1	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age at menopause; BF = months breast feeding; BMI = Body mass index; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; FP = Fertility problems; HB = History benign breast disease; HR = History radiation; I = Income; M = Menopausal status; OC = Oral contraceptive use; P = Parity; PH = Physical Activity; PSH = passive smoking from husband; R = Race; RE = Residence; W = weight;; WH = waist to hip ratio.

Table 7.4.1l. Passive smoking and breast cancer risk: case-control studies

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Kropp and Chang-Claude (2002)	Never active	No passive	44/144	--	Ref	AL, BF, BMI, E, FH, M
Germany 1992-1995		Any passive	153/310	1.59	1.06-2.39	
		Former passive	92/191	1.55	1.00-2.40	
		Current passive	61/119	1.67	1.04-2.69	
		Overall risk		1.59	1.06-2.39	
Lash and Aschengrau (2002)	Passive smokers	Never	80/53	1.0	Ref	AF, AL, BMI, EC, FH, HB, P
United States, 1987-1995		Ever passive	361/366	0.72	0.55-0.95	
		Overall risk		0.85	0.63-1.10	
Shrubsole *et al.* (2004)		No passive	176/184	1.0	Ref	A, AF, AM, AME, BMI, E, I,
China 1996-1998	All women	Spouse only	231/289	0.9	0.7-1.2	M, PH
Shanghai Breast Cancer Study		Work only	170/158	1.1	0.8-1.5	
		Spouse and work	287/305	1.1	0.8-1.4	
	Premenopausal	Spouse and work	536/599	1.10	0.83-1.46	
		Overall risk		1.02	0.81-1.29	
Gammon *et al.* (2004)		Spousal (mo)				
United States 1996-1997	Ever passive	Never exposed	155/170	1.0	Ref	A, BMI at age 20, FH, FP,
Case source = pathology depts.	Premenopausal	ETS only	163/166	1.21	0.78-1.90	HB, M, P, W
Controls = Population	Post menopausal	ETS only	280-291	0.93	0.68-1.29	
		Overall risk		1.04	0.81-1.35	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age at menopause; BF = months breast feeding; BMI = Body mass index; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; FP = Fertility problems; HB = History benign breast disease; HR = History radiation; I = Income; M = Menopausal status; OC = Oral contraceptive use; P = Parity; PH = Physical Activity; PSH = passive smoking from husband; R = Race; RE = Residence; W = weight;; WH = waist to hip ratio.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Morabia *et al*. (1996)	Never active	No ETS	23/241	--	Ref	A, AF, AM, BMI, E, FH, OC
Switzerland, 1992-1993		1-50 hrs/day-year	44/185	2.2	1.3-3.7	
Case Source = Clinic/Breast lab		> 50 "	54/191	2.5	1.5-4.2	
Controls = population		All sources	98/379	2.3*	1.5-3.7	
Lash and Aschengrau (1999)	Passive-only	Duration Years				
United States, 1983-1986		Never	40/139	1.0	Ref	A, BMI, EC, FH, HB, HR, DE
		≤ 20	28/56	3.2	1.5-7.1	
		> 20	43/148	2.1	1.0-4.1	
Case Source = general population		Age First Exposure				
Controls = Population		< 12 yrs old	14/25	4.5	1.2-16.0	A, BMI, EC, FH, HB, HR, P
		12-20 yrs old	11/30	3.8	1.1-13.0	
		≥ 21 yrs old	34/118	2.4	0.9-6.1	
	Ever active	Age First Exposure				
		< 12 yrs old	26/33	7.5	1.6-36.0	A, BMI, EC, FH, HB, HR, DA,
		12-20 yrs old	10/31	3.9	0.8-20.0	C, DE
		≥ 21 yrs old	46/105	4.7	1.6-14.0	

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)	Factors Adjusted
Johnson *et al.* (2000)	Premenopausal	Never regular ETS[a]	14/35	-- Ref	A, AF, AH, AL, AM, BMI, E, P,
Canada, 1994-1997	Duration residential	1-6 years	15/24	1.2 0.4-3.4	PH, RE
	plus occupational	7-16 years	21/23	1.8 0.7-4.9	
Case Source = Population Registry	ETS	17-21 years	25/34	2.0 0.8-5.0	
Controls = Population		22-35 years	76/57	3.3 1.5-7.5	
		≥ 36 years	71/56	2.9 1.3-6.6	
				p trend = 0.0007	
		1-13 smoker-years[b]	14/20	1.5 0.5-4.4	A, AF, AH, AL, AM, BMI, E, P,
		14-32 smoker-years	47/57	2.0 0.9-4.5	PH, RE
		33-70 smoker-years	65/58	2.9 1.3-6.6	
		≥ 71 smoker-years	82/59	3.0 1.3-6.6	
				p trend = 0.03	
	Postmenopausal	Never regular ETS	52/92	-- Ref	A, AF, AH, AL, AM, BMI, E, P
	Duration residential	1-30 years	117/152	1.1 0.7-1.9	
	plus occupational	31-56 years	110/129	1.3 0.8-2.1	
	ETS	> 57 years	107/125	1.3 0.8-2.1	
				p trend = 0.27	
		1-45 smoker-years	105/155	1.0 0.6-1.7	
		46-89 smoker-years	114/126	1.3 0.8-2.1	
		> 89 smoker-years	115/125	1.4 0.9-2.3	
				p trend = 0.07	

[a] Sum of the total yrs residential exposure and total yrs occupational exposure

[b] Sum of lifetime residential exposure (# smokers in home × yrs) plus sum of occupational exposure (# employees who smoked regularly in immediate area × # yrs at that job)

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Lash and Aschengrau (2002)	Passive smokers	Duration ETS (yrs)				
United States, 1987-1995		Never	80/53	1.0	Ref	AF, AL, BMI, EC, FH, HB, P
		0-< 20	54/49	0.87	0.59-1.3	
		20-< 40	79/58	0.94	0.66-1.3	
		≥ 40	31/34	0.75	0.47-1.2	
		Age first lived with smoker				
		< 12	66/44	0.99	0.67-1.4	
		12-20	20/20	0.84	0.49-1.4	
		> 20	58/57	0.79	0.54-1.1	
		Pregnancy demarcated passive				
		All before first	23/11	1.1	0.64-1.9	
		Before + after first	59/42	0.85	0.56-1.3	
		All after first	19/32	0.55	0.31-0.96	
		Never gave birth	58/43	1.0	0.60-1.8	
Kropp and Chang-Claude (2002)	Passive	Never ETS	44/144	--	Ref	AL, BF, BMI, E, FH, M
		1-10 years	20/43	1.51	0.78-2.95	
Germany 1992-1995		≥ 11 years	68/154	1.45	0.92-2.29	
		Only as adult	65/113	1.80	1.12-2.89	
	Lifetime passive	1-50 hrs/day-years	64/149	1.42	0.90-2.26	
		≥ 50 hrs/day-years	88/153	1.83	1.16-2.87	
				P trend = 0.009		

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)	Factors Adjusted
Shrubsole *et al*. (2004)	Total group	Work none	176/184	-- Ref	A, AF, AM, AME, E, FH, HB, P,
China, 1996-1998		1-59 min/d	108/139	0.9 0.6-1.3	PH, PSH, WH
Shanghai Breast Cancer Study		60-179	138/143	1.1 0.8-1.6	
		180-299	99/99	1.1 0.8-1.7	
		300+	112/82	1.6 1.0-2.4	
				P trend = 0.02	
	Premenopausal	Work none	113/126	-- Ref	
		1-59 min/d	83/117	0.9 0.6-1.4	
		60-179	102/114	1.0 0.7-1.6	
		180-299	80/86	1.1 0.7-1.7	
		300+	92/97	1.6 1.0-2.5	
				P trend = 0.03	
	Postmenopausal	Work none	63/58	-- Ref	
		1-59 min/d	25/22	1.1 0.5-2.3	
		60-179	36/29	1.3 0.6-2.6	
		180-299	19/13	1.4 0.6-3.7	
		300+	20/15	1.4 0.6-3.1	
				P trend = 0.37	

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Gammon *et al*. (2004)	Total Group	Never ETS	155/170	1.0		A, BMI, FH, FP, HB, M, P
		Passive Only	443/457	1.04	0.81-1.35	Weight in prior year
		Active Only	127/131	1.06	0.76-1.48	
		Passive and Active	631/625	1.15	0.90-1.48	
	Ever Passive Only	1-192 months	83/83	1.07	0.73-1.57	
	Spouse + other	193-360	161/205	0.84	0.62-1.14	
		361+	194/166	1.22	0.90-1.66	
	Ever Passive Only	1-181 months	85/69	1.50	1.05-2.14	
	Spouse exposure	182-325	66/79	1.01	0.70-1.47	
		326+	109/68	2.10	1.47-3.02	
	Ever passive only	1-304 months	60/59	0.97	0.64-1.47	
	Parental exposure	305-548	191/199	1.03	0.79-1.33	
	Prior to age 18	549+	567/617	0.93	0.78-1.12	

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1K. Passive smoking and breast cancer risk: case-control studies with gene modification

Case-control Study	Genotype and Menopausal Status								Factors Adjusted
Millikan *et al.* (1998)	PREMENOPAUSAL				POSTMENOPAUSAL				
	NAT1*10		NAT1-non*10		NAT1*10		NAT1-non*10		
Never Active Smokers w/ ETS exposure									
No ETS	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	A, AF, AL, AM, FH, HB, P, R
ETS after age 18	1.7	0.7-4.3	1.3	0.5-3.2	1.2	0.6-2.6	1.3	0.5-3.6	
	NAT2-rapid		NAT2-slow		NAT2-rapid		NAT2-slow		
Never Active Smokers w/ ETS exposure									
No ETS	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	A, AF, AL, AM, FH, HB, P, R
ETS after age 18	2.3	0.9-6.2	1.2	0.5-2.8	0.8	0.4-1.8	1.9	0.7-5.2	
Morabia *et al.* (1998)	PREMENOPAUSAL				POSTMENOPAUSAL				
	ER- Cases		ER+ Cases		ER- Cases		ER+ Cases		
Smoking Status									A
Never	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	
Ever passive	4.2	0.9-19.0	1.7	0.7-4.0	3.4	1.0-12.1	1.8	1.0-3.2	
Morabia *et al.* (2000)	PREMENOPAUSAL				POSTMENOPAUSAL				
	NAT2-rapid		NAT2-slow		NAT2-rapid		NAT2-slow		
Smoking Status									A, E, FH
Never	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	
Ever passive	3.3	0.7-15.7	3.2	0.9-11.5	11.6	2.2-62.2	1.1	0.3-4.3	
Lilla *et al.* (2005)	SULT1A1*1/*1				SULT1A1*2				
	NAT2-rapid		NAT2-slow		NAT2-rapid		NAT2-slow		
Smoking Status									
Never	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	A, AL, BF, BMI, E, FH, M, P
Ever passive	3.23	1.05-9.92	1.35	0.62-2.91	1.28	0.50-3.31	1.18	0.53-2.66	

Factors adjusted for: A = Age; AF = Age first childbirth; AL = Alcohol consumption; AM = Age menarche; BF = Breastfeeding; BMI = Body mass index; E = Education; FH = Family history breast; HB = History benign breast disease; M = Menopausal status; P = Parity; R = Race

Table 7.4.1L. Passive smoking and breast cancer risk: cohort studies

Cohort Study	Smoking Exposure	#Cases	Adjusted RR	95% CI	Factors Adjusted
Hirayama (1984)[a]	Never active No ETS		--	Ref	A, AF, AM, BMI, E, FH, HB, OC
Japan, 1966-1981	Spousal All	115	1.32	0.83-2.09	
Study size = 142,857					
Jee *et al.*, (1999)	Spousal Smoking Status				
Korea Medical Insurance Corp,	Non-smoker	DNS	1.0	Referent	A, RE, SES, SO, SV
1992-1997	Current	DNS	1.3	0.9-1.8	
Study Size=160,130	Current +30 yrs	DNS	1.7	1.0-2.8	
Total Cases=138	Ex-smoker	DNS	1.2	0.8-1.8	
Wartenberg *et al.* (2000)	Spousal Smoking Status (at baseline 1982):				
American Cancer	Never smoker	273	1.0	Referent	A, AF, AL, AM, AME, BMI, DF, DV,
Society CPS II	Current smoker	166	1.0	0.8-1.2	E, FH, HB, HRT, NSA, O, OC, R, SO
United States, 1982-1994	Former smoker*	230	1.0	0.8-1.2	
Study Size=146,488	ETS-Home	DNS	1.1	0.9-1.3	
Total Deaths=669	ETS-Work	DNS	0.8	0.6-1.0	
	ETS-Other Places	DNS	0.9	0.7-1.2	
Nishino *et al.* (2001)	Spousal	67	0.58	0.32-1.1	A, AF, AL, AM, BMI, DV, P
Egan *et al.* (2002)	Parental smoking				
Nurse's Health Study	Neither parent	472	1.00	Referent	A, AM, AF, AH, AL, AME, CAR, FH,
United States, 1982-1996	Mother Only	36	0.98	0.70-1.38	HB, HRT, M, P, WT18, WTA
Study Size = 78,206	Father Only	587	1.12	0.99-1.27	
Total Cases = 3,140	Both	127	0.92	0.76-1.13	
	Current Work or Home				
	None	184	1.00	Referent	
	Occasionally	611	1.16	0.98-1.36	
	Regularly, W or H	306	1.00	0.83-1.20	
	Regularly, W and H	57	0.90	0.67-1.22	

[a] From Wells (1998a) letter, Am J Epidemiol 147; 991-2. DNS = Data not presented in original publication.

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; PH = Physical activity; R = Race; RE = Residence; SES = Socioeconomic status; SO = Spousal Occupation; SV = Spousal vegetable intake; WT18 = Weight 18 years; WTA = Adult weight

Table 7.4.1L. Passive smoking and breast cancer risk: cohort studies

Cohort Study	Smoking Exposure	#Cases	Adjusted RR	95% CI	Factors Adjusted
Reynolds *et al.* (2004a)	Household				A,AF,AL,AM,BMI,FH,HRT,PH
California Teachers Study	**Full study**				
United States 1995-2000	Never	316	1.00	Referent	
	Childhood only	307	0.92	0.78-1.07	
	Adulthood only	211	0.94	0.79-1.12	
	Any	848	0.94	0.82-1.07	Excluding passive smokers from referent
	Pre-/perimenopausal				
	Never	78	1.00	Referent	
	Childhood only	96	0.93	0.69-1.26	
	Adulthood only	31	1.01	0.66-1.54	
	Any	179	0.93	0.71-1.44	Excluding passive smokers from referent
	Postmenopausal				
	Never	205	1.00	Referent	
	Childhood only	180	0.93	0.76-1.14	
	Adulthood only	161	0.88	0.71-1.08	
	Any	583	0.92	0.78-1.08	Excluding passive smokers from referent
Hanaoka et al., (2005)	**Full study**				A, AL, AM, BMI, E, FH, HB, HU, M, O, P
Japan Public Health Center	Never + no ETS	40	1.0	Referent	
Japan, 1990-1999	ETS	122	1.1	0.8-1.6	
	Premenopausal at baseline				
	Never + no ETS	9	1.0	Referent	
	ETS	68	2.6	1.3-5.2	
	Postmenopausal at baseline				
	Never + no ETS	31	1.0	Referent	
	ETS	52	0.6	0.4-1.0	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; PH = Physical activity; R = Race; RE = Residence; SES = Socioeconomic status; SO = Spousal Occupation; SV = Spousal vegetable intake; WT18 = Weight 18 years; WTA = Adult weight

Table 7.4.1M. Passive smoking and breast cancer risk: cohort studies which assessed dose-response

Cohort Study	Smoking Exposure		#Cases	Adjusted RR (95% CI)		Factors Adjusted
Wartenberg *et al.* (2000)	**Spousal – Amount** (at baseline 1982)					
American Cancer	Never smoker		217	1.0	(Referent)	A, AF, AL, AM, AME, BMI, DF, DV,
Society CPS II	Current/former smoker	<1	49	0.9	(0.6-1.2)	E, FH, HB, HRT, NSA, O, OC, R, SO
United States	(packs/day):	1	67	0.9	(0.7-1.1)	
1982-1994		> 1 to <2	43	1.1	(0.8-1.6)	
Study Size = 146,488		≥ 2	45	1.0	(0.7-1.3)	p trend=0.8
Total Deaths = 669	**Spousal – Duration** (at baseline 1982)					
	Years smoked, current	1-10	29	0.8	(0.6-1.2)	
(Lifelong never-smoking	or former smoker	11-20	31	0.7	(0.5-1.0)	
women married to current or			62	1.0	(0.7-1.3)	
former smokers)		≥ 31	82	1.1	(0.9-1.4)	p trend=0.7
	Spousal Pack-years	1-12	46	0.8	(0.6-1.2)	
		> 12-25	41	0.8	(0.6-1.1)	
		> 25-41	58	1.0	(0.8-1.4)	
		> 41	59	1.0	(0.8-1.4)	p trend=0.8
	Years smoked; current	1-10	DNS	DNS	(DNS)	
	smoker	11-20	DNS	2.5	(1.3-5.1)	
	21-30		DNS	1.1	(0.7-1.6)	
		>31	DNS	0.9	(0.6-1.2)	p trend=DNS
	Reported ETS exposures from all sources combined (at baseline 1982)					
	Daily Hours	1-hour	DNS	1.0	(0.8-1.2)	
		2- to 4-hour	DNS	1.0	(0.8-1.3)	
		5- to 8-hour	DNS	0.9	(0.7-1.2)	
		>9 hour	DNS	0.7	(0.4-1.3)	p trend=DNS
Egan *et al.* (2002)	Years lived w/ smoker:	< 5	646	1.00	(Referent)	A, AM, AF, AH, AL, AME, CAR, FH,
Nurse's Health Study	21-30	5-9	84	0.88	(0.69-1.09)	HB, HRT, M ,P, WT18, WTA
United States, 1982-1996		10-19	166	0.91	(0.77-1.08)	
Study Size=78,206		20-29	179	0.93	(0.79-1.10)	
Total Cases=3,140		30+	146	1.03	(0.86-1.24)	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; R = Race; SO = Spousal Occupation; WT18 = Weight 18 years; WTA = Adult weight. DNS = Data not presented in original publication.

Table 7.4.1M. Passive smoking and breast cancer risk: cohort studies which assessed dose-response

Cohort Study	Smoking Exposure		#Cases	Adjusted RR (95% CI)		Factors Adjusted
Hanaoka et al., (2005)	**Premenopausal**					A, AL, AM, BMI, E, FH, HB, M, O, OC,P,
Japan, 1990-1999	Work and/or public	none		1.0	(Referent)	Public health center
Total cases = 180		~1-3 d/mo		0.6	(0.4-2.4)	
Premenopausal cases=68		> 3 d/mo		2.2	(1.4-3.7)	p trend=0.002

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; R = Race; SO = Spousal Occupation; WT18 = Weight 18 years; WTA = Adult weight. DNS = Data not presented in original publication.

7.4.2. Stomach Cancer

7.4.2.1. Summary of Previous Findings

As discussed in the previous OEHHA report (Cal/EPA, 1997), the single mortality cohort of Hirayama (1984) reported unadjusted risk estimates for ETS exposure (nonsmoking women with smoking spouses) and stomach cancer. No association was observed. However, these associations with active smoking were not adjusted for dietary or other risk factors for stomach cancer. In summary, thus far there is no epidemiological evidence for an association between ETS exposure and stomach cancer, but research on this issue has been extremely limited.

7.4.2.2. Recent Epidemiological Data

Three primary studies investigating the relationship between passive smoking and stomach cancer were available for review (Jee *et al*., 1999; Nishino *et al.*, 2001; Mao *et al.*, 2002).

Jee et al., 1999. This study, described in Section 7.2.3, included stomach cancer incidence in a study of lung cancer among Korean women whose husbands smoked. In this study there was no association between exposure to spousal ETS and stomach cancer. Among spouses of current smokers, the risk of stomach cancer was 0.9 (95% CI 0.6; 1.2), and 1.0 (95% CI 0.7; 1.5) among spouses of ex-smokers after adjustment for husband's and wife's ages, SES, residency, husband's occupation, and husband's vegetable consumption.

Nishino et al., 2001. As previously described, the Japanese prospective cohort analyzed for several tobacco-related cancers, including cancer of the stomach among non-smoking women exposed via smoking spouses. Eighty-three cases of stomach cancer (57 among non-smokers) were identified in the cohort. No elevated risk was associated with spousal ETS exposure after either age-adjustment [RR 0.95 (95% CI 0.58-1.6)] or adjustment for other multiple factors including dietary [RR 0.98 (95% 0.59-1.6)].

Mao et al., 2002. A population-based Canadian case-control study assessed the stomach cancer risk associated with both active and passive smoking in eight Canadian provinces. Cases were obtained from population-based cancer registries between 1994 and 1997 (1,175 cases responded, 63%). Population controls were frequency matched as with the previously described breast cancer study (Johnson *et al.*, 2000). Mailed questionnaires were used to obtain a variety of demographic, economic, occupational, residential, dietary and smoking data. Active smoking risk estimates were adjusted for age, residence, education, social class, and dietary factors (meat, vegetables, fruit and juice intake).

Never-smoking males exposed to ETS had elevated stomach cancer risk (subsite cardia) associated with total ETS exposure (residential and occupational years exposed) which was statistically significant at the highest exposure duration [1-22 years: adjusted OR 3.5 (95% CI 0.7-17.3); 23-42: adjusted OR 2.8 (95% CI 0.5-14.2); $\geq$ 43: adjusted OR 5.8 (95% CI 1.2-27.5)], and which showed evidence of a trend with increasing exposure, p for trend 0.05. No increased risk was associated with distal stomach cancer. Only seventeen cases were reported in females, with no risk estimates reported.

7.4.2.3. Summary of ETS and Stomach Cancer

The single, well-designed population-based case-control study provides minimal evidence that ETS exposure may increase the risk of stomach cancer, particularly cancer of the cardia (Mao *et al.*, 2002). However, additional studies will be required to determine the association between ETS exposure and stomach cancer risk, particularly by subsite and sex.

7.4.3. Brain Tumors

7.4.3.1. ETS and Adult Brain Cancer Risk

7.4.3.1.1. Previous Findings

Three studies, one cohort (mortality) and two case-control studies, previously reviewed by OEHHA (Cal/EPA, 1997), presented limited evidence of a relationship between ETS exposure and brain tumors. The cohort study, which analyzed cancer mortality outcomes among nonsmoking women of smoking spouses, identified 34 deaths related to brain cancer, with an apparent significant dose response with the amount of husband's daily cigarette consumption (Hirayama 1984). The two case-control studies gave inconsistent results (Sandler *et al.*, 1985b; Ryan *et al.*, 1992): the one study specifically designed for brain tumors (meningiomas and gliomas) found a significant association between ETS and meningioma [RR 2.5 (95% 1.0-6.1)]; however, results are confused by a comparison group which potentially included active smokers. Therefore, the association between ETS exposure and adult brain malignancies remains inconclusive.

7.4.3.1.2. Recent Epidemiological Data

Only one new primary study was located (Hurley *et al*., 1996), however this study emphasized active smoking with only cursory treatment of the effects of ETS exposure. In addition, one published abstract reported a dose-related trend in brain cancer risk with ETS exposure in a Canadian case-control study; however, limited data were provided (KC Johnson; personal communication).

Hurley et al. (1996). This Australian case-control study was conducted within the Melbourne adult brain tumor study, a study designed to investigate glioma risk and occupational exposure to chemicals and electromagnetic radiation. Cases were 416 individuals with histologically confirmed glioma diagnosed between 1987 and 1991. There were 422 population controls matched by age and gender. Information relating to smoke exposure, diet, alcohol use, and demographics was collected by questionnaires followed by interviews. Risks were estimated by logistic regression analyses adjusted for age, gender and date of diagnosis or selection. There was no adjustment for diet or exposure to N-nitroso-containing compounds, possibly because they did not alter the results by more than 10%.

The risks associated with active smoking were generally elevated, especially for men, but the results appeared inconsistent with a causal role for smoke in glioma incidence (see Table 7.4.3A). For example, men who smoked for less than 10 years had a higher and significant risk for glioma (OR 2.49, 95% CI 1.25; 4.29) than did those who had smoked longer. Similarly, those who had started smoking after age 20, and so presumably had a shorter smoking history, had a higher risk (2.73, 95% CI 1.48; 5.02) than did those who started before age 20. When

smoking was measured as pack years, the highest risk was associated with the lowest number of years although none of these values was significant. The authors recognized that their results may be the result of chance, response bias or uncontrolled confounding. Indeed, the results suggest that systematic bias is a strong possibility. These results may also reflect an interaction between smoking and some unidentified environmental exposure.

Table 7.4.3A Active smoking and risk of glioma in adult men and women.

	All subjects		Women	Men
	Exposed cases/controls	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Never smoked		1.00	1.00	1.00
Ever smoked	242/232	1.29 (0.95; 1.75)	0.99 (0.62; 1.62)	1.64 (1.10; 2.45)
Pack years				
0		1.00	1.00	1.00
0-9	76-72	1.19 (0.79; 1.80)	0.89 (0.47; 1.70)	1.59 (0.91; 2.79)
9-24	63/81	1.01 (0.66; 1.54)	0.77 (0.37; 1.61)	1.20 (0.71; 2.04)
≥ 24	62/77	1.04 (0.66; 1.64)	1.06 (0.66; 1.71)	1.23 (0.71; 2.12)
Duration (yrs)				
Never		1.00	1.00	1.00
<10	54/43	1.37 (0.84; 2.24)	0.75 (0.35; 1.60)	2.49 (1.25; 4.29)
10-20	52/59	1.05 (0.66; 1.68)	1.10 (0.45; 2.68)	1.12 (0.64; 1.97)
≥ 20	117/128	1.25 (0.86; 1.83)	1.17 (0.63; 2.19)	1.48 (0.90; 2.42)
Start age (yr)				
Never		1.00	1.00	1.00
< 20	172/170	1.21 (0.85; 1.64)	1.17 (0.67; 2.08)	1.42 (0.93; 2.18)
>20	68/62	1.48 (0.80; 1.93)	0.78 (0.40; 1.52)	2.73 (1.48; 5.02)

In the context of ETS, there was no significant association reported between glioma and passive smoke exposure among nonsmokers as defined by living with a smoker (OR 0.97, 95% CI 0.61; 1.53). However, whereas the results for active smoking were presented for men and women separately and combined, with significant effects only seen for men, the results for passive smoking presumably represent both genders combined. It is thus not possible to tell whether passive smoking differentially affected men's risks as it appeared to do for active smoking. In addition, in the analysis of passive smoking, there is no indication whether any adjustments were made for possible confounding or consideration given to other sources of ETS exposure. While this study does not provide evidence for an association between ETS exposure and glioma, the results for active smoking are inconclusive.

7.4.3.2. ETS and Brain Cancer Risk in Children/Young Adults

7.4.3.2.1. Previous Findings

In the 1997 report, OEHHA reviewed a total of ten published studies examining the potential relationship between ETS exposure and the risk of developing childhood brain cancer. The ten studies varied in the method of case ascertainment, age of eligible cases (< 15 years, ≤ 18 years, <20 years, <25 years at time of diagnosis), availability of paternal smoking data (six of ten studies), and whether the study was specifically designed to identify potential risk factors for developing childhood brain cancer. Data from the ten studies did not support an association between childhood cancer and maternal smoking during or before pregnancy. Three population-

based (Preston-Martin *et al.*, 1982; John *et al.*, 1991; McCredie *et al.*, 1994) and one hospital based (Howe *et al.*, 1989) case-control studies found a small increased risk for brain tumors relative to paternal smoking, with two studies finding statistically significant associations (Preston-Martin *et al.*, 1982; McCredie *et al.*, 1994). The range of risk estimates for paternal smoking in these positive studies ranged from 1.5 (p=0.03) (Preston-Martin *et al.*, 1982) to 2.2 (95% CI 1.25-3.85) (McCredie *et al.*, 1994).

7.4.3.2.2. Recent Epidemiological Data

Table 7.4.3B summarizes results from twelve published studies reporting on childhood brain cancer risk and ETS exposure. The studies are described below.

Bunin et al., 1994. This U.S./Canada case-control study identified 155 cases of astrocytic glioma and 199 cases of primitive neuroectodermal tumor (PNET) through a pediatric oncology cooperative group, the Children's Cancer Group. Cases were diagnosed before age 6 in 1986 to 1989 and matched to population-based controls on race, age, and residential area. Data on maternal and paternal smoking (prior and during pregnancy) and maternal ETS exposure were collected via interview. No elevated risk was observed for either astrocytoma or PNET for either maternal (ever, during pregnancy or maternal ETS) or paternal smoking (ever or during pregnancy). All statistically non-significant risk estimates remained near unity; adjusted ORs ranged from 0.9-1.0 (Table 7.4.3B).

Cordier et al., 1994. This case-control study of childhood brain cancer investigated a variety of risk factors in children diagnosed prior to age 15 in Ile de France. Cases were derived from 13 hospitals and matched to population controls by year of birth. Interviews were conducted with the families of 75 of the possible 109 cases. Maternal smoking during pregnancy was associated with an elevated, statistically non-significant risk of childhood brain cancers (all histologies combined), adjusted for age, education, sex and maternal age [adjusted OR 1.6 (95% CI 0.7-3.5)]. Prenatal exposure to tobacco smoke, whether from maternal smoking, other household sources, or workplace smoke, was also associated with an elevated but not statistically significant risk [adjusted OR 1.5 (95% CI 0.8-2.8)]. The highest risk which was statistically significant was associated with postnatal, childhood exposure to tobacco smoke (maternal, household or other sources) [adjusted OR 2.3 (95% CI 1.1-4.6)] (Table 7.4.3B). No estimates or discussion on risk related to paternal smoking were provided. The authors reported that no dose-response of risk estimates based on duration of exposure or quantity of tobacco was found (no data presented).

Filippini et al., 1994. This case-control study across several Northern Italy provinces enrolled 91 of 103 primary brain cancer cases identified from hospital and other medical resources diagnosed between 1985 and 1988 in children under age 15. Population controls were matched on age, sex and residence. The comparison or unexposed group was defined as mothers that either never smoked or were ex-smokers at "time of conception" and had no ETS exposure either immediately prior to conception or during pregnancy. Ever-lifetime parental smoking was associated with a slightly elevated, but statistically non-significant, risk of childhood brain tumors after adjustment for parental education [maternal ever lifetime smoking OR 1.2 (95% CI 0.8-2.0); paternal ever lifetime smoking OR 1.3 (95% CI 0.7-2.2)]. Non-smoking mothers exposed to ETS during pregnancy had an elevated, but statistically nonsignificant risk of having a child diagnosed with a brain tumor [adjusted OR 2.0 (95% CI 1.0-4.0)]. However, the risk

estimate became significant for the highest exposure category. There was evidence of a dose-response [ORs of 1.7 (95% CI 0.8-3.8) and 2.2 (95% CI 1.1-4.6) for ≤ 2 hrs and > 2 hrs/day ETS exposure, respectively] (Table 7.4.3B).

Linet et al., 1996. This nested case-control Swedish study identified 570 incident childhood brain tumor cases through linkages of the Swedish Birth and Cancer registries. Population-based controls (five per case) matched on sex and age were selected from the Birth Registry (study years 1973-89). The majority of cases (98%) were diagnosed prior to age 15 with 10 cases diagnosed in adolescents ages 15 to 17. Unfortunately, maternal smoking status was only ascertained since 1983, therefore 466 cases and 2330 controls lacked smoking data. This left a total of 96 cases and 484 controls for which there were data on which to base an analysis of the effect of maternal smoking. No statistically significant risk was associated with maternal smoking for all brain tumors combined or for the individual tumor subgroups; however, the majority of cases had no data on maternal smoking.

Norman et al., 1996. This large, population-based case-control study identified incident brain cancer cases from three Surveillance, Epidemiology, and End Results Program (SEER) cancer registries in Los Angeles, Seattle and the San Francisco Bay Area, among children and young adults under age 20 between 1984 and 1991. No statistically significant association was found between the risk of childhood brain tumors (all histologies combined) and maternal or paternal smoking before pregnancy or with maternal smoking during pregnancy. An elevated but statistically non-significant risk of brain tumors was associated for paternal smoking alone during pregnancy [adjusted OR 1.2 (95% CI 0.90-1.5)] and for maternal smokers with additional exposure to ETS [adjusted OR 1.2 (95% CI 0.93-1.4)] (Table 7.4.3B). Similarly elevated, but non-significant risk estimates were reported for maternal ETS exposure among non-smoking mothers and/or smoking mothers after cases were stratified by age into cases diagnosed ≤ 5 years of age or > 5 years of age; adjusted ORs ranged from 1.1 (95% CI 0.76-1.5) to 1.3 (95% CI 0.87-1.9). Although the authors stated that effects of early childhood exposure to tobacco smoke were also explored, only one result was reported. No significant elevation in risk for brain tumors was found for children that lived for 6 months or more with a smoker [OR 0.93 (95% CI 0.74-1.17)].

Ji et al., 1997. As part of the population-based case control study in Shanghai, China, investigators evaluated the association between parental smoking and childhood brain cancer incidence. Cases diagnosed from 1981 through 1991 were ascertained from a population-based cancer registry among children under the age of 15. A total of 107 cases matched to population controls based on age, sex and local governmental sampling unit were included. Only paternal smoking was analyzed in this study.

Paternal smoking status (ever versus never) was associated with an elevated, but not statistically significant, risk for all childhood brain cancers combined [adjusted RR 1.4 (95% C.I. 0.6-3.2)] after adjustment for birth weight, income, paternal age, education and alcohol consumption. Adjusted risk estimates were highest for children of fathers that smoked for longer periods or more heavily during conception [adjusted RR 2.7 (95% C.I. 0.8-9.9), children of fathers smoking more than 5 pack-years before conception] (Table 7.4.3B). The level of paternal smoking after birth was not associated with an increased risk of childhood brain cancer. Additionally, as found in the study for all cancer sites combined, the risk was greatest in children diagnosed under age

5; cases in children ages 5 and older did not appear associated with paternal preconception smoking.

Sorahan et al. 1995; 1997a; 1997b. Three United Kingdom case-control studies of childhood cancer deaths in relation to reported parental tobacco consumption have been published from the Oxford Survey of Childhood Cancers (OSCC) (Sorahan *et al.*, 1995; Sorahan *et al.* 1997a; Sorahan *et al.*, 1997b). All three OSCC studies found no statistically significant association between maternal smoking (prior to or during pregnancy) and risk of childhood death due to tumors of the central nervous system (CNS) for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981, with risk estimates remaining near unity [RR range 0.9-1.1]. However, one of the studies identified a slightly higher, but statistically nonsignificant positive relationship between paternal smoking and childhood deaths due to tumors of the CNS [unadjusted OR 1.20 (95% CI 0.96-1.51)] (Sorahan *et al.* 1997a). The investigators also conducted a pooled analysis, consisting of 1,071 matched pairs total for CNS tumors. Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significant relative risk estimate [RR 1.30 (95% CI 1.06-1.59)] for tumors of the central nervous system from all three time periods combined (Sorahan *et al.*, 1997b). The newer study adjusted for several important confounders, including social class and paternal age, with little effect on the risk estimates (Sorahan *et al.*, 1997b) (Table 7.4.3B).

Sorahan et al., 2001. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) report included a reanalysis of 32 incident cases with maternal and 29 with paternal smoking data, among children under age 15 diagnosed with tumors of the central nervous system, 1980-1983 (Birch *et al.*, 1990; Sorahan *et al.*, 2001). Maternal and paternal smoking habits prior to conception were analyzed and presented separately, and the presented CNS-specific risk estimates were not adjusted for other factors. Daily levels of cigarette smoking (cigarettes/day) by either parent were not positively associated with increased risk of childhood CNS tumors (p-value for trend=0.67 and 0.71, for paternal and maternal smoking, respectively) (Table 7.4.3B).

Schuz et al., 1999. This population-based German case-control study interviewed 1,867 of 2,358 eligible incident childhood cancer cases identified through the German Childhood Cancer Registry (all sites combined), diagnosed among children under age 15 between 1992 and 1997. In the study, 399 cases of tumors of the central nervous system were included. Interview data included parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Data were presented independently for maternal smoking during pregnancy and paternal smoking before pregnancy (cigarettes/day). No association between parental smoking and risk of childhood brain tumors was found with statistically non-significant adjusted ORs ranging 0.8-1.1 (adjusted for urbanization and socioeconomic status based on income and parental education; Table 7.4.3B).

Filippini et al., 2002. A multi-country, multi-center study on childhood brain tumors organized by the International Agency for Research on Cancer (IARC) identified incident cases of cancer over a range of time periods (1980's and 1990's) in the U.S., Europe, Israel, Canada, and Australia. From the 1,640 eligible cases, 1,218 agreed to participate (74%) through maternal interview. Population controls were obtained at each study site by varying methods. Smoking questions included obtaining information on maternal smoking (before and during pregnancy),

paternal smoking (during pregnancy), other maternal ETS exposure (household or workplace), and childhood ETS exposure during year one. The overall risk for childhood brain cancer, all histological groups combined, was not significantly associated with either maternal or paternal smoking (before or during pregnancy) or with childhood ETS exposure after birth for the first year (adjusted for age, sex and study center). However, analysis by subtype did find elevated cancer risk for astroglioma with paternal smoking [adjusted OR 1.2 (95% CI 1.0-1.5)] and for primitive neuroectodermal tumor (PNET) with maternal ETS exposure [adjusted OR 1.3 (95% CI 1.0-1.7)]. Analysis stratified by age at diagnosis identified an increased overall cancer risk for children diagnosed under age 1 with paternal smoking during pregnancy [adjusted OR 1.7 (95% CI 1.0-2.9)]. However, overall no consistent association between childhood brain cancer and paternal smoking was observed. The occasional, scattered, slightly increased or decreased risks noted in certain subgroups was ascribed by the authors to multiple testing in the analysis.

7.4.3.3. Summary of ETS and Brain Cancer

In adults, the epidemiological evidence for an association between ETS exposure and risk of brain tumor remains weak and inadequately researched. More recent studies have focused on the potential association between ETS and childhood brain tumors. In children, recent studies or others not previously reviewed by OEHHA provide no substantial evidence for an association between maternal smoking and childhood brain tumors, with risk estimates generally near unity. Two European case-control studies reported more elevated, but nonetheless nonsignificant increases in risk, OR 1.6-1.7 for any maternal smoking (Cordier *et al.*, 1994; Filippini *et al.*, 1994). However, brain cancer risk was significantly elevated among children with any postnatal ETS exposure, OR 2.3 (95% CI 1.1-4.6) (Cordier *et al.*, 1994). Several studies indicated a slightly stronger association with paternal smoking and brain cancer than noted in the previous CAL/EPA (1997) report, although the association is still somewhat weak. The most recent and largest individual study (Filippini *et al.*, 2002) did not consistently observe statistically elevated brain cancer risk.

Paternal smoking was generally reported as ever active or ever smoking during pregnancy. Generally risk estimates were similar to or slightly higher than maternal smoking, but nonsignificant (Norman *et al.*, 1996; Ji *et al.*, 1997; Sorahan *et al.*, 1997a; Sorahan *et al.*, 1997b; Filippini *et al.*, 2002). However, the pooled estimate of risk from the OSCC studies (together the largest sample size of the studies reviewed), comparing paternal smokers versus paternal nonsmokers, was significant [RR 1.30 (95% CI 1.06-1.59)] for deaths from tumors of the central nervous system for all three time periods combined (Sorahan *et al.*, 1997b). One study also reported data mildly suggestive of a dose response (but without significant trend tests) for brain tumors and paternal smoking (Ji *et al.*, 1997). Overall, the generally positive, but inconsistent, associations reported between paternal smoking and childhood brain tumors, in combination with biologically plausible hypothesis, provide suggestive evidence of an association between ETS, or possibly pre-conceptual paternal smoking, and brain cancer in children.

Table 7.4.3B. Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother	Father
Bunin *et al.*, 1994	Astrocytoma:	Maternal smoking ever[a]	Paternal smoking ever
(Age <6)	86/82 (M), 86/82 (P)	1.1 (0.7-18.0)	1.1 (0.7-18.0)
		During pregnancy	During pregnancy
	64/63	1.0 (0.6-1.7)	1.0 (0.6-1.7)
		ETS during pregnancy	
	83/83	0.9 (0.6-1.5)	
	PNET	Maternal smoking ever[b]	Paternal smoking ever
	85/88	0.9 (0.6-1.5)	0.9 (0.6-1.5)
		During pregnancy	During pregnancy
	60/58	1.0 (0.6-1.7)	1.0 (0.6-1.7)
		ETS during pregnancy	
	79/81	0.9 (0.8-1.2)	
Cordier *et al.*, 1994		Maternal during pregnancy[c]	
(Age <15)	19/23	1.6 (0.7-3.5)	
		Any exposure pregnancy (mother, family, work)	
	51/70	1.5 (0.8-2.8)	
		Any exposure during childhood (mother, family, work)	
	41/51	2.3 (1.1-4.6)	
Filippini *et al.*, 1994		Maternal smoking lifetime[d]	Paternal smoking lifetime[d]
(Age <15)	90/304	1.2 (0.8-2.0)	1.3 (0.7-2.2)
			Paternal 3 month prior[d]
	90/300		1.3 (0.8-2.2)
		Maternal ETS conception[d]	
	38/123	Total 1.6 (0.8-3.3)	
	15/53	< 2 hr/day 1.5 (0.7-3.5)	
	23/70	> 2 hr/day 1.7 (0.8-3.7)	
		P trend = 0.08	
		Maternal smoking conception[d]	
	38/105	Total 1.9 (1.0-3.8)	
	32/87	1-10 cpd 2.0 (1.0-4.0)	
	6/18	>10 cpd 1.6 (0.5-4.8)	
		P trend = 0.36	
		Maternal ETS pregnancy[d]	
	57/155	Total 2.0 (1.0-4.0)	
	20/63	< 2 hr/day 1.7 (0.8-3.8)	
	37/92	> 2 hr/day 2.2 (1.1-4.6)	
		P trend=0.02	
		Maternal smoking pregnancy[d]	
	18/59	Total 1.6 (0.7-3.7)	
	14/48	1-10 cpd 1.6 (0.7-3.8)	
	4/11	>10 cpd 1.7 (0.4-6.6)	
		P trend=0.73	

PNET=Primitive neuroectodermal tumor. (M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls.

[a] ORs adjusted for income Table 2 Bunin *et al.* (1994).

[b] Unadjusted ORs Table 2 Bunin *et al.* (1994).

[c] ORs adjusted for child's age, sex and maternal age Table 4 Cordier *et al.* (1994).

[d] ORs adjusted for child's age, sex, paternal education Tables 4 to 6 Filippini *et al.* (1994).

Table 7.4.3B. Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother		Father
Linet *et al.*, 1996 (Age ≤ 17)	96/484	Maternal smoking[e]		
		Non-smoker	1.0 (Referent)	
		1-9 cpd	1.3 (0.7-2.2)	
		≥ 10 cpd	1.0 (0.5-2.1)	
Norman *et al.*, 1996 (Age <20)	540/801	Maternal smoking lifetime[f]		Paternal smoking lifetime[f]
		Total	0.82 (0.64-1.04)	1.1 (0.84-1.3)
		1-10 cpd	0.84 (0.63-1.1)	1.2 (0.86-1.7)
		>10 cpd	0.75 (0.54-1.03)	0.98 (0.72-1.3)
		Maternal smoking pregnancy[f]		Paternal smoking pregnancy[f]
		Active	0.98 (0.72-1.3)	1.2 (0.90-1.5)
		Active/Passive	1.2 (0.93-1.4)	DNS
Ji *et al.* , 1997 (Age <15)	107/107			Paternal Smoking:
		Ever Active[g]		1.4 (0.6-3.2)
		Duration (years)[g]:	< 10	0.8 (0.2-3.8)
			10-14	1.3 (0.4-4.1)
			≥ 15	3.4 (0.9-12.5)
				P trend = 0.10
		Pack-year prior to conception[g]	≤ 2	1.5 (0.5-4.4)
			> 2 - < 5	1.7 (0.5-5.8)
			≥ 5	2.7 (0.8-9.9)
				P trend = 0.14
		Pack-year after birth[g]	≤ 2	1.3 (0.4-3.7)
			> 2 - < 5	1.8 (0.6-5.2)
			≥ 5	1.0 (0.3-3.3)
				P trend = 0.96
Sorahan *et al.*, 1995; 1997a and b (Deaths, age < 15)		Maternal smoking at interview Increase risk by level		Paternal smoking at interview Increase risk by level
1953-1955 (1997a)	229/229	1.04 (0.81-1.35)[h]		1.20 (0.96-1.51)[h]
1971-1976 (1997b)	410/410	1.07 (0.95-1.19)[i]		1.02 (0.93-1.11)[i]
1977-1981 (1995)	312/312 (M), 299/299 (P)	1.06 (0.94-1.20)[j]		1.09 (0.95-1.20)[j]
Pooled Estimate for 3 time periods (1997b)	1043/1058(M), 1016/1035 (P)	1.01 (0.84-1.23)[k]		1.30 (1.06-1.59)

(M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls.

[e] ORs adjusted for child's age and sex Table 2 Linet *et al.* (1996).

[f] ORs adjusted for child's age, sex and race Table 3 Norman *et al.* (1996).

[g] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

[h] Unadjusted RR represents change risk one categorical level of smoking, maternal/paternal daily smoking analyzed simultaneously, Table 2 Sorahan *et al.* (1997a).

[i] Table 2 Sorahan *et al.* (1997b), unadjusted RR estimate change one level daily consumption.

[j] Table 4 Sorahan *et al.* (1995) unadjusted RR estimate change one level daily consumption.

[k] ORs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b)

Table 7.4.3B. Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother		Father
Schuz *et al.*, 1999	399/2588	Maternal during pregnancy[l]		Paternal before pregnancy[l]
(Age <15)		1-10 cpd	0.8 (0.6-1.1)	0.8 (0.5-1.2)
		11-20 cpd	1.6 (0.9-2.8)	1.1 (0.8-1.4)
		>20 cpd	0.8 (0.2-3.9)	1.0 (0.7-1.4)
Filippini *et al.*, 2002		Maternal ETS		Paternal before pregnancy:
(Age ≤ 19)	345/1,190 (P)	1.3 (1.0-2.9) PNET		1.2 (1.0-1.5)
				astroglial diagnosis under 1 yr of age 1.7 (1.0-2.9)
Sorahan *et al.*, 2001		Maternal at conception[m]		Paternal at conception
(Age < 15)	72/72 (M)	<10 cpd	6.56 (1.36-31.73)	0.51 (0.09-2.97)
	66/65 (P)	10-19	1.28 (0.55-3.03)	1.25 (0.42-3.72)
		20-29	1.30 (0.52-3.22)	0.21 (0.21-1.33)
		30-39	NA	0.15 (0.01-1.54)
		≥ 40 cpd	NA	0.64 (0.08-4.79)
			P trend=0.71	*P* trend=0.67

[l] ORs adjusted for age, sex, and socioeconomic status Table 4 Schuz *et al.* (1999).

[m] Unadjusted ORs presented in Table 3 of Sorahan *et al.* (2001) for GP controls

(M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls. PNET=Primitive neuroectodermal tumor.

7.4.4. Leukemia

7.4.4.1. Active Smoking and Leukemia

Previously, OEHHA reported evidence that cigarette smoking may be related to an increased risk of leukemia. Several prospective cohorts have reported an increased risk of various magnitude and statistical significance, for either all leukemia combined or for selected subtypes, while other studies including several case-control studies found no elevated risk (Cal/EPA, 1997). No new primary studies were located for this update.

7.4.4.2. ETS and the Risk of Leukemia in Adults

7.4.4.2.1. Previous Findings

The OEHHA report (Cal/EPA, 1997) noted that the evidence was insufficient to evaluate an association between ETS exposure and adult leukemia, and cited a single study examining the association between ETS exposure and adult onset leukemia (Sandler *et al.*, 1985a). This one study reported an elevated, non-significant risk for all hematopoietic malignancies combined among nonsmoking women exposed as children to parental smoking (maternal and paternal). No estimates related to other potential sources of ETS, including spouses or workplace, were reported.

7.4.4.2.2. Recent Epidemiological Data

No new primary studies were located.

7.4.4.3. ETS and the Risk of Leukemia in Children

7.4.4.3.1. Previous Findings

In the 1997 report, OEHHA reviewed a total of eight published studies examining the potential relationship between ETS exposure and the risk of developing leukemia. The epidemiological evidence for parental smoking and risk of childhood leukemia was considered inconclusive and often conflicting. No association was observed in the one cohort study reviewed (Pershagen *et al.*, 1992). Two of seven case-control studies identified a significant increase in leukemia risk with maternal smoking (Stjernfeldt *et al.*, 1986a; Stjernfeldt *et al.*, 1986b; John *et al.*, 1991). The case control studies varied in the type of cases enrolled (acute lymphocytic, non-acute lymphocytic, acute myeloid, or all leukemias combined), the age of cases and other potential risk factors. In summary, OEHHA considered the evidence insufficient to assess the association between ETS exposure and leukemia in children/adolescents. (Cal/EPA, 1997).

7.4.4.3.2. Recent Epidemiological Data

Table 7.4.4A summarizes data from the ten studies reporting on childhood leukemia risk associated with ETS exposure.

Klebanoff et al., 1996. In the previously described United States cohort analyzed by Klebanoff *et al.* (1996), a subset analysis was conducted for leukemia risk (17 of 51 reported childhood cases ages 8 or under). Data to determine the proportion of lymphoblastic cases were not available. In this cohort, the children of smoking mothers were not at increased risk of developing leukemia (all types combined) [adjusted RR 0.82 (95% CI 0.31-2.11)]. No data on

paternal or other passive smoking exposure were available. Limited covariate analysis was presented, but did not alter the risk estimates to any substantial degree.

Shu et al., 1996. Data from the Children's Cancer Group (CCG) case-control study, a cooperative clinical trials group within the U.S and Canada, evaluated the relationship between infant leukemia risk and parental alcohol consumption and/or cigarette smoking during pregnancy or during the month prior to it. Three hundred two leukemia cases (203 acute lymphoid leukemias [ALLs], 88 acute myeloid leukemias [AMLs] and 11 other leukemia types) were diagnosed in children at 18 months of age or younger between 1983 and 1988, and matched to 558 controls by residence and year of birth. Maternal and paternal smoking data were collected via telephone interview. Maternal smoking during pregnancy (versus nonsmoking mothers) was negatively associated with infant leukemia risk [total leukemia adjusted OR 0.66 (95% CI 0.46-0.94) after adjustment for sex, maternal education and alcohol consumption], as well as AML separately [OR 0.45 (95% CI 0.21-0.96)]. Paternal smoking one month prior to pregnancy was related to a statistically significant elevated risk of ALL [adjusted OR 1.56 (95% CI 1.03-2.36)], while paternal smoking during pregnancy was associated with an elevated but non-significant risk of ALL [adjusted OR 1.45 (95% CI 0.95 -2.19) after adjustment for sex, paternal age, education, and maternal alcohol consumption)]. The risk of ALL did not increase with increasing paternal cigarette consumption either one month prior to or during pregnancy (p for trend = 0.12). Paternal smoking was not associated with the risk of AML [adjusted ORs 0.75 (95% CI 0.35-1.62) and 0.82 (95% CI 0.38-1.78), one month prior to and during pregnancy, respectively]. The study observed no statistical interaction between maternal and paternal alcohol consumption and smoking.

Ji et al., 1997. As part of the population-based case control study in Shanghai, China, the association between parental smoking and the risk of childhood acute leukemia was evaluated. As described previously, cases diagnosed from 1981 through 1991 were ascertained from a population-based cancer registry among children under the age of 15. A total of 166 cases of acute leukemia (114 ALL and 52 AML) were matched to population controls based on age, sex and local governmental sampling unit. Only paternal smoking was analyzed in this study. Paternal preconceptual versus postconceptual and postnatal smoking effects were derived in several ways by parsing out the window of paternal smoking effect as follows: 1. 13% of control fathers and 12% of case fathers began smoking after the birth of the index child. Paternal smoking that began after the birth of the index child was not associated with an increased risk of childhood cancers**.** 2**.** Increased levels of smoking (40% of fathers who smoked) were not related to an increase in cancer. 3. Preconceptual smoking was assessed in some detail. It was only associated with an increase in cancer for fathers with at least 5 years preconceptual exposure. Risk increased with increasing preconceptual exposure as detailed by increased duration or total pack years. 4. Childhood cancer diagnosed after 5 yrs of age was not linked to paternal preconceptual smoking (etiologically probably a different group of cancers even though histologically the same). 5**.** There was no assessment of any effect of maternal exposure to passive smoke in this study. Again though, the effect was only noted with a substantial number of prenatal years of paternal smoking. This is strengthened by in vitro evidence of DNA damage in sperm cells and mutations in germ cells.

Paternal smoking status (ever versus never) was positively associated, although not statistically significantly, with increased risk for all childhood acute leukemias [adjusted OR 1.3 (95% CI

0.7-2.4), adjusted for birth weight, income, paternal age, education and alcohol consumption)]. As found in the analysis for all sites combined, adjusted risk estimates were highest among fathers that smoked for longer periods or more heavily during conception, with significantly elevated adjusted risks in the highest exposure category for acute leukemia [OR 2.4 (95% CI 1.1-5.6)], and for ALL [OR 3.8 (95% CI 1.3-12.3) among children of fathers smoking more than 5 pack-years before conception]. For AML the association was positive but not statistically significant [OR 2.3 (95% CI 0.4-14.8)]. A significant trend between increasing acute leukemia risk and increasing cumulative paternal preconception smoking (pack-years before conception) was observed for acute leukemia (ALL and AML combined) (P=0.02), and ALL (P=0.01). The level of paternal smoking after birth was not associated with an increased risk of childhood acute leukemia (combined, ALL or AML separately).

Sorahan et al. 1995; 1997a; 1997b. Three United Kingdom case-control studies of childhood cancer deaths in relation to reported parental tobacco consumption have been published from the Oxford Survey of Childhood Cancers (OSCC). All three OSCC studies found no statistically significant association between maternal smoking (prior to or during pregnancy) and risk of childhood death due to leukemia for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981, with risk estimates remaining near unity. However, the relative risk of leukemia was significantly elevated in association with prenatal paternal smoking for acute lymphocytic (ALL) [OR 1.16 (95% CI 1.06-1.27)] but not myeloid leukemia [OR 1.02 (95% CI 0.89-1.16)], for deaths occurring 1977-1981 (Sorahan *et al.*, 1995). By comparison the opposite result, significant risk for AML but not ALL-related deaths, was reported for 1971-1976 [myeloid leukemia OR 1.27 (95% CI 1.10-1.47) and ALL OR 1.07 (95% CI 0.99-1.16] (Sorahan *et al.*, 1997b), although statistical significance is almost reached for ALL. In the earliest time period, 1953-1955, the association between paternal smoking and leukemia risk remained nonsignificant for both ALL [OR 1.08 (95% CI 0.91-1.27)] and myeloid leukemia [OR 0.98 (95% CI 0.73-1.32)]. In the final mortality analysis, a pooled analysis was conducted, consisting of 2,364 matched pairs total for all leukemia combined (ALL and myeloid leukemia were not reported separately). Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significantly elevated risk estimate for leukemia [adjusted OR 1.20 (95% CI 1.05-1.37)] for all three time periods combined (Sorahan *et al.*, 1997b). The estimate for maternal smoking remained near unity [adjusted OR 1.02 (95% CI 0.90-1.16)] (Sorahan *et al.*, 1997b).

Brondum et al., 1999. Another study from the Children's Cancer Group (CCG) utilized information on 1,842 ALL cases and 517 AML patients, diagnosed between January 1, 1989 and June 15, 1993. ALL cases were aged 15 years or younger, while AML patients were under age 18. Population-based controls (random digit dialing) were matched to cases by age, race, and residence (telephone area code). Maternal and paternal smoking data were collected via telephone interview – current smoking, ever smoking, smoking during month prior to pregnancy, during pregnancy, or after pregnancy. ALL and AML were analyzed separately.

The risk of leukemia (ALL or AML) was not statistically associated with maternal or paternal current smoking or ever smoking. The risk of ALL was not associated with paternal smoking (ever smoked) [adjusted OR 1.04 (95% CI 0.90-1.20)], or maternal smoking (ever smoked) [adjusted OR 1.04 (95% CI 0.91-1.19], after adjustment for income, race and education. Similar results were reported for AML: paternal ever smoking [adjusted OR 0.88 (95% CI 0.67-1.16)],

and maternal ever smoking [adjusted OR 0.95 (95% CI 0.74-1.22)]. Evaluating parental smoking by the time periods either parent smoked (the month prior to pregnancy, during pregnancy, or for the month prior to and during pregnancy combined), did not substantially alter risk estimates. The highest risk estimates were observed for ALL and paternal smoking [<10 cigarettes/day (lifetime), OR 1.16 (95% CI 0.88-1.51); <10 years smoked, OR 1.12 (95% CI 0.91-1.38); and, 10-<20 years smoked, OR 1.22 (95% CI 1.00-1.47)]. However, no significant trends for increasing risk of ALL with paternal lifetime daily cigarette consumption, years smoked, or pack-years were identified. In the case of AML, estimates for parental smoking (maternal or paternal) and risk of AML remained consistently below 1.0 for the various exposure periods. The adjusted ORs for both ALL and AML were also not statistically elevated when total parental smoking was evaluated (neither ever smoked, both parents ever smoked, father only ever smoked, mother only ever smoked), except in the cases of AML homes where only the mother had ever smoked [OR 1.78 (95% CI 1.15-2.75)]. The authors report (no data presented) that the elevated ORs were observed regardless of age group, morphologic subgroup, and exposure periods (prior to pregnancy, individual trimesters). The risk estimate with maternal (not father) ever smoking for one AML morphologic subgroup, M0-M2/granulocytic sarcoma, was substantially elevated [OR 2.69 (95% CI 1.04-6.95)].

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 755 acute leukemia cases (650 ALL and 105 ANLL cases) were included among children under age 15. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Analyses were conducted for acute non-lymphocytic leukemias (ANLL) and for 3 immunological subtypes of ALL (common ALL, pre-beta ALL, and t-ALL). For "common" ALL (450 cases), a slightly increased risk with increasing number of cigarettes per day (maternal smoking) was observed [1-10 cig/day: OR 1.1 (95% CI 0.9-1.4); 11-20 cig/day: OR 1.2 (95% CI 0.8-2.0); 20+ cig/day: OR 2.1 (95% CI 0.7-6.3)]. Paternal smoking the 3 months prior to conception was not associated with childhood leukemia risk, with the heaviest paternal smoking category (>20 cigarettes/day) associated with an OR 1.1 (95% CI 0.8-1.5) for common-ALL.

Infante-Rivard et al, (2000) conducted a case-control study based out of several major cancer treatment facilities enrolled the families of children diagnosed between 1980 and 1993 (study initiated in 1989) in Quebec, Canada. Four hundred and ninety-one incident cases (510 eligible) of acute lymphoblastic leukemia (ALL) in children under age 10 were enrolled. Population controls (493 of 588 eligible) were matched by age, sex and region of residence at time of diagnosis. Additionally, this study investigated the relationship or interaction between specific genetic polymorphisms of a primary metabolic cytochrome P450, the CYP1A1 (3 different alleles analyzed), maternal smoking and ALL risk (genotyping available on 158 cases). Maternal and paternal smoking habits were obtained via telephone interview. A small increased ALL risk which was not statistically significant was associated with maternal smoking during the later trimesters [adjusted OR 1.2 (95% CI 0.8-1.6), second and third trimester]. No association was observed for either maternal or paternal smoking between birth and date of diagnosis. In the case-only genotype analysis, nonsignificant increases in ALL risk for maternal smoking (reported as interaction odds ratios) were observed for two alleles, CYP1A1*4 and CYP1A1*2A. A third allele, CYP1A1*2B, appeared protective (Table 7.4.4B). Although the small sample size (when stratified by genotype) limits broad interpretation of the genotype findings, the study

found some evidence that variants of CYP1A1 could modify even the small risk of ALL associated with parental smoking in this study.

A later study by the same group, although lacking exposure data on tobacco smoking, further demonstrated a role for genetic polymorphisms of metabolic enzymes in the modification of risk in childhood ALL (Krajinovic *et al.*, 2002). This study investigated whether polymorphisms in the genes encoding for three other enzymes involved in the xenobiotic biotransformation, CYP2E1, MPO and NQO1, were additional risk-modifying factors in childhood ALL. This case-control study included 174 patients of French-Canadian origin identified from a Montreal hospital between August 1988 and September 1998 (median age 5.2). Three hundred and thirty seven controls were obtained from an institutional DNA bank. Carriers of one variant CYP2E1 (CYP2E1*5) were at significantly increased risk for ALL [OR 2.8 (95% CI 1.2-6.4), adjusted for sex and age)]. NQO1 (NQO1*2 and *3) contributed to a statistically significant increased ALL risk [OR 1.7 (95% CI 1.2-23.4)]. No association was identified for MPO alone, but wild type MPO, in combination with specific CYP2E1 and NQO1 variants, elevated the risk of ALL further [OR 5.4 (95% CI 1.2-23.4)], suggesting a potential combined effect.

Sorahan et al., 2001. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) report included a reanalysis on 85 ALL cases with maternal smoking data and 57 ALL cases with paternal smoking data diagnosed among children under age 15 between 1980 and 1983 (Birch *et al.*, 1990; Sorahan *et al.*, 2001). Maternal and paternal smoking habits were analyzed and presented separately by dose level (< 10 cig/day, 10-19 cig/day, 20-29 cig/day, 30-39 cig/day, > 40 cig/day). ALL-specific risk estimates for paternal smoking increased with increasing dose level [1-10 cig/day: OR 0.99 (95% CI 0.35-2.85); 10-19 cig/day: OR 1.34 (95% CI 0.62-2.91); 20-29 cig/day: OR 1.32 (95% CI 0.72-2.45); 30-39 cig/day: OR 2.33 (95% CI 0.71-7.63); 40 cig/day: OR 5.29 (95% CI 1.31-21.30), p for trend=0.06)]. At the highest exposure, the OR was statistically significant. This is consistent with Ji *et al.* (1997). Maternal smoking did not show a similar pattern (P for trend 0.56) (Table 7.4.4A).

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Klebanoff *et al.*, 1996 (Age < 9)	17 Cohort study (All types)	During/Current at Diagnosis	0.82 (0.31-2.11)[a]	Not available
Shu *et al.*, 1996 (Age ≤ 18 months)	302/558 (All types)	Month prior	0.71 (0.51-1.01)[b]	1.28 (0.90-1.81)[b]
		During Pregnancy	0.66 (0.46-0.94)	1.23 (0.86-1.75)
		1-10 cpd[c]	0.66 (0.41-1.04)	1.39 (0.69-2.82)
		11-20 cpd	0.64 (0.39-1.06)	1.15 (0.74-1.80)
		> 20 cpd	0.62 (0.22-1.79)	1.36 (0.81-2.28)
			p trend=0.03	p trend=0.23
	203/558 (ALL[d])	Month prior	0.84 (0.51-1.28)	1.56 (1.03-2.36)
		During Pregnancy	0.78 (0.51-1.18)	1.45 (0.95-2.19)
		1-10 cpd	0.78 (0.45-1.32)	2.40 (1.00-5.72)
		11-20 cpd	0.79 (0.44-1.42)	1.33 (0.79-2.34)
		> 20 cpd	0.48 (0.12-1.90)	1.51 (0.82-2.77)
			p trend=0.18	p trend=0.12
	88/558 (AML[d])	Month prior	0.48 (0.22-1.05)	0.75 (0.35-1.62)
		During Pregnancy	0.45 (0.21-0.96)	0.82 (0.38-1.78)
		1-10 cpd	0.46 (0.16-1.31)	0.42 (0.09-1.95)
		11-20 cpd	0.41 (0.15-1.13)	0.73 (0.27-1.94)
		> 20 cpd	0.69 (0.08-5.78)	1.29 (0.44-3.74)
			p trend=0.07	p trend=0.98

[a] RR (Proportional hazards ratio) no adjustment for other factors reported in text of Klebanoff *et al* (1996).
[b] ORs adjusted for maternal alcohol, maternal/paternal education, maternal/paternal age and sex from Tables 4 and 5 in Shu *et al.* (1996).
[c] cpd=cigarettes/day
[d] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Ji *et al.*, 1997 (Age <15)	166/166 (Acute Leukemias, All types)	Ever Active	Not available	1.3 (0.7-2.4)[e]
		Duration (years):		
		< 10	Not available	0.9 (0.3-2.3)
		10-14	Not available	1.0 (0.5-2.2)
		≥ 15	Not available	1.7 (0.8-3.7)
				p trend=0.23
		Pack-year prior conception		
		≤ 2	Not available	0.7 (0.3-1.8)
		> 2 to < 5	Not available	1.0 (0.4-2.1)
		≥ 5	Not available	2.4 (1.1-5.6)
				p trend=0.02
		Pack-year after birth		
		≤ 2	Not available	1.3 (0.6-2.6)[c]
		> 2 to < 5	Not available	1.6 (0.7-3.5)
		≥ 5	Not available	1.0 (0.4-2.4)
				p trend=0.94
	114/114 (ALL[f])	Pack-year prior conception		
		≤ 2	Not available	0.8 (0.2-2.5)[g]
		> 2 to < 5	Not available	1.0 (0.4-2.7)
		≥ 5	Not available	3.8 (1.3-12.3)
				P trend=0.01
		Pack-year after birth		
		≤ 2	Not available	1.1 (0.4-2.8)
		> 2 to < 5	Not available	1.8 (0.6-5.2)
		≥ 5	Not available	1.8 (0.6-5.5)
				P trend=0.33
	52/52 (AML)	Pack-year prior conception		
		≤ 2	Not available	0.9 (0.1-7.3)[g]
		> 2 to < 5	Not available	0.6 (0.1-3.1)
		≥ 5	Not available	2.3 (0.4-14.8)
				P trend=0.36
		Pack-year after birth		
		≤ 2	Not available	5.0 (0.8-32.5)
		> 2 to < 5	Not available	6.1 (0.8-45.1)
		≥ 5	Not available	0.5 (0.1-2.7)
				P trend=0.24

[e] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

[f] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia

[g] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Sorahan *et al.*, 1995; 1997a; 1997b				
(Deaths, Age < 15)				
1953-1955 (1997a)	367/367 (ALL[j])		1.24 (1.01-1.52)[h]	1.08 (0.91-1.27)[h]
	115/115 (AML)		1.20 (0.85-1.68)[h]	0.98 (0.73-1.32)[h]
	27/27 (Monocytic)		1.21 (0.58-2.54)[h]	1.10 (0.61-2.01)[h]
	216/216 (Other/Unspecified)		1.18 (0.91-1.55)[h]	1.14 (0.93-1.39)[h]
1971-1976 (1997b)	573/573 (ALL)		0.98 (0.89-1.07)[i]	1.07 (0.99-1.16)[i]
	190/190 (AML)		1.00 (0.83-1.20)[i]	1.27 (1.10-1.47)[i]
	25/25 (Monocytic)		0.66 (0.36-1.19)[i]	0.84 (0.56-1.26)[i]
	47/47 (Other/Unspecified)		0.91 (0.67-1.24)[i]	0.99 (0.75-1.30)[i]
1977-1981 (1995)	400/400 (M[j]) (ALL)		0.94 (0.83-1.05)[k]	
	371/371 (P)			1.16 (1.06-1.27)[k]
	151/151 (M) (AML)		0.93 (0.79-1.10)[k]	
	147/147 (P)			1.02 (0.89-1.16)[k]
	22/22 (M) (Other/Unspecified)		1.23 (0.69-2.20)[k]	
	19/19 (P)			0.66 (0.44-0.99)[k]
Pooled Estimate - for 3 time periods (1997b)	2312/2317 (M) (All leukemias) 2254/2281 (P)		1.02 (0.90-1.16)[l]	1.20 (1.05-1.37)[l]

[h] Unadjusted RR represents change risk one categorical level of smoking, maternal/paternal daily smoking analyzed simultaneously, Table 2 Sorahan *et al.* (1997a).

[i] Table 2 Sorahan *et al.* (1997b), unadjusted RR estimate change one level daily consumption.

[j] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia (M)=Maternal exposed; (P)= Paternal exposed.

[k] Table 4 Sorahan *et al.* (1995) unadjusted RR estimate change one level daily consumption.

[l] ORs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b).

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Brondum *et al.*, 1999	Total	Current	1.02 (0.87-1.19)[m]	1.06 (0.90-1.25)[m]
(Age <15 ALL[n])	1914/1987 (ALL)	Ever	1.04 (0.91-1.19)	1.04 (0.90-1.20)
		Lifetime daily		
	1842 (M)	< 10 cpd	1.02 (0.83-1.26)	1.16 (0.88-1.51)
	1618 (P)	10-19 cpd	1.04 (0.86-1.26)	1.04 (0.83-1.31)
		20+ cpd	1.04 (0.87-1.26)	1.06 (0.88-1.26)
			p trend=0.59	p trend=0.59
		Lifetime duration		
		< 10 yrs	1.16 (0.98-1.38)	1.12 (0.91-1.38)
		10-19 yrs	1.03 (0.86-1.22)	1.22 (1.00-1.47)
		20+ yrs	0.66 (0.49-0.93)	0.91 (0.72-1.14)
			p trend=0.27	p trend=0.79
		During Pregnancy	1.06 (0.91-1.23)	1.07 (0.91-1.25)
		Both parents ever smoked	1.09 (0.91-1.30)	
		Father only ever smoked		1.04 (0.86-1.26)
		Mother only	1.10 (0.88-1.38)	
(Age < 17 AML)	Total	Current	0.97 (0.73-1.30)[m]	0.91 (0.67-1.24)[m]
	530/612 (AML)	Ever	0.95 (0.74-1.22)	0.88 (0.67-1.16)
		Lifetime daily		
	517 (M)	< 10 cpd	1.25 (0.88-1.76)	1.04 (0.62-1.74)
	450 (P)	10-19 cpd	0.87 (0.61-1.24)	0.92 (0.61-1.37)
		20+ yrs	0.73 (0.30-1.07)	0.81 (0.58-1.14)
			P trend=0.13	P trend=0.22
		Lifetime duration		
		< 10 yrs	1.02 (0.75-1.41)	1.06 (0.71-1.58)
		10-19 yrs	0.83 (0.58-1.18)	0.98 (0.69-1.45)
		20+ yrs	1.05 (0.64-1.70)	0.65 (0.44-0.96)
			P trend=0.66	P trend=0.06
		During Pregnancy	0.89 (0.66-1.20)	0.88 (0.65-1.19)
		Both parents ever smoked	0.85 (0.59-1.22)	
		Father only ever smoked		1.32 (0.91-1.93)
		Mother only	1.78 (1.15-2.75)	

[m] ORs adjusted for annual income, parental race and education Tables 4 and 5 Brondum *et al.* (1999).

[n] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia (M)=Maternal exposed cases/controls, (P)= Paternal exposed cases/controls, cpd=cigarettes/day

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Schuz *et al.*, 1999	982/982 (M[o])	During pregnancy		
(Age <15)		1-10 cpd	0.8 (0.6-1.1) [p]	Not available
	(Acute	11-20 cpd	0.5 (0.3-0.9)	Not available
	leukemias)	> 20 cpd	1.3 (0.4-4.7)	Not available
	955/955 (P)	Before pregnancy		
		1-10 cpd	Not available	1.1 (0.8-1.5) [p]
		11-20 cpd	Not available	1.0 (0.8-1.2)
		> 20 cpd	Not available	0.9 (0.7-1.2)
Infante-Rivard *et al.*, 2000				
(Age <10)	491/491 (M)	During Pregnancy:		
	486/486 (P)	1st Trimester:		
	(ALL)	1-20 cpd	1.1 (0.8-1.6) [q]	Not available
		20+ cpd	1.0 (0.7-1.6)	Not available
		2nd Trimester:		
		1-20 cpd	1.2 (0.8-1.6)	Not available
		20+ cpd	1.2 (0.7-1.9)	Not available
		3rd Trimester:		
		1-20 cpd	1.2 (0.8-1.6)	Not available
		20+ cpd	1.2 (0.8-2.0)	Not available
		Postnatal < Diagnosis		
		1-20 cpd	1.0 (0.7-1.4)	1.0 (0.7-1.4)
		20+ cpd	1.0 (0.6-1.3)	1.0 (0.7-1.3)
Sorahan *et al.*, 2001		At conception		
(Age < 15)	140/142 (M)	< 10 cpd	1.34 (0.46-3.87)[r]	0.99 (0.35-2.85)[r]
	139/132 (P)	10-19	1.11 (0.59-2.08)	1.34 (0.62-2.91)
	(ALL)	20-29	0.98 (0.51-1.85)	1.32 (0.72-2.45)
		30-39	0.26 (0.03-2.38)	2.33 (0.71-7.63)
		≥ 40 cpd	(30+ max category)	5.29 (1.31-21.30)
			p trend=0.56	p trend=0.06

[o] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia (M)=Maternal exposed cases/controls, (P)= Paternal exposed cases/controls, cpd=cigarettes/day

[p] ORs adjusted for age, sex, and socioeconomic status Table 3 Schuz *et al.* (1999).

[q] ORs adjusted for age, sex, maternal age and education Table 2 Infante-Rivard *et al.* (2000).

[r] Unadjusted ORs presented in Tables 1 and 2 of Sorahan *et al.* (2001) for GP controls.

Table 7.4.4B Maternal Smoking and CYP1A1 Allelic Variants in Childhood Leukemia*

Smoking Habits (cigarettes/day)	# Cases/ Controls	OR (95% CI) CYP1A1*2A	# Cases/ Controls	OR (95% CI) CYP1A1*2B	# Cases/ Controls	OR (95% CI) CYP1A1*4
1st Trimester:						
1-20 cpd	7/37	1.0 (0.4-2.9)	1/44	0.1 (0.01-0.9)	2/43	1.1 (0.2-6.4)
20+ cpd	6/17	2.1 (0.7-6.6)	2/21	0.5 (0.1-2.4)	2/21	1.0 (0.3-11.7)
2nd Trimester:						
1-20 cpd	5/42	0.5 (0.2-1.6)	2/46	0.2 (0.1-1.1)	3/45	2.2 (0.4-11.8)
20+ cpd	5/9	2.8 (0.8-9.7)	1/13	0.4 (0.1-3.7)	2/12	5.3 (0.8-36.8)
3rd Trimester:						
1-20 cpd	5/41	0.6 (0.2-1.7)	2/45	0.3 (0.1-1.2)	3/44	2.3 (0.4-12.2)
20+ cpd	5/9	2.8 (0.8-9.8)	1/31	0.4 (0.1-3.7)	2/12	5.4 (0.8-37.3)

* Acute lymphocytic leukemia. Interaction ORs adjusted for age and sex of child. Table 3 Infante-Rivard *et al.* (2000)

7.4.4.4. Summary of ETS and Leukemia

In adults, no additional studies investigating the association between ETS exposure and hematopoietic tumors were available for review. The 1997 Cal/EPA document noted that the evidence was insufficient to assess potential associations with childhood leukemia from the studies available at that time. In general, the subsequent studies have not found an association with maternal smoking. There is strengthened (though not conclusive) evidence of an association with paternal preconceptional smoking. Thus, evidence to date is suggestive of an association between preconceptional paternal smoking and leukemia risk, but not postconceptional ETS exposure. The observed associations may be the result of heritable germ cell mutations.

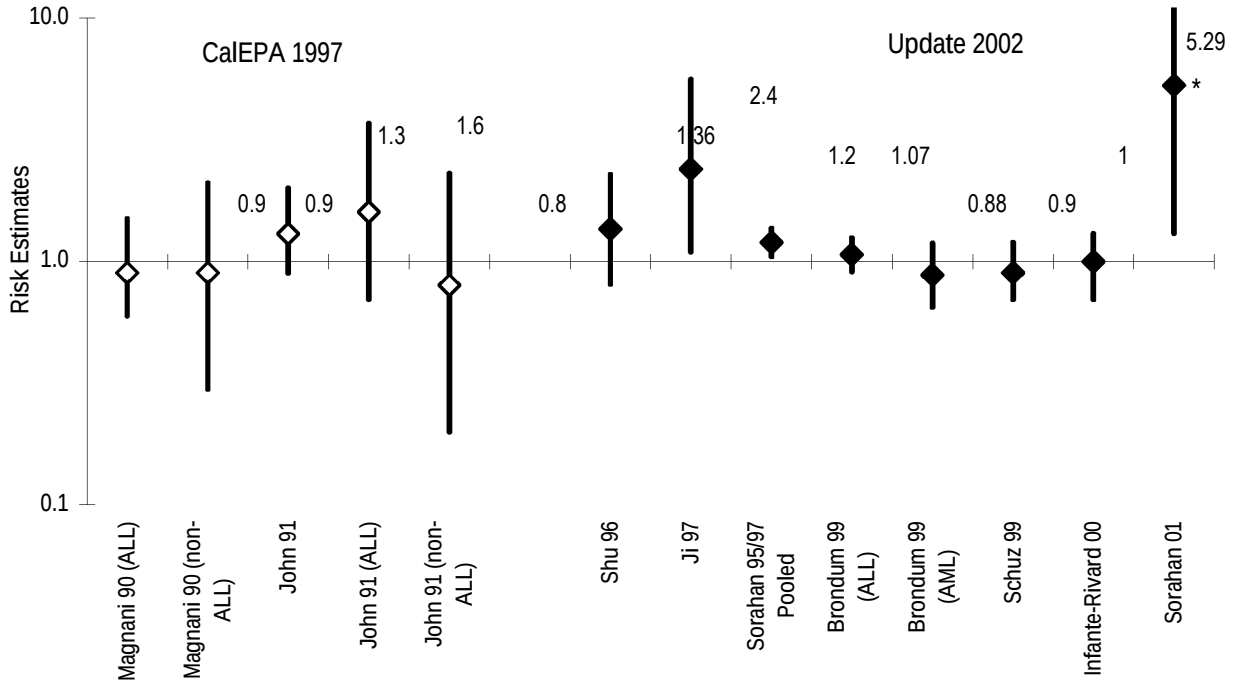
In the studies investigating parental smoking and overall childhood cancer, several included analysis of leukemia risk associated with parental smoking (Sorahan *et al.*, 1995; Klebanoff *et al.*, 1996; Ji *et al.*, 1997; Sorahan *et al.*, 1997a; Sorahan *et al.*, 1997b; Schuz *et al.*, 1999; Sorahan *et al.*, 2001) while others focused only on childhood leukemia (Shu *et al.*, 1996; Brondum *et al.*, 1999; Infante-Rivard *et al.*, 2000). Recent study results on the relationship between parental smoking and leukemia remain mixed, with leukemia risks associated with maternal smoking generally null (Klebanoff *et al.*, 1996; Shu *et al.*, 1996; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997b; Infante-Rivard *et al.*, 2000; Sorahan *et al.*, 2001), in contrast to the several positive, but weak associations reported for paternal smoking (Ji *et al.*, 1997; Sorahan *et al.* 1997b; Sorahan *et al.*, 2001). However, other studies also reported no association between paternal smoking and leukemia (Brondum *et al.*, 1999; Schuz *et al.*, 1999; Infante-Rivard *et al.*, 2000).

Two studies presented evidence suggestive of a dose-response between paternal smoking and ALL, with pack-years prior to conception (Ji *et al.*, 1997) or with daily cigarette consumption at conception (Sorahan *et al.*, 2001). Both studies were based on cases under age 15, however, the results presented in the U.K. study were unadjusted (Sorahan *et al.*, 2001). Ji *et al.* (1997) found the highest risk estimates for both ALL [adjusted OR 3.8] and AML [adjusted OR 2.3] with increasing pack-years prior to conception. Additionally, the case-control study on infants ≤ 18

months (Shu *et al.*, 1996) also was suggestive of a dose-response between ALL risk and daily paternal cigarette consumption (P for trend 0.12), with a significant adjusted OR 1.56 (95% CI 1.03-2.36) associated with smoking one month prior to conception. However in the majority of studies, risks associated with paternal smoking (ever active) remained below 1.2 (Figure 7.4.6 below). The associations seen in Ji *et al.* (1997) and Sorahan *et al.* (2001) relate to active smoking prior to conception and not necessarily exposure of the developing fetus to ETS.

Similar to earlier discussion on the overall childhood cancer risk and ETS related risks, the studies reporting results for leukemia varied in study design (particularly age of study population), definition of ETS exposure (binomial, daily dose, cumulative dose, maternal or paternal or both) and timing of exposure (ever active, during conception, during pregnancy, postnatally), making comparison of results across studies difficult. Age-specific incidence patterns in leukemia vary substantially by age and race/ethnicity. Although ALL remains the most frequently diagnosed malignancy in children under age 15, the childhood and adolescent incidence peaks before age 4 (Campleman *et al.*, 1999; Ries *et al.*, 1999), with rates in California highest among Hispanics and non-Hispanic whites (Campleman *et al.*, 1999). In contrast to earlier studies previously reviewed by OEHHA, these more recent studies distinguished between ALL and non-ALL cases and the majority adjusted for at least some other potential confounders including social class, income, race and/or education.

Figure 7.4.6. Paternal smoking and risk of childhood leukemia.*



*NOTE: Studies reviewed in Cal/EPA 1997 and Update 2002 used a variety of exposure measurements. ALL = acute lymphocytic leukemia. AML = acute myeloid leukemia. Sorahan *et al.* (2001) provides an unadjusted risk estimate.

7.4.5. Lymphomas and Non-Hodgkin's Lymphoma

7.4.5.1. ETS and Lymphoma Risk

7.4.5.1.1. Previous Findings

Previously, OEHHA summarized six reports with at least some examination of the relationship between ETS exposures and childhood lymphomas, whether Hodgkin's Disease, non-Hodgkin's lymphoma (NHL) or all lymphomas combined (Cal/EPA, 1997). Several studies found elevated but statistically non-significant increased risk for either all lymphomas or NHL with maternal smoking, but small case numbers limited dose specific estimates. In summary, OEHHA found the data insufficient to assess potential associations between ETS exposure and lymphoma risk.

7.4.5.1.2. Recent Epidemiological Data

Table 7.4.5A summarizes data from the six studies reporting estimates of lymphoma risk associated with ETS exposure.

Ji et al., 1997. As part of the case-control study discussed earlier, a subset of 87 childhood lymphoma cases (72 non-Hodgkin's lymphoma) was analyzed. Lymphoma risk among children of fathers that ever smoked was elevated with adjusted OR 4.0 (95% CI 1.3-12.5). The risks were highest for children with fathers who smoked more than 5 pack-years before conception [adjusted OR 4.5 (95% CI 1.2-16.8)], or greater than 10 pack-years [OR 5.7 (1.3-26.0)]. Some evidence for a dose-response between duration of paternal smoking and childhood lymphoma risk was observed for active-smoking in years [p for trend 0.05; < 10 years: OR 1.3 (95% CI 0.2-7.0); 10 to 14 years: OR 3.4 (95% CI 0.9-12.7); > 15 years: OR 3.5 (95% CI 0.9-13.7)], and for pack-years, p for trend 0.03; < 5 pack-years: OR 2.8 (95% CI 0.6-12.8); >5 to <10 pack-years: OR 1.3 (95% CI 0.3-5.5); > 10 pack-years: OR 5.7 (95% CI 1.3-26.0)]. The increase in lymphoma risk with increasing cumulative paternal preconception cigarette smoking was marginally significant [p for trend 0.07; < 2 pack-years: OR 3.1 (95% CI 0.8-11.4); >2 to <5 pack-years: OR 1.8 (95% CI 0.4-7.8); > 5 pack-years: OR 4.5 (95% CI 1.2-16.8)]. Additionally, levels of paternal smoking after birth were also associated with increased lymphoma risk [p for trend 0.08; < 2 pack-years: OR 3.9 (95% CI 0.9-16.0); >2 to <5 pack-years: OR 2.7 (95% CI 0.8-9.6); > 5 pack-years: OR 5.0 (95% CI 1.2-22.4), estimates adjusted for birth weight, income, paternal age, education and alcohol consumption].

Sorahan et al., 1995; 1997a; 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed lymphoma risk relative to maternal smoking (prior to or during pregnancy) utilizing childhood deaths due to lymphoma for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. In the final mortality analysis, a pooled analysis was conducted, consisting of 503 matched pairs total for all lymphoma combined (risks for NHL and Hodgkin's Disease were not reported separately). Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significantly elevated risk estimate [adjusted RR 1.67 (95% CI 1.23-2.26)] for lymphoma from all three time periods combined (Sorahan *et al.*, 1997b). The estimate for maternal smoking remained near unity [adjusted OR 0.96 (95% CI 0.73-1.27)] (Sorahan *et al.*, 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 234 cases of non-Hodgkin's lymphoma (NHL) among children under age 15 were

included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Risk of NHL was positively associated with heavy maternal smoking during pregnancy, > 20 cigarettes per day [adjusted OR 5.2 (95% CI 1.2-22.4)] and light paternal smoking prior to pregnancy, 1-10 cigarettes per day [adjusted OR 1.6 (95% CI 1.0-2.5)]. Risk estimates associated with either lower maternal smoking (1-10 or 11-20 cigarettes/day) or higher paternal smoking (11-20 or >20 cigarettes/day), ranged between 1.0 and 1.3 and were not statistically significant (adjusted for urbanization and socioeconomic status) (see Table 7.4.5A).

Sorahan et al., 2001. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) report included a reanalysis on reticuloendothelial malignancies (excluding ALL), for 95 cases with maternal and 85 cases with paternal smoking data (parental smoking analyzed separately). For paternal smoking at conception, elevated risk estimates were observed for four of five exposure strata of cigarettes/day [< 10 cpd: OR 1.32 (95% CI 0.32-5.51); 10-19 cpd: OR 2.65 (95% CI 0.83-8.46); 20-29 cpd: OR 3.69 (95% CI 1.49-9.15); 30-39 cpd: OR 0.29 (95% CI 0.03-2.56); 40+ cpd: OR 1.20 (95% CI 0.29-5.50), p for trend 0.35)]. The majority of exposed cases, 50 of 56, were categorized under <30 cigarettes/day. Elevated risks were also associated with maternal smoking prior to pregnancy [< 10 cpd: OR 1.20 (95% CI 0.41-3.47); 10-19 cpd: OR 2.81 (95% CI 1.07-7.39); 20-29 cpd: OR 1.38 (95% CI 0.58-5.50), p for trend 0.36].

7.4.5.1.3. Nonhuman Epidemiology

Bertone et al., 2002. This was a case control study of the association between ETS exposure and malignant lymphoma in pet cats. Malignant lymphoma occurs commonly in domestic cats and is histologically similar to that in humans. In recent years, with the reduction in the role of feline leukemia virus due to vaccination, other environmental causes have been entertained. Pet dogs and cats have been considered as potential sentinels for environmental health hazards in humans.

Cats diagnosed with biopsy-confirmed malignant lymphoma were compared with cats diagnosed with renal disease. Characteristics of the animals, including breed, age, hair length, reproductive status and general medical history were collected along with data on the animals' diets, time spent in and out of doors, exposure to flea control products, and housing. Exposure to ETS for the two years prior to diagnosis was assessed by questionnaire and included type and quantity of tobacco products used, number of years the cat lived with smokers, number of household smokers, and average number of cigarettes smoked per day.

Multivariate analysis revealed that, compared with cats having no ETS exposure, cats with any exposure to ETS showed a significantly elevated risk of malignant lymphoma (RR 2.4, 95% CI 1.2; 4.5). There was also evidence of dose dependence based on years of exposure (trend p = 0.003), number of household smokers (trend p = 0.005), number of cigarettes smoked per day (trend p= 0.006), and ETS exposure index (years of ETS exposure times number of cigarettes smoked per day; trend p = 0.008).

Since no biochemical measures of ETS were made, it is difficult to quantify the effective doses the cats received. An attempt to mitigate possible misclassification of ETS exposure levels was made by including information on house size and time spent out of doors in the multivariate analysis. Neither of these factors altered the risk estimates. Misclassification of exposure in this study is likely to be nondifferential and would be expected to bias towards the null. The

apparent elevated risk and its dose-dependent nature strongly support a role for ETS in malignant lymphoma in these animals.

Table 7.4.5A Maternal or Paternal Smoking and Risk of Lymphoma in Children

Study (Age of Subjects)	# Cases/ # Controls (Type of lymphoma)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Ji *et al.* (1997) (Age <15)	87/87 (All lymphomas)	Ever active smoker	Not available	4.0 (1.3-12.5)[a]
		Age initiated smoking		
		≥ 25	Not available	4.3 (1.0-17.9)[a]
		20 to 24	Not available	1.9 (0.5-7.3)
		< 20	Not available	5.6 (1.5-21.2)
				p trend=0.92
		Cigarettes per day		
		< 10	Not available	3.4 (0.8-14.0)[a]
		10 to 14	Not available	1.1 (0.3-4.8)
		≥ 15	Not available	3.8 (0.9-16.5)
				p trend=0.09
		Duration years		
		≤ 10	Not available	1.3 (0.2-7.0)[a]
		> 10 to 14	Not available	3.4 (0.9-12.7)
		≥ 15	Not available	3.5 (0.9-13.7)
				p trend=0.05
		Duration pack-years		
		≤ 5	Not available	2.8 (0.6-12.8)[a]
		> 5 to < 10	Not available	1.3 (0.3-5.5)
		≥ 10	Not available	5.7 (1.3-26.0)
				p trend=0.03
		Pack-year prior conception		
		≤ 2	Not available	3.1 (0.8-11.4)[a]
		> 2 to <5	Not available	1.8 (0.4-7.8)
		≥ 5	Not available	4.5 (1.2-16.8)
				p trend=0.07
		Pack-year after birth		
		≤ 2	Not available	3.9 (0.9-16.0)[a]
		> 2 to <5	Not available	2.7 (0.8-9.6)
		≥ 5	Not available	5.0 (1.2-22.4)
				p trend=0.08

[a] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

Table 7.4.5A Maternal or Paternal Smoking and Risk of Lymphoma in Children

Study (Age of Subjects)	# Cases/ # Controls (Type of lymphoma)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Sorahan *et al.*, 1995, 1997a and b (Deaths, Age < 15)		Current at interview (after death)		
1953-1955 (1997a)	125/125 (All Lymphomas)		0.79 (0.55-1.14) [b]	1.37 (1.02-1.83) [b]
1971-1976 (1997b)	165/165 (All Lymphomas)		1.05 (0.89-1.23) [c]	1.07 (0.92-1.23) [c]
1977-1981 (1995)	139/139 (All Lymphomas)		0.98 (0.83-1.17) [d]	1.14 (0.99-1.31) [d]
Pooled Estimate for 3 time periods (1997b)	486/493 (M[e]) (All Lymphomas) 476/477 (P) (All Lymphomas)		0.96 (0.73-1.27) [f]	1.67 (1.23-2.26) [f]
Schuz *et al.*, 1999 (Age <15)	228/2571 (M) 221/2540 (P) (NHL)	During pregnancy 1-10 11-20 > 20	 1.3 (0.9-1.9)[g] 1.0 (0.4-2.5) 5.2 (1.2-22.4)	 Not available Not available Not available
		Before pregnancy 1-10 11-20 > 20	 Not available Not available Not available	 1.6 (1.0-2.5)[g] 1.1 (0.7-1.6) 1.1 (0.7-1.8)
Sorahan *et al.*, 2001 (Age < 15)	95/91 (M) 85/86 (P) (Other RES)	At conception < 10 10-19 20-29 30-39 ≥ 40	 1.20 (0.41-3.47)[h] 2.81 (1.07-7.39) 1.38 (0.58-3.26) (20-29 max) p trend=0.36	 1.32 (0.32-5.51) [h] 2.65 (0.83-8.46) 3.69 (1.49-9.15) 0.29 (0.03-2.56) 1.20 (0.29-5.05) p trend=0.35

[b] Unadjusted RR represents risk with change of one categorical level of smoking, maternal/paternal daily smoking analyzed simultaneously, Table 2 Sorahan *et al.* (1997a).

[c] Table 2 Sorahan *et al.* (1997b), unadjusted RR estimate change in one level of daily consumption.

[d] Table 4 Sorahan *et al.* (1995) unadjusted RR estimates associated with change of one level daily consumption.

[e] (M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls. NHL=Non-Hodgkins Lymphoma, RES=other reticuloendothelial neoplasms (excludes ALL).

[f] ORs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b).

[g] ORs adjusted for age, sex, and socioeconomic status Table 4 Schuz *et al.* (1999).

[h] Unadjusted ORs presented in Table 3 of Sorahan *et al.* (2001) for General Practitioner controls.

7.4.5.2. Summary of ETS and Lymphoma

In summary, the more recent data on ETS exposure and risk of lymphomas and NHL remain inconclusive for adults, primarily due to a lack of investigations. The evidence is strongly suggestive of a relationship with childhood lymphomas (all combined) or NHL. Although small increased risks were reported in some previously reviewed studies (Cal/EPA, 1997), results were inconsistent and based on small numbers. However, in these recently published childhood studies, although largely reporting risk for all lymphomas combined, paternal smoking was significantly associated with overall lymphoma risk (Ji *et al.*, 1997; Sorahan *et al.*, 1997b) with some evidence for a dose-response trend in duration years or pack-years including prior to conception (Ji *et al.*, 1997). More studies on specific lymphoma cell types with more thorough exposure assessment and inclusion of older adolescents at higher risk of lymphomas will help elucidate this potential relationship.

7.4.6. Other Rare Childhood Cancers

7.4.6.1. ETS and Neuroblastoma

7.4.6.1.1. Previous Findings

The previous OEHHA report cited a single case-control study based on 104 of 139 (74.8% response) incident cases from a pediatric cancer registry diagnosed between 1970 and 1979 (Kramer *et al.*, 1987). Parental smoking prior to pregnancy was determined via interview following diagnosis. An elevated, but not statistically significant, risk was observed for maternal smoking during pregnancy [OR 1.26 (90% C.I. 0.76-2.09)] or prior to conception (OR 1.26). Similar results were observed for paternal smoking prior to birth [OR 1.60 (90% C.I. 0.94-2.74)].

7.4.6.1.2. Recent Epidemiological Data

Four case control studies, including the three OSCC reports, investigated the association between neuroblastoma and ETS exposure. The series of studies by Sorahan provide some evidence suggestive of an association between paternal smoking and neuroblastomas. The smaller Schuz study did not support this.

Sorahan et al., 1995; 1997a; 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed for paternal smoking (prior to or during pregnancy) and risk of childhood death due to neuroblastoma for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. Risk estimates varied by time period, ranging between OR 0.93-1.04 for maternal smoking, and OR 1.00-1.48 for paternal smoking. The only significant elevation in risk reported was for paternal smoking and neuroblastoma deaths reported 1953 to 1955 [OR 1.48 (95% 1.09-2.02)]. In the final mortality analysis, a pooled analysis was conducted, consisting of 472 matched pairs total for neuroblastoma diagnosed during all three time periods. Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significantly elevated risk estimate [adjusted OR 2.02 (95% CI 1.45-2.82)] for neuroblastoma from all three time periods combined (Sorahan *et al.* 1997b). The estimate for maternal smoking remained near unity [adjusted OR 0.95 (95% CI 0.71-1.26)] (Sorahan *et al.*, 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 160 cases of neuroblastoma among children were included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Risk of neuroblastoma was weakly associated with light maternal smoking during pregnancy [1-10 cigarettes/day: adjusted OR 1.5 (95% CI 1.0-2.2), based on 39 cases]. Risk estimates at higher smoking strata were inconsistent (i.e., at 11-20 and > 20 cigarettes/day, ORs 0.6 and 2.5, respectively), but were each based on only three cases. Paternal smoking was not significantly associated with an increased neuroblastoma risk [adjusted ORs range 0.6-1.2].

7.4.6.2. Wilms' Tumor of the Kidney

7.4.6.2.1. Previous Findings

The Cal/EPA (1997) report summarized four studies examining the role of ETS and Wilms' tumor, only one of which was designed specifically to identify risk factors for Wilms' tumor (Bunin *et al.*, 1987). This one hospital based case-control study reported no association with maternal smoking during pregnancy, however no risk estimates were presented. The three other case-control studies presented suggestive, but inconsistent and statistically nonsignificant risk estimates, between maternal smoking and the risk of Wilms' tumor (Stjernfeldt *et al.*, 1986a;b; McKinney and Stiller, 1986; Buckley *et al.*, 1986).

7.4.6.2.2. Recent Epidemiological Data

Several of the previously described studies presented limited data on the potential association between ETS and Wilms' tumor (Schuz *et al.*, 1999; Sorahan *et al.*, 1995; Sorahan *et al.* 1997a;b). These studies do not provide adequate evidence of any association between parental smoking and childhood cancers of the kidney.

Sorahan et al., 1995, 1997a, 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed for paternal smoking (prior to or during pregnancy) and risk of childhood death due to Wilms' tumor for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. In the final mortality analysis, a pooled analysis was conducted, consisting of 278 matched pairs for Wilms' tumor diagnosed during all three time periods. Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave an elevated but non-significant risk estimate [adjusted OR 1.27 (95% CI 0.85-1.92)] for Wilms' tumor from all three time periods combined (Sorahan *et al.*, 1997b). The estimate for maternal smoking was significantly negatively associated with Wilms' tumor [adjusted OR 0.67 (95% CI 0.46-0.99)] (Sorahan *et al.*, 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 147 cases of nephroblastoma among children under age 15 were included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Risk of nephroblastoma was not associated with either maternal smoking during pregnancy [(1-10 cigarettes/day: OR 0.9 (95% CI 0.5-1.4); 11-20 cigarettes/day: OR 1.2 (95% CI 0.5-3.0)] or paternal smoking prior to pregnancy [1-10 cigarettes/day: OR 0.8 (95% CI 0.4-1.4); 11-20 cigarettes/day: OR 0.8 (95% CI 0.5-1.3); >20 cigarettes/day: OR 0.9 (95% CI 0.5-1.6)].

7.4.6.3. Germ Cell Tumors

7.4.6.3.1. Previous Findings

The Cal/EPA (1997) report briefly mentioned a single study that analyzed the association between germ cell tumors (41 cases) and paternal smoking within a larger case control study (555 cases) (McKinney and Stiller, 1986). No difference was observed for either maternal or paternal smoking habits between cases and controls.

7.4.6.3.2. Recent Epidemiological Data

One additional primary case-control study (described previously) provides no evidence for an association between ETS and germ-cell malignancies (Shu *et al.*, 1995).

Shu et al., 1995. A case-control study of childhood malignant germ-cell tumors, 105 cases and 639 population controls, was derived from the Children's Cancer Group (U.S. and Canada) to analyze a variety of potential risk factors for germ-cell malignancies. Cases were diagnosed in children under age 15 with a variety of germ–cell malignancies (34 percent ovarian, 23 percent testicular, and 43 percent extra-gonadal). Mothers of cases were less likely than controls to have smoked, with an adjusted OR for risk of germ-cell tumors of 0.6 (95% CI 0.3-1.0) for ever smoking 3 months prior to or during pregnancy (adjusted for age, sex, gestational age, parity, maternal education). No relationship was observed between paternal smoking and risk of germ-cell tumors.

7.4.6.4. Bone and Soft-Tissue Sarcomas

7.4.6.4.1. Previous Findings

The previous OEHHA report (Cal/EPA, 1997) summarized results from three case-control studies; two specifically addressed rhabdomyosarcoma (Grufferman *et al.*, 1982; Magnani *et al.*, 1989) while the other analyzed soft tissue and bone sarcomas from a larger study (McKinney and Stiller, 1986). The association between maternal smoking and the risk of soft tissue sarcomas or bone sarcomas was elevated, but not significantly, in one study (McKinney and Stiller, 1986). The other two studies did not observe increased risk for either rhabdomyosarcoma specifically or all other soft tissue sarcomas combined. However, one study did report a statistically significant elevated risk for rhabdomyosarcoma for paternal smoking [RR 3.9 (95% C.I. 1.5-9.6)], even after adjusting for income, education and paternal occupations [RR 2.8, p = 0.07].

7.4.6.4.2. Recent Epidemiological Data

Two case-control studies, including three reports from the OSCC mortality study, described previously, reported limited risk estimates for ETS exposure and the potential association with bone or soft-tissue sarcomas (Schuz *et al.*, 1999; Sorahan *et al.* 1995, Sorahan *et al.* 1997a; b). These studies do not provide sufficient evidence of an association between parental smoking and bone or soft tissue sarcomas.

Sorahan et al., 1995, 1997a, 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed for paternal smoking (prior to or during pregnancy) and risk of childhood death due to bone sarcomas for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. In the final mortality analysis, a pooled analysis was conducted, consisting of 232 matched pairs for bone sarcomas diagnosed during all three time periods. Site-

specific pooled estimates of risk comparing parental smokers versus parental nonsmokers gave elevated non-significant risk estimates [RR 1.24 (95% CI 0.80-1.93) and 1.31 (95% CI 0.87-2.00)] for paternal and maternal smoking, respectively (Sorahan *et al.* 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 97 cases of bone sarcomas and 137 cases of soft tissue sarcomas reported among children under age 15 were included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. No elevated risk estimates were reported for either maternal or paternal smoking.

7.4.6.5. Summary of ETS and Other Rare Childhood Cancers

The epidemiological evidence on the association between ETS exposure and other rare childhood cancers remains inconclusive. Many studies included cases in children under age 15, unfortunately excluding older adolescents, ages 16 to 19, that have higher age-specific incidence of several important histological types of sarcomas and germ-cell tumors (Campleman *et al.*, 1999; Ries *et al.*, 1999). However, the population-based nature of the studies does provide limited evidence suggesting a potential for a positive association between ETS and bone or soft tissue sarcomas, neuroblastoma or Wilms' tumor. Not surprisingly, given that these are rare events, small case numbers limit the ability to observe a statistically significant effect. Therefore, 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 exposures) in explaining the findings. Future studies will require data collection on and control of other potential risk factors.

7.5. Chapter Summary and Conclusions

To summarize, the body of evidence supports that ETS exposure is causally associated with cancers of the lung and the nasal sinus. Epidemiologic studies, supported by animal data, provide evidence consistent with a causal association between ETS exposure and breast cancer in younger primarily premenopausal women. The evidence is suggestive of a causal association between ETS exposure and cervical cancer, nasopharyngeal cancer, and "all cancers" for adults and children (paternal smoking only). The evidence suggests an association between paternal smoking and childhood brain tumors and lymphoma; it is not possible at this point to separate the direct effects of pre-conceptual paternal smoking on the sperm from the effects of postnatal ETS exposure of the child for these two endpoints. Evidence is suggestive of an association between pre-conceptual paternal smoking, but not postnatal ETS, and childhood leukemia. Finally, currently there is insufficient evidence to assess potential associations between ETS exposure and cancers of the bladder, stomach, brain, hematopoietic system and lymphatic system in adults, and rare childhood cancers; thus the evidence are inconclusive for these cancers.

Appendix 7A

7.ApA.1 Primary Studies of Active Smoking and Breast Cancer Risk

A review of recent studies evaluating the association between active smoking and breast cancer is presented here as background, to aid in understanding the discussion on passive smoking risk, and for completeness in updating the previous document (Cal/EPA, 1997). This is not an attempt to provide an exhaustive review on the subject. As summarized below, 5 recent cohort and 14 case-control studies (primary studies) reported on the association of active smoking with breast cancer since the previous OEHHA document. In addition, the study by Morabia *et al*. (1996) is included below as it is an important study of active smoking and breast cancer reviewed in the 1997 report.

Morabia et al. (1996) examined the relationship of breast cancer with active and passive smoking among Swiss women in a population-based case control study. Cases (n = 244) were women <75 years old with a first diagnosis of invasive breast cancer in 1992-1993, while population controls (n = 1,032) were 30-74 years of age. Data were collected by interview with questions covering the major known or postulated risk factors for breast cancer as well as smoking history. Smoke exposure data were recorded year by year from age ten to the date of the interview, and included both passive and active exposures, duration of exposures (hours per day) and intensities (cigarettes per day). In this study, passive exposure was defined as having been exposed to ETS for at least one hour per day for at least 12 consecutive months. Women recruited during the second year of the study also completed a semiquantitative food frequency questionnaire to control for possible dietary confounders. Multivariate analyses were adjusted for age, education, BMI, age at menarche, age at first live birth, oral contraceptive use, history of familial breast cancer and cancer biopsy. Dietary data were available for 150 cases and 336 controls, and were used to adjust the multivariate analyses of the whole group (n = 1,276) for alcohol and saturated fat intake.

As shown in Table 7.ApA.1, both active and passive smoke exposure were associated with an increased risk of breast cancer that was statistically significant for all cases except ever active smoking of 1-9 cpd when compared to controls who were neither actively nor passively exposed. The fourth column of the table shows that the estimated risks for active smoking become non-significant when the control group included both non-exposed individuals and those exposed to ETS. Inclusion of ETS-exposed individuals in some studies of active smoking and breast cancer may explain their failure to find an association.

Table 7.ApA.1. Breast cancer risk associated with active and passive smoking

Exposure	Multivariate *vs*. unexposed	+ dietary adj. *vs* unexposed	*vs*. unexposed with passive exposure
Active 1-9 cpd	2.4 (1.3; 4.4)	2.2 (1.0; 4.4)	1.2 (0.8; 2.0)
10-19 cpd	3.6 (2.0; 6.2)	2.7 (1.4; 5.4)	1.7 (1.1; 2.5)
≥ 20 cpd	3.7 (2.1; 6.7)	4.6 (2.2; 9.7)	1.9 (1.2; 2.9)
Ever passive	2.3 (1.5; 3.7)	3.2 (1.7; 5.9)	

(from Morabia *et al.,* 1996)

A strength of this study's design was its ability to quantify potential selection, recall and detection biases. Selection bias was assessed by collecting smoking status on non-participants; the authors indicated there was some *"slightly conservative selection bias* (that) *may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their true smoking status."* Interviewers were blind to the interviewees' case-control status. No evidence for differential recall between controls and cases was found based on questions regarding attitudes towards ETS exposure. This study thus supports an association of both passive and active smoking with breast cancer.

Millikan et al. 1998. An ongoing population-based case-control study (498 cases and 473 controls), the Carolina Breast Cancer Study (CNCS), examined the effects of active smoking on breast cancer risk and modification by genetic variation of N-acetylation metabolism (NAT). Risk estimates were adjusted for age, race, reproductive factors, alcohol, and family history of breast cancer. No association was observed between breast cancer and current active smoking versus never smokers in all or stratified by menopausal status (see Table 7.ApA.5). However, elevation in postmenopausal breast cancer risk was associated with former smoking [OR 1.5 95% CI 1.0-2.4], with risks highest among women smoking in the past 3 years [OR 3.4 (95% CI 1.4-8.1], versus those who had quit smoking 4-9 years previously [OR 3.0 (95% CI 1.3-6.7], or 10-19 years previously [OR 0.6 (95% CI 0.3-1.4)] (Table 7.ApA.6). Neither NAT1 or NAT2 genotype were individually associated with breast cancer risk, but some evidence suggested a modification of smoking effects among postmenopausal ex-smokers, particularly those that quit in the past 3 years (see Table 7.ApA.7). The reported odds ratios for active smoking are compared to non-smokers rather than non-smokers without ETS exposure, though the authors note, *"when we excluded women with exposure to ETS from the referent group, ORs for active smoking were unchanged or slightly attenuated."*

Lash and Aschengrau 1999. A U.S. case-control study identified 334 incident cases of breast cancer from 1983 to 1986 among residents of five Massachusetts communities. Ever active smokers had an elevated risk of breast cancer when compared to nonsmokers (no active or passive exposure) [adjusted OR 2.0 (95% CI 1.1-3.6)] (Table 7.ApA.5). The association with active smoking varied significantly by whether women smoked prior to first pregnancy, with higher risk among those smoking before versus after first pregnancy [adjusted OR 5.6 (95% CI 1.5-21) and OR 2.1 (95% CI 1.1-4.0), respectively]. No dose response was observed for cigarettes per day, however, only 16 cases reported smoking greater than 20 cigarettes per day. Similarly, no trend was observed by years smoking (Table 7.Ap.A.6). This study did not report results separately by menopausal status as 90% of the cases were in postmenopausal women. A limitation of the study was lack of control for socioeconomic status. Since breast cancer is associated with higher SES, and higher SES is associated with lower smoking, the odds ratios for smoking may have been biased to be too low.

Delfino et al., 2000. A U.S. case-control study recruited women with suspicious breast masses detected either clinically or by mammography. Passive exposure evaluation was limited to the residential setting. One hundred and thirteen cases of breast cancer and 278 controls with benign breast disease were enrolled. Since benign breast disease may share risk factors with breast cancer cases, including smoking, three analyses with varying control groups based on histopathology were conducted, all controls (n=278), low-risk controls (107), and high-risk

controls (148). Additional analysis included genotyping of N-acetyltransferase 2 (NAT2) to determine any modification by variation of NAT2 genetic polymorphisms on breast cancer risk.

Utilizing all controls, no significant increase in breast cancer risk was found among current or former active smokers compared to the reference non-exposed women (no active or passive smoking). No association was seen with either duration or quantity of cigarettes smoked per day (Table 7.ApA.5) or NAT2 status. Limitations of the study include lack of adjustment for socioeconomic status and alcohol consumption, which are risk factors for breast cancer and associated with smoking, and limited sample size in sub-strata.

Johnson et al., 2000. A population-based case-control study utilized data from the Canadian National Enhanced Cancer Surveillance System including 805 premenopausal and 1,512 postmenopausal women with incident primary breast cancer cases. Among premenopausal women, ever smokers (current and ex-smokers) compared to nonsmokers who were not regularly exposed to ETS, a significantly elevated breast cancer risk was identified [adjusted OR 2.3 (95% CI 1.2-4.5)]. ORs were adjusted for alcohol, education, age, age at first childbirth, adult height, age at menarche, BMI, parity, physical activity and residence. Postmenopausal women ever smokers had an adjusted OR 1.5 (95% CI 1.0-2.3). For ever smokers, the premenopausal risk estimates were higher when childhood exposures to passive smoke (under age 20) were also included [adjusted current smoker, OR 2.1 (95% CI 1.0-4.4), and ex-smoker, OR 2.6 (95% 1.3-5.3)] (Table 7.ApA.5). Postmenopausal breast cancer risk among current smokers also increased when childhood ETS exposure was included [OR 1.8 (95% CI 1.1-2.9)]. Among postmenopausal women, statistically significant dose-response relationships were observed between breast cancer risk and years smoking (P for trend 0.003), or total pack-years (P for trend 0.01) (Table 7.ApA.6).

These authors also examined breast cancer risk associated years of smoking before a first full-term pregnancy among parous women, and total lifetime smoking among nulliparous women. Premenopausal analyses were limited by small numbers of women smoking more than 30 years and no patterns of increased risk were observed. For postmenopausal parous women, no increase in risk was observed for less than 30 years of smoking, but 30 or more years of smoking were associated with a risk factor adjusted OR of 1.36 (95% CI 1.11-1.67). For parous women who had smoked at least 30 pack-years, smoking before pregnancy for 1-4, 5-7 and 8 or more years, were associated with breast cancer, with OR's of 1.19, 1.26 and 1.88 (95% CI 1.23-2.87), respectively. Nulliparous women with 30 years of smoking or more had an OR of 2.43 (95% CI 1.25-4.72). This analysis is without removing passive smokers from the referent non-exposed category.

These data suggest that women smoking for many years, especially before a first full-term pregnancy, have increased postmenopausal breast cancer risk (Johnson *et al.*, 2003). Among postmenopausal women a dose-response relationship between breast cancer risk and increasing years of active smoking, increasing pack-years and decreasing years since cessation was observed. This study's strengths include the population-based design, the ability to analyze risk separately for pre- and postmenopausal women, the lifetime passive and active smoking assessment, and the ability to control for other risk factors, including alcohol consumption, education, reproductive factors and physical activity. A limitation of the study was lack of

consideration of time-since-first-exposure in the dose-response analyses (years of smoking and pack-years).

Rookus et al. (2000) analyzed data from a Dutch population-based case-control study (n = 918) of breast cancer and oral contraceptives, in which lifetime histories of active and passive smokers were collected by interview. Passive smokers were defined as lifetime non-smokers with at least 20 years daily domestic or occupational exposure to ETS, or with exposure to someone smoking daily in their bedroom for more than one year. ORs were adjusted for lifetime physical activity level and other potential confounders. When passive smokers were included in the reference group of never smokers, the ORs for current and ex-smokers were 1.0 (95% CI: 0.8-1.3) and 1.3 (95% CI: 1.0-1.6), respectively. However, compared to non-exposed controls, the risks for current smokers and ex-smokers were higher (OR: 1.2, 95% CI:0.8-1.6 and 1.4, 95% CI: 1.0-2.0, respectively). This study is of interest because it directly addresses the concern that many studies may miss the effect of active smoking if passive smoking is inadequately measured and controlled for and because ETS exposure from both domestic and occupational situations was measured.

Marcus et al. 2000. A population-based case-control study, the Carolina Breast Cancer Study, analyzed data from 864 incident breast cancer cases to evaluate the relationship between adolescent exposure to active or passive smoking and breast cancer risk. After adjusting for a number of confounders including age at menarche and first birth, alcohol consumption and BMI, relative to all non-smokers, breast cancer risk was significantly elevated among current [OR 2.1 (95% CI 1.2-3.4)], but not former smokers [OR 0.7 (95% CI 0.3-1.8)], initiating smoking prior to age 15 (ages 10-14) (see Table 7.ApA.6). Risk estimates were also higher among women smoking more than 20 years and initiating active smoking prior to age 15 [10-14 years old: OR 1.9 (95% CI 1.0-3.4); 15-19 years: OR 1.2 (95% CI 0.9-1.7); ≥ 20 years old: OR 1.5 (95% CI 1.0-2.2)]. A limitation of this study was the use of a referent population in which adult exposure to ETS was determined by a single question (have you lived with a housemate since the age of 18 years who smoked?).

Morabia et al. 2000, 1998. A population-based case-control study in Geneva, Switzerland investigated the association of breast cancer with passive and active smoking (Morabia *et al.*, 1996). An analysis of interactions between smoking and genotype evaluated the influence of slow and fast acetylation, based on genotypic variation in N-acetyltransferase 2 (NAT2) (Morabia *et al.*, 2000). Pooling premenopausal and postmenopausal women, the adjusted OR for breast cancer was 3.3 (95% CI 1.7-6.5) for active smokers (adjusted for age, education, and family history of breast cancer) (Table 7.ApA.5). After stratification by NAT2 status, breast cancer risk with active smoking increased for high acetylators (all women). In premenopausal women the NAT2 genotype did not influence the adjusted OR [2.9 (95% CI 1.1-7.5) for fast and slow acetylators]; however, among postmenopausal women, a statistically significant association with breast cancer was found in fast acetylators with active smoking [adjusted OR 8.2 (95% CI 1.4-46.0)], with a smaller and statistically nonsignificant effect observed in slow acetylators [adjusted OR 2.9 (95% CI 0.8-11.2)] (Table ApA.7). The number of unexposed cases (no active, no passive) was small in both fast and slow acetylators (<5 cases). However, when the authors repeated the analysis with a second, never-active smoker referent category, which included passive smokers (thereby mimicking the referent population in several previous studies), the OR for breast cancer in postmenopausal women among slow acetylators was 2.5 (95% CI 1.0-6.2),

and among fast acetylators the OR was reduced to 1.3 (95% CI 0.5-3.3). These differences indicate the importance of considering passive exposures in studies evaluating associations between breast cancer and tobacco smoke.

This group of breast cancer cases and controls was also used to determine the relationship between smoking and breast cancer by estrogen receptor status (Morabia *et al.*, 1998). Among the subjects for whom estrogen status was available, 74.4% of the tumors were ER+. Active tobacco smoking was a risk factor for both ER+ and ER- tumors among both pre- and postmenopausal women. Age-adjusted ORs were consistently higher for ER- tumors; however, risk estimates were not statistically different from ER+ breast tumor risk. For all women combined, ever-active smoking was associated with a significantly elevated risk for ER- tumors [age-adjusted OR 3.8 (95% CI 1.4-10.3) and OR 4.3 (95% CI 1.4-13.2) for < 20 and ≥ 20 cigarettes per day (cpd), respectively]. By comparison, ER+ breast cancer risks among ever-active smokers were lower [age-adjusted OR 2.2 (95% CI 1.3-3.6) and OR 2.4 (95% CI 1.4-4.5) at <20 and ≥ 20 cigarettes per day, respectively]. Breast cancer risk for ER- tumors was highest among postmenopausal women with ever-active smoking [age-adjusted < 20 cpd: OR 5.2 (95% CI 1.5-18.7); ≥ 20 cpd: OR 5.7 (95% CI 1.4-24.2). A limitation of this study was lack of adjustment for alcohol consumption, a potentially confounding factor.

Couch et al. (2001) examined the association of active smoking with the risk of breast cancer among women in families at high risk for breast cancer. This analysis focused on 132 families (of 534 breast cancer probands studied at University of Minnesota) thought to be at the greatest risk of breast cancer as indicated by having three or more members with either breast or ovarian cancer. Data on cancer incidence and breast cancer risk factors, including smoking habits, were collected by telephone interview.

The effects of smoking and relationship to the index case (proband) are shown in Table 7.ApA.2, analyzed both with data from all respondents (surrogates and self-reporters), and from self-respondents alone. Compared with never-smokers, ever smoking sisters and daughters of the proband had significantly elevated risks for breast cancer that were not seen among more distant relatives (granddaughters, nieces and marry-ins) after adjusting for age at menarche and first birth, BMI, alcohol, and oral contraceptive use.

Table 7.ApA.2. Breast cancer risk as a function of smoking status and relation to the case: all families.

		All respondents		Self-respondents	
Relationship	**Smoking**	**Cases**	**RR (95% CI)**	**Cases**	**RR (95% CI)**
Sister & daughter	**Never**	63	1.0	12	1.0
	Ever	32	1.8 (1.2; 2.7)	14	2.4 (1.2; 5.1)
Granddaughter & Niece	**Never**	108	1.0	47	1.0
	Ever	80	1.1 (0.8; 1.5)	40	1.2 (0.8; 1.8)
Marry-in	**Never**	112	1.0	47	1.0
	Ever	76	1.2 (0.9; 1.6)	39	1.2 (0.8; 1.9)

When the analysis was restricted to families with the highest risk, in this case, families with five or more cases of breast or ovarian cancer, ever-smoking among first-degree relatives of the

proband was associated with substantially elevated risk compared to never-smoking (RR 5.8, 95% CI 1.4-23.9) (Table 7.ApA.7).

This study suggests that smoking increases the risk of breast cancer among women at higher risk due to family history. Reporting bias is unlikely to have been great enough to explain the large risk increase among daughters and sisters given the similarity in risk estimates based on self-respondents alone and on self-respondents plus surrogates. The study did not take into account exposure to passive smoke among first-degree relatives. If a significant number of the proband women were themselves active smokers, their daughters may have received substantial ETS exposure at a susceptible stage in their own breast development.

Krajinovic et al., 2001. In a Canadian hospital-based case-control study with 149 breast cancer cases and 207 controls, the influence of multiple carcinogen-metabolizing enzymes (analysis of genetic variants) on breast cancer risk was investigated, including the potential modification of risk due to smoking. The risk from active cigarette smoking was elevated, although not statistically significant, among women carriers of the NAT2 rapid acetylator variant genotype [OR 2.6 (95% CI 0.8-8.2)] (Table 7.ApA.7), suggesting that gene-exposure interactions may influence breast cancer risk among active smokers. Interpretation is limited by the hospital-based study design.

Manjer et al. (2001) examined the association between smoking and the incidence of hormone receptor negative breast cancer among 10,902 women in Malmo, Sweden. The women in this prospective study had a mean age of 49.7 years at baseline, and were followed until 1997 for an average of 12.4 years. Analyses of estrogen and progesterone receptor status were performed for the 268 cases for which tumor tissue was available. At baseline, a self-administered questionnaire was used to assess smoking habits. Ever-smokers were defined as those who had ever smoked daily for at least six months. Current and ex-smokers were defined as ever-smokers who were or were not still smoking, respectively. Among ex-smokers, time since cessation was also recorded.

As shown in Table 7.ApA.3, ever smoking elevated the risk for all tumor types but not significantly so. However, for ER^- tumors the risks were more than doubled by ever smoking. There was no significant association between smoking and either ER+ or PgR+ tumors. A significant increase in risk for PgR^- tumors was only noted for ex-smokers.

Table 7.ApA.3. Smoking status and risk of cancer by tumor hormone receptor type

Tumor	Smoking	Cases	Adj RR (95% CI)	Tumor	Smoking	Cases	Adj RR (95% CI)
All	Never	127	1.00				
	Current	102	1.10 (0.84; 1.44)				
	≤ 19 cpd	72	1.05 (0.78; 1.42)				
	≥ 20 cpd	30	1.17 (0.78; 1.76)				
	Ex	68	1.34 (0.99; 1.81)				
ER+	Never	96	1.00	ER^-	Never	20	1.00
	Current	62	0.88 (0.63; 1.22)		Current	29	2.21 (1.23; 3.96)
	≤ 19 cpd	45	0.87 (0.60; 1.25)		≤ 19 cpd	20	2.04 (1.07; 3.88)
	≥ 20 cpd	17	0.82 (0.49; 1.39)		≥ 20 cpd	9	2.62 (1.17; 5.87)
	Ex	41	1.03 (0.71; 1.50)		Ex	19	2.67 (1.41; 5.06)
PgR+	Never	54	1.00	PgR^-	Never	62	1.00
	Current	45	1.10 (0.73; 1.66)		Current	46	1.08 (0.73; 1.60)
	≤ 19 cpd	33	1.11 (0.71; 1.74)		≤ 19 cpd	32	1.02 (0.65; 1.58)
	≥ 20 cpd	12	1.07 (0.57; 2.03)		≥ 20 cpd	14	1.13 (0.62; 2.03)
	Ex	20	0.94 (0.56; 1.58)		Ex	40	1.61 (1.07; 2.41)

The risk of cancer was significantly elevated for the ER^- /PgR^- combination (Table 7.ApA.4). The combination of ER^- /PgR+ also resulted in high risks but the confidence intervals were wide and included no effect. The results were similar when the analyses were restricted to peri- and postmenopausal women.

Table 7.ApA.4. Smoking status and risk of cancer: interaction of receptor types

	PgR Status			
ER status	**PgR+**		**PgR–**	
ER+	n = 105		n = 94	
	Never	1.00	Never	1.00
	Current	1.00 (0.65; 1.55)	Current	0.72 (0.43; 1.20)
	≤ 19 cpd	1.05 (0.65; 1.69)	≤ 19 cpd	0.67 (0.37; 1.20)
	≥ 20 cpd	0.95 (0.48; 1.90)	≥ 20 cpd	0.69 (0.31; 1.54)
	Ex	0.78 (0.44; 1.39)	Ex	1.26 (0.79; 2.12)
ER–	n = 14		n = 54	
	Never	1.00	Never	1.00
	Current	2.43 (0.66; 9.00)	Current	2.14 (1.11; 4.12)
	≤ 19 cpd	1.87 (0.43; 8.07)	≤ 19 cpd	2.06 (1.01; 4.23)
	≥ 20 cpd	2.70 (0.47; 15.6)	≥ 20 cpd	2.58 (1.04; 6.41)
	Ex	3.11 (0.76; 12.7)	Ex	2.55 (1.25; 5.20)

This study supports an association between ever-active smoking and an increased risk of breast cancer, most notably for tumors that are ER^-. In addition, the observation of non-significantly decreased risks for ER+ tumors among ever-smokers would be consistent with the anti-estrogenic effects often attributed to cigarette smoke exposure. Strengths of this study include its prospective nature, which limits bias associated with recall and case status. Investigator bias was

limited through the use of self-administered questionnaires. Smoking habits were ascertained only at baseline. This study suffered from no assessment of passive smoke exposure.

Collaborative Group study of breast cancer, alcohol, and smoking, 2002. In an effort to determine whether alcohol and smoking are independently associated with breast cancer risk, an international collaborative research group pooled data from 53 cohort and case-control studies of female breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2002). For the cohort studies case-control sampling was performed (all cases and 4 controls for each case), and thus, the investigators were able to treat the pooled data as one case control study of 58,515 cases of breast cancer. After controlling for alcohol, the investigators found no association of smoking with breast cancer risk (odds ratio = 0.99, 95% CI 0.92–1.05, for current smokers compared to never smokers). Alcohol, on the other hand, after controlling for smoking, was significantly associated with breast cancer risk (odds ratio = 1.46, 95% CI 1.33–1.61, at 45+ g/day alcohol), and smoking status did not modify the association. The investigators did not report data for ETS.

This study utilized limited exposure measures classifying smoker exposure only as ever vs. never and as ex- or current. They note under "Methods," "no attention was given to the reported associations of breast cancer with environmental tobacco smoke." Since this study includes nearly all of the published studies in the literature prior to 2002, it dilutes recent studies with more sensitive measurement of exposure effects resulting from utilizing non-ETS exposed referent categories, as well as those that consider potentially sensitive populations (e.g., exposure prior to first full term pregnancy, specific genotypes, and exposure greater than 30 years) (Terry *et al.*, 2002; Wells, 2003).

Egan et al., 2002. A U.S. cohort study (Nurse's Health Study) analyzed the influence of active and passive smoking on the incidence of invasive breast cancer. This analysis includes 78,206 women followed prospectively from 1982 until June 1996, reporting 3,140 cases of invasive breast cancer. The relative risk of breast cancer was 1.04 (95% CI 0.94-1.15) for current smoking and 1.09 (95% CI 1.00-1.18) for ex-smokers (previous active smoking, adjusted for age, age at menarche, age at first birth, history benign disease, family history of breast cancer, menopausal status, age at menopause, weight, height, alcohol, dietary factors, and hormone use). The relative risk was higher among ex-smokers that recently quit smoking [adjusted RR 1.17 (95% CI 1.01-1.40)] compared to never-smokers. If women exposed to passive smoke were excluded from the unexposed category, then the relative risks for current and past active smoking increased slightly [adjusted RR 1.15 (95% CI 0.98-1.34) and 1.17 (95% CI 1.01-1.34), respectively].

Analysis of breast cancer risk according to years of active smoking before and after childbirth was conducted to determine the influence of smoking on the immature breast. Smoking for any duration after childbirth was unrelated to breast cancer risk; however, risks were slightly elevated for smoking prior to childbirth [5 or more years of smoking adjusted RR 1.13 (95% CI 0.99 - 1.30), and 10 or more years adjusted RR 1.13 (95% CI 0.94 -1.37)]. The effect of smoking before pregnancy was stronger in women that began smoking younger. Compared to never-smokers, women initiating smoking before 16 years of age had significantly elevated breast cancer risk [adjusted RR 1.31 (95% CI 1.07-1.61)]. Among nulliparous women, no association was found between active smoking duration and breast cancer incidence. Additionally, smoking intensity before childbirth was marginally associated with increased breast cancer incidence [< 1

pack/day: adjusted RR 1.12 (95% CI 0.95-1.31); ≥ 1 pack/day: adjusted RR 1.21 (95% CI 0.98-1.51), p for trend 0.05].

This study suggests that overall active smoking was related to an increased risk of breast cancer in some groups. The risks appear higher when smoking was initiated at a young age or smoking occurred before first childbirth. The strengths of this study are its size, and the substantial data on reproductive risk factors, family history, and other potential confounders. Unfortunately, this study is subject to misclassification of ETS-exposed nonsmokers as a non-exposed population, thereby minimizing any potential observable risk.

Terry et al., 2002. A prospective Canadian cohort recently reported on the association between active smoking and breast cancer in 89,835 women enrolled within a multi-center, randomized trial of mammography screening. Women were recruited between 1980 and 1985 and followed through December 1993. Cancer cases (n = 1,306) were ascertained through linkages with population-based cancer database and national vital statistics. Active smoking, including average use and duration, were determined from baseline data.

The age-adjusted relative risk for breast cancer for current smoking was statistically significant [RR 1.15 (95% CI 1.05-1.27)], relative to all never-smokers. After adjustment for multiple factors (including age, study center, BMI, education, physical activity, multiple reproductive and menstrual factors, family history of breast disease, menopausal status, alcohol consumption and hormone replacement therapy), risk for current smokers remained similar [RR 1.14 (95% CI 1.03-1.27)]. Breast cancer risk increased with duration of smoking; women smoking over 40 years had a statistically elevated risk [RR 1.61 (95% CI 1.19-2.19)], with a significant p for trend 0.003. The risk for women smoking > 20 cigarettes per day for over 40 years was 1.83 (95% CI 1.29; 2.61).

Band et al., 2002. Cigarette smoking appears to have competing effects in the etiology of breast cancer, potentially reducing cancer risk via an antiestrogenic effect while increasing the risk of chemical carcinogenesis. Evidence from studies in active smokers demonstrates that cigarette smoke is anti-estrogenic (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986; Baron *et al*., 1990; Jensen and Christiansen, 1988; Terry and Rohan, 2002)).

Breast cells undergo three periods of development, *in utero*, during puberty, and during pregnancy and lactation (Russo and Russo, 1994), which are characterized by rapid cell proliferation and differentiation. Band *et al.* (2002) examined the role of the timing of onset of cigarette smoking relative to menarche, pregnancy and menopause, in 1,018 diagnosed cases of breast cancer vs. 1,025 age-matched population controls. Information was collected by postal questionnaire on ethnic origin, marital status, education, smoking history and alcohol consumption, height, current weight and weight at age 18, age at menarche, parity, history of breast biopsy for benign breast disease, family history of breast cancer, and lifetime occupational history. Also collected were data on breastfeeding, birth control use and hormone replacement therapy. Of the 1,018 cases, 318 were premenopausal (44 yrs), and 700 were postmenopausal (64 yrs). Of the 1,025 controls, 340 were premenopausal (43 yrs), while 685 were postmenopausal (64 yr).

Among premenopausal women, smoking initiated within 5 years of menarche was associated with a significant risk of breast cancer in ever-pregnant women who smoked before their first pregnancy (adjusted OR 1.69, 95% CI 1.13; 2.51). A dose response was observed both in terms of cigarettes per day and in terms of pack years, particularly in nulliparous women where smoking <20 cpd was associated with an OR of 1.45 (95% CI 0.49; 4.29) which increased with higher cigarette consumption (≥ 20 cpd) to 7.08 (95% CI 1.63; 30.8). Among nulliparous women, smoking greater than 20 pack-years was also associated with significant risk OR 7.48 (95% CI 1.59; 35.2) (Table 7.ApA.6). In contrast, none of the smoking categories was significantly associated with breast cancer among postmenopausal women. Indeed, among postmenopausal women whose body-mass index increased from age 18 to present and who started to smoke after a full-term pregnancy, the risk of breast cancer was significantly reduced (0.49, 95% CI 0.27-0.89).

A strength of this study is the control for a large number of potentially confounding factors. The results demonstrated in this study support the authors' hypothesis that active cigarette smoking exerts two competing effects on breast cancer risk: 1) tumorigenic by action of the carcinogens in smoke and 2) protective by way of smoke's anti-estrogenic effects. In that hypothesis, the carcinogenic effect would be displayed most prominently in those whose exposures began close to menarche and before first pregnancy. This would characterize a time when estrogen levels were relatively high (thus less prone to significant disruption) and breast tissue sensitive due to rapid proliferation and incomplete differentiation. The antiestrogenic (protective) effects would be most pronounced in the postmenopausal women whose onset of smoking began after first pregnancy and who were relatively obese, leading to higher estrogen levels from aromatization of adrenal androgens in fat cells.

In this study, mailed questionnaires eliminated interviewer bias. The study was population-based with a high response rate, which minimizes selection bias. In addition, the proportion of never- and ever-smokers was similar among responders and non-responders for both cases and controls. However, the information for non-responders was obtained for only small subsets. The authors claim that recall and misclassification of age at commencement of smoking was not likely to systematically differ between cases and controls since smoking was not generally perceived as related to breast cancer. The absence of information on passive smoking could have led to misclassification of passive smokers as non-exposed but this would bias towards the null.

Kropp and Chang-Claude, 2002. This population-based case-control study examined the association between active and passive smoke exposure and breast cancer risk in women up to 50 years of age in southern Germany. Cases were defined as having incident in situ or invasive breast cancer diagnosed under the age of 51 (n = 468), and were matched by age and study region to 1,093 randomly selected controls. Multivariate analyses were adjusted for number of months of breastfeeding, BMI, education, family history, menopausal status and alcohol intake, number of pregnancies, use of oral contraceptives, and age at menarche and at first pregnancy. The referent category included only never smokers who had no residential or occupational ETS exposure. Active smoking was associated with breast cancer when analyzed by duration of active smoking (in years) (p for trend = 0.047) and age at initiation of smoking (p for trend = 0.015)(Table 7.ApA.6). Age at initiation of smoking was found to modify the effect of active smoking, with increased ORs in older age-at-initiation groups. Among high active smokers, high passive smoke exposure increased breast cancer risk about 50% over active smoking alone [OR

1.78 (95% CI 1.16-2.71) with additional passive smoking vs. 1.12 (95% CI 0.64-1.97) with no additional passive smoking].

Chang-Claude et al. (2002) examined the role of polymorphisms in the N-acetyltransferase 2 (NAT2) gene in the effects of active and passive smoke exposure on breast cancer risk. The current study was based on a population-based case-control study of 706 breast cancer patients diagnosed by age 50 and 1,381 controls. Data, including active smoking and childhood, adult and workplace smoke exposures, were collected by self-administered questionnaire The reference group contained neither ever-active smokers (>100 cigarettes in their lifetimes) nor ever-passive smokers (> 1 hr ETS per day for at least 1 year).

Smoke exposure was associated with increased risks of breast cancer that were similar in passive (OR 1.5, 95% CI 1.0; 2.2) and active (OR 1.4, 95% CI 0.9; 2.2) smokers. Among active smokers, there was a statistically significant trend for increased breast cancer risk with either increasing pack-years of smoking (>11 pk-yrs OR 1.79 (1.01;3.18) or duration (>20 yrs OR 1.84 (1.05;3.24) associated with slow acetylator status, and a decrease in risk with increased time since smoking cessation. This study was limited by its small size and possible recall bias.

Lash and Aschengrau, 2002. This case-control study of the association between active or passive smoking and breast cancer was conducted in a manner similar to their earlier study on this same topic (Lash and Aschengrau, 1999), but in a different population. The 666 cases were diagnosed with invasive breast cancer between 1987 and 1993 and, along with 615 controls, were drawn from residents of eight Massachusetts towns on Cape Cod. Smoking status was determined as ever active, ever passive only, and never active never passive. Odds ratios were adjusted for a history of radiation therapy, BMI, family history of breast cancer, histories of breast cancer and/or benign breast disease, alcohol consumption, age at first birth and parity.

In contrast to their previous study (Lash and Aschengrau, 1999), the risk of breast cancer among active smokers compared to never active never passive smokers was significantly decreased (OR 0.72, 95% CI 0.55-0.95). Neither duration of active smoking nor smoking before or after first pregnancy were associated with elevated breast cancer risk. (see Table 7.ApA.6).

The cases in this study were matched to controls by age and vital status, but no information was provided on either the age distribution or the menopausal status of the participants, both of which may be important in the interpretation of the reported null result. These results are in apparent conflict with the authors' earlier study. The present study was published as a brief communication and a more detailed report addressing these issues may be forthcoming.

Saintot et al. (2003). This study examined the interactions between polymorphisms of several xenobiotic enzymes and tobacco exposure in breast cancer risk among 282 breast cancer patients. This study employed a case-only design that does not permit calculation of ORs for exposure or genotype alone, but has higher statistical power for detecting gene-environment interactions than in a case-control study.

Breast cancer cases were recruited from the surgical wards of the Cancer Centre in Montpelier, France. between 1998 and 2001. Genetic polymorphisms were characterized for three enzymes: phenol-sulfotransferase (SULT1A1), cytochrome P450 1B1 (CYP1B1), and catechol-O-

methyltransferase (COMT). SULT1A1 activates the hydroxylated metabolites of some PAHs, and reduces the activity of estrogen. Individuals who are homozygous for His at codon 231 have lower transferase activity than either the heterozygote or the common homozygous Arg/Arg. CYP1B1 activates PAHs and heterocyclic aromatic amines, and catalyzes the hydroxylation of estrogens to the genotoxic catechol estrogen. Conversion of Val to Leu at codon 432 decreases the efficiency of catechol estrogen formation. COMT inactivates catechol estrogens by conjugation. The COMT (Met/Met) genotype has a significantly reduced methylation activity compared to the (Val/Val) genotype.

Unconditional logistic regression analysis was used to estimate the interaction between tobacco smoke exposure and the polymorphisms after adjustment for age at menarche, age at first full-term pregnancy, parity, oral contraceptive use, hormone replacement therapy, age at menopause and BMI. The analysis generates an OR of interaction (ORi), which is valid only if the gene polymorphisms and exposure in the population are mutually independent. The authors verified this assumption by estimating gene-exposure associations in controls from other published studies.

Current smokers with the Any Val CYP1B1 allele had a higher risk of breast cancer (ORi 2.32, 95% CI 1.00; 5.38) compared to the control group of never smokers with the Leu/Leu genotype characterized by lower catalytic efficiency for the 4-hydroxylation of estrogens (Table 7.ApA.7). Current smokers with the His SULT1A1 variant had significantly elevated risk (ORi 2.55, 95% CI 1.21; 5.36) compared to never exposed Arg/Arg homozygotes. For these two enzymes, there was no significant effect in passive or former smokers. There were no statistically significant interactions between smoke exposure and the COMT polymorphisms.

The authors analyzed the interactions between different levels of smoke exposure among ever smokers and the CYP1B1 and SULT1A1 polymorphisms with stratification for menopausal status. Among carriers of the Val CYP1B1 variant, the "high-activity" form, breast cancer risk was significantly elevated for those who had smoked more than 5 cigarettes per day ($p<0.01$), or for more than 20 years ($p = 0.01$), or greater than 10 pack-years, or who started smoking before age 20. The results were similar for both pre- and postmenopausal women (see Table 7.ApA.7). Also as seen in the table, premenopausal women with the His SULT1A1 allele were at greater risk than unexposed women homozygous for Arg SULT1A1. This effect was statistically significant for women who had smoked more than 5 cigarettes per day ($p = 0.05$) or for more than 20 years ($p = 0.01$)

This study finds increased risk of breast cancer risk among both pre- and postmenopausal smokers carrying the Val CYP1B1 allele or among premenopausal smokers with the His SULT1A1 variant allele. However, the comparison groups are never-smokers with the Leu/Leu genotype for CYP1B1, and the Arg/Arg genotype for SULT1A1. A more telling comparison might have been between smokers and never-smokers with the same genotypes or among smokers with different genotypes. The results nevertheless suggest a significant gene-environment interaction for active smoking as well as plausible mechanisms for this interaction.

Zheng *et al.* (2002) conducted a case-control study to examine the role of polymorphisms of GSTM1 and GSTT1 in the association between exposure to cigarette smoke and breast cancer as modified by amount and duration of smoking, age at smoking initiation, and menopausal status.

A total of 338 incident cases of histologically confirmed breast cancer and 345 controls, frequency-matched by age, provided blood for genotype determination. Personal data were collected by standardized, structured questionnaires administered by trained interviewers. Unconditional logistic regression was used to analyze the association between GSTM1 and GSTT1 polymorphisms and breast cancer risk among smokers versus never-smokers after adjustment for BMI, alcohol use, months of lactation, age at first full-term pregnancy, family breast cancer history, menopausal status, age at menarche and age at menopause.

This study found no association between breast cancer risk and GSTM1 genotype irrespective of menopausal or smoking status. There was, however, significantly elevated risk associated with the GSTT1 null genotype itself, regardless of smoking status, in postmenopausal women (OR 1.9, 95% CI 1.2; 2.9). While none of the estimates reached statistical significance, there were suggestions that in postmenopausal women with the GSTT1 null genotype, smoking was associated with increased breast cancer risk (Table 7.ApA.7).

This study suggests that the GSTT1 null genotype may be associated with increased breast cancer risk among postmenopausal smokers if they started smoking before age 18. There is limited evidence of a dose-related increase in risk with duration of smoking, but not by pack-years or cigarettes consumed per day. However, stratification by genotype and menopausal status resulted in small numbers in the various smoking categories thus limiting the study's ability to detect significant associations.

Al-Delaimy et al. (2004) investigated the association between active smoking and invasive breast cancer as a function of estrogen receptor (ER) status in the Nurses' Health Study II, a large prospective cohort study. Data were collected biennially by mailed questionnaire during the ten-year follow-up. Breast cancer risk was modeled using multivariate Cox proportional hazard regression, stratified by age and adjusted for BMI, height, oral contraceptive use, parity, ages at menarche and at first birth, family history of breast cancer or benign breast disease, alcohol consumption and menopausal status.

Analysis of the entire cohort, irrespective of ER status, generally did not show a significant association between smoking and breast cancer except at the longest duration: 20+ years (RR 1.21, 95% CI 1.01; 1.45; p for trend 0.04). There was also a significant trend for duration of smoking prior to the first pregnancy ($p = 0.01$). However, when compared by ER status, ER+ women were at significantly greater risk of breast cancer if they smoked than were ER- women. For ER+ women there were significant trends associated with total duration of smoking ($p = 0.003$), with the highest risk at 20+ years (RR 1.37, 95% CI 1.07; 1.74), and with duration of smoking prior to first pregnancy ($p = 0.003$). Smoking initiation at earlier ages (before ages 15 or 19) also significantly elevated breast cancer risk among ER+ women (age 15: RR 1.49, 95% CI 1.03; 2.17) but not ER- women (RR 1.19, 95% CI 0.69; 2.08). This study suggests that smoking increases breast cancer in a fashion that is dependent on age at smoking initiation, duration of exposure, and perhaps most critically, estrogen receptor status. However, it likely underestimates the true association between tobacco smoke and breast cancer because no attempt was made to ensure that the non-smokers in the reference group were not exposed to ETS.

Reynolds et al. (2004a) conducted a prospective analysis of breast cancer risk associated with passive and active smoking in the California Teacher Study (CTS), a large cohort of professional

school employees. Of the 329,000 eligible women, 35% (116,544) were included in the study and followed from 1995 to 2000 with diagnosis of 2,005 breast cancer cases. A survey at baseline collected information on smoking history among active and former smokers, as well as on passive exposure among never-smokers. Other risk factors included in multivariate analyses were age, ethnicity, family history of breast cancer, alcohol consumption, age at menarche, pregnancy history, physical activity, BMI, menopausal status, and estrogen hormone therapy. Current smoking was associated with a significantly elevated risk (Hazard Ratio, HR) of breast cancer in the full cohort regardless of whether passive smokers were included (HR 1.32, 95% CI 1.10; 1.57), or excluded (HR 1.25, 95% CI 1.02; 1.53) from the reference group (Table 7.ApA.5). However, passive smoking in this analysis did not include workplace and other exposures. This effect was most pronounced in postmenopausal current smokers.

Among active smokers compared to never-smokers, there appeared to be an increase in risk with increased smoking intensity irrespective of menopausal status (Table 7.ApA.6). Similarly, the duration of smoke exposure was related to breast cancer risk in the total group (p trend = 0.009) and in postmenopausal women (p trend = 0.032), but not premenopausal women (p trend = 0.616). However, no statistical interaction with menopausal status was found. Initiation of smoking prior to, but not after, age 20 also elevated risk in the total sample and in postmenopausal women.

This study found significant associations between breast cancer and active but not passive smoking. When the analysis was limited to the 35,123 nondrinkers in this cohort, current smokers continued to have a significantly elevated risk of breast cancer (HR 1.66, 95% CI 1.15-2.40). This is in fact a higher HR than the study as a whole and refutes concerns that associations between smoke exposure and breast cancer are actually measuring a surrogate of alcohol exposure. A limitation of this study is utilizing a referent group that includes those passively exposed from sources outside the household.

Gammon et al. (2004) utilized data collected for the Long Island Breast Cancer Study Project, a case-control study, to evaluate the effects of both active and passive tobacco smoke exposure on breast cancer incidence. Information on active and passive smoke exposure (in the home only), alcohol use, menstrual history, hormone use, demographics, physical activity, pregnancy history, occupational history, residency history, pesticide use, and a number of other factors was obtained by interviewer-administered questionnaire. Breast cancer risk was evaluated in relation to active smoking, passive exposure only, active and passive exposure or neither, using unconditional logistic regression and accounting for a large number of covariates. Estimates were also made by various measures of active and passive smoke exposure including intensity and duration, timing of exposure in relation to first pregnancy, childhood exposures (both active and passive), and spousal exposure. Work exposure and other exposure to ETS were not evaluated in this study.

For all women, there was no statistically significant elevation in odds ratio compared to never exposed for active smoking, or both active and passive smoking (Tables 7.ApA.5 and 6). Risk appears to be elevated slightly for active plus passive smokers, although not significantly (OR 1.15; 95% CI 0.90-1.82).

This study's strengths include: accounting for a large number of confounders, an overall large sample of cases and controls, a lifetime assessment of residential passive smoke exposure and active smoking history, and a referent group that excluded active smokers. However, similar to many ETS studies, sources of exposure other than that in the home are lacking. Occupational exposures were much more common in the past and lack of accounting for this exposure is problematic. Thus there may be nonsmokers in the non ETS-exposed category that were exposed to ETS at work. This type of misclassification biases towards the null.

Zhang *et al*.(2004) published in the abstracts of the 37th annual meeting of the Society for Epidemiologic Research (June, 2004). In that study, 49,165 Canadian women aged 40 – 59 were followed for 14 years: Women had an elevated risk of breast cancer death if they had smoked 30 years or more (HR = 1.90;95% CI, 1.29, 2.80), compared to never smokers. When compared to nondrinkers who had never smoked, light to moderate drinkers (>0 and <20 g/day of alcohol) who smoked for more than 30 years were twice as likely to die of breast cancer (HR = 1.98; 95% CI, 1.13, 3.48). Heavy drinkers (20+ g/day of alcohol) who smoked this long had almost a three-fold risk of breast cancer death (HR = 2.72; 95% CI, 1.30, 5.67). Heavy drinkers who smoked 40+ cigarettes/day experienced an almost four-fold risk of breast cancer death (HR = 3.85; 95% CI, 1.34, 11.09). There was a positive dose response relationship between years smoked and breast cancer mortality ($p<0.05$) among both drinkers and non-drinkers, after adjusting for cigarettes per day smoked, alcohol consumption, and other potential confounders. Apparent in this study is an at least additive effect of alcohol and smoking and an effect of smoking independent from drinking .

Hanaoka *et al.* (2005) investigated the role of tobacco smoke exposure in the etiology of breast cancer in a prospective cohort study of middle-aged Japanese women. In 1990, a self-administered questionnaire collected baseline data on personal and family medical histories, smoking habits, alcohol use, dietary habits and other lifestyle factors. Passive smoking was defined as a history of exposure to residential ETS or routine exposure to ETS in any work and/or public setting. The age at inititation and frequency of exposure were also determined. Cancer incidence and mortality data were collected during follow-up through the end of 1999. Of the 21,805 women participating in the study, 180 developed breast cancer. Relative risks were estimated by the Cox proportional hazards model with adjustment for age, area, education, employment status, BMI, family history of breast cancer, benign breast disease, age at menarche, parity, menopausal status, and hormone and alcohol use.

There was a significantly elevated risk of breast cancer among premenopausal women who were ever smokers (RR 3.9, 95% CI 1.5; 9.9: Table 7.ApA.5). However, after menopause, no elevated risk was evident. Among all women (pre- and postmenopausal), active smoking was associated with an elevated risk of breast cancer that was of borderline statistical significance (RR 1.7, 95% CI 1.0; 3.1).

This population-based prospective study has the advantages of general applicability and limited recall or selection bias. Smoking habits and passive exposures were assessed in more than one environment, and thus better capture the subjects' actual exposures than studies based on marriage to a smoking spouse. The referent group consisted of those without exposure to ETS either as adults (home or occupation/out of home exposures) or childhood (home only). Smoking and occupational/out of home exposure was only assessed at baseline. Cessation of smoke

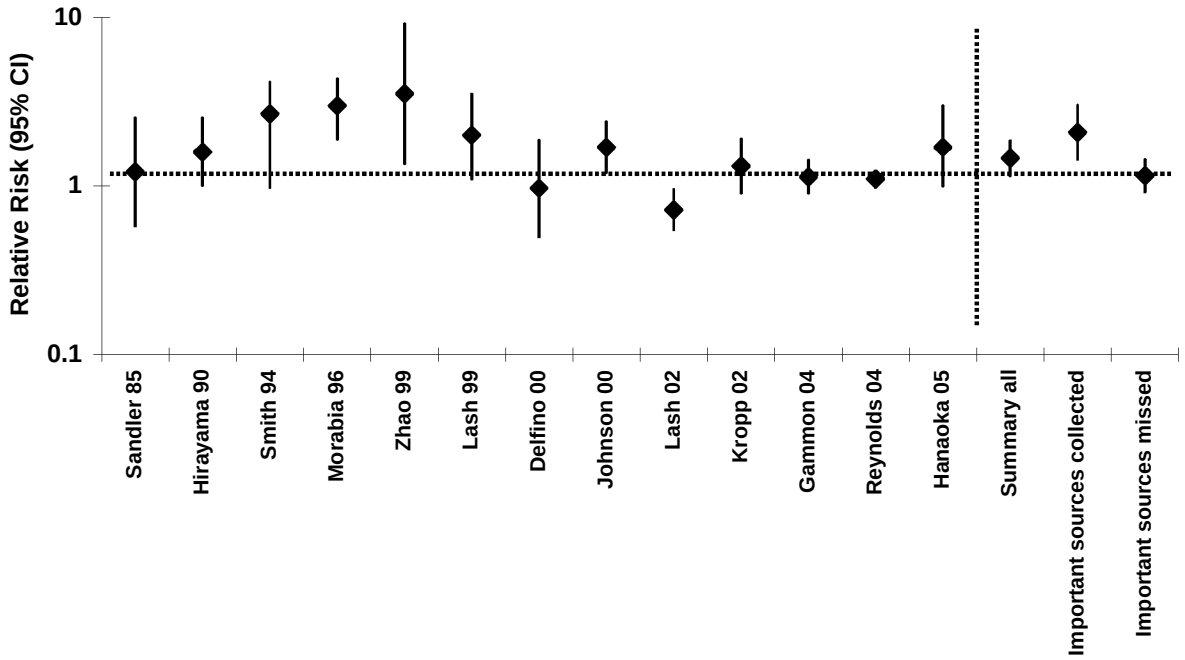
exposure during the 10-year follow-up could result in some misclassification that might bias the results towards the null. Due to the small size of the study, some strata in the analysis are only sparsely populated thus limiting the study's power to detect an effect. Data presented are inadequate to determine if a dose response for active smoking was present. Nevertheless, this study provides clear evidence that active smoking significantly increases the risks of breast cancer among premenopausal women. This is the first prospective cohort study to utilize a referent population that excluded both ETS exposure in childhood and from adult residential and occupational sources.

Gram et al. (2005) examined breast cancer risk in women related to age of smoking initiation in a large prospective cohort in Norway and Sweden from 1991 through 2000. Comparing smokers to never- smokers, they found significantly increased risks for smoking >10 cigarettes/day for 20+ years (RR 1.34; 95%CI 1.06-1.70), and initiating smoking prior to first birth (1.27; 95%CI 1.00-1.62), before menarche (RR 1.39; 95%CI 1.03-1.87), or before age 15 years (RR 1.48; 95%CI 1.03-2.13) (Table 7.ApA.5 and 6). Their findings support a link between active smoking during peri-adolescence and before childbirth and increased breast cancer risk.

7.ApA.2 Active Smoking: Discussion and Conclusion

While there continues to be some heterogeneity in study results, overall, the studies presented in Appendix 7A in this update (along with in vitro and animal data on carcinogenesis) provide evidence of a role for active smoking in causation of breast cancer, and include evidence of a dose-response. In 11 of 13 studies examining breast cancer risk from active smoking (Figure Figure 7.ApA.1 below) compared to a referent population of never-smoking women not exposed to ETS, point estimates were greater than 1 (many of them significantly so). Of the six studies considered by OEHHA as "most informative" based on best exposure assessment and design (see Section 7.4.1.6) (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Hanaoka *et al*., 2005), all have point estimates above one (Figure 7.ApA.1). There are now studies providing some evidence for gene-environment interactions, as well as studies demonstrating susceptible subpopulations with highly significant increased breast cancer risk associated with active smoking (e.g., those with familial high risks in Couch *et al*., 2001). Furthermore, some studies demonstrate significant risks related to the hormonal receptor status of the tumor (Manjer *et al*., 2001; Morabia *et al*., 1998). Finally, six recent prospective cohort studies (supported by similar findings in case control studies) found statistically significantly elevated breast cancer risk associated with active smoking for at least some of the metrics of exposure (Egan *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*. 2004a, Hanaoka, 2005; Zhang *et al*., 2004; Gram *et al*., 2005). A number of studies (Table 7.ApA.5) found statistically significant elevated breast cancer risk for current or ever active smokers (Lash and Aschengrau, 1999; Johnson *et al*., 2000; Terry *et al*., 2002; Morabia, 2002, Reynolds *et al*., 2004; Zhang *et al*., 2004; Hanaoka *et al*., 2005). Long duration of exposure or higher pack-years (Table 7.ApA.6) was associated with significantly elevated breast cancer risks in a number of studies (Millikan *et al*., 1998; Lash and Aschengrau, 1999; Johnson *et al*., 2000; Band *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*., 2004; Gram *et al*., 2005). A meta-analysis conducted by Johnson (2005) examined 13 studies of active smokers (controlling for passive smoking) and found a significantly elevated risk, OR 1.48 (95% CI 1.17-1.86). In those studies with a more complete passive exposure assessment, and thus cleaner referent groups, the breast cancer risk from active smoking was estimated at 2.08 (95% CI 1.44-3.01).

Figure 7.ApA.1 Summary Breast Cancer Risk Estimates for Active Smoking Compared to Never Smoking Women who were Never Regularly Exposed to ETS (Based on Johnson 2005, table 5)



Morabia *et al*. (1996), Kropp and Chang-Claude (2002), and Johnson *et al*. (2000) all reported that the risk estimate for breast cancer in active smokers increased when ETS-exposed women were excluded from the non-exposed referent group. In a case-control study, Johnson *et al*. (2000) demonstrated statistically significant elevated risks when comparing smokers to never-active never-passive nonsmokers (OR 2.3; 95% CI 1.2-4.5) after accounting for a number of confounders including reproductive health, SES, and alcohol consumption. When childhood exposures were included, risks increased. Significant dose-response trends were observed for both years of smoking and pack-years. Johnson *et al*. (2003) found increased risks in parous women related to number of years of smoking before a first full-term pregnancy.

Considering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and elevated breast cancer risk.

7.ApA.3. Breast Cancer After Exposure *In Utero*

Sanderson et al. 1996. Data from two population-based case-control studies were combined and examined for associations between perinatal factors and risk of developing invasive breast cancer, including maternal smoking. Age, menopausal status, and maternal smoking were

considered as confounders in the relationship between perinatal factors and breast cancer risk. Among women age 30 years or younger, maternal smoking was associated with an increased risk of breast cancer [OR 1.9 (95% CI 1.0-3.4)] (see Table 7.ApA.8); after adjusting for birth weight (as maternal smoking is associated with low birthweight), a statistically nonsignificant increased risk remained [OR 1.9 (95% CI 0.9-3.8)]. This adjustment for birth weight may represent some degree of over adjustment. In women ages 50-64, a statistically nonsignificant increase in breast cancer was associated with maternal smoking [OR 1.3 (95% CI 0.9-2.1), adjusted for age and menopausal status]. However, data on birthweight were missing for 11% of women ages 21-30 and 25% of women age 50-64. Additionally, no other smoking exposure, whether active or passive, was included in the analysis.

Weiss et al., 1997. A multi-center U.S. case-control study analyzed various prenatal and perinatal risk factors for breast cancer among young women (under age 55), particularly factors with the potential for estrogenic effects, including maternal tobacco smoking during pregnancy. In women diagnosed under age 45 with complete maternal data, no significant association was observed between maternal smoking during pregnancy and breast cancer risk in the daughter [OR 1.06 (95% CI 0.8-1.4)] after adjustment for age, family history, reproductive history, body mass index, alcohol consumption, and mammogram utilization (Table 7.ApA.8). Additionally, although smoking status of the actual cases/controls (daughters) was reportedly included in the questionnaire, no data on the prevalence of smoking exposure (active or passive) was included or adjusted for in this published report.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Studies included in Cal/EPA, 1997						
Morabia *et al.* (1996)	Total Study	No current or passive	28/241	-	Referent	A, AF, AL, AM, BMI, E, FH,
Switzerland, 1992-1993		Ever active	31/131	2.2	1.0-4.4	HB, OC, SF
Studies included in this update						
Millikan *et al.* (1998)	Total Study	Never	248/253	-	Referent	A, AF, AL, AM, FH, HB, P, R
Carolina Breast Cancer Study		Current	93/93	1.0	0.7-1.4	
United States, 1993-1996		Former	157/127	1.3	0.9-1.8	
Case Source = population registry						
Controls = population	Premenopausal cancer	Never	123/110	-	Referent	A, AF, AL, AM, FH, HB, P, R
		Current	46/45	0.9	0.5-1.5	
		Former	72/62	1.0	0.6-1.6	
	Postmenopausal cancer	Never	125/143	-	Referent	A, AF, AL, AM, FH, HB, P, R
		Current	47/48	1.2	0.7-2.0	
		Former	85/65	1.5	1.0-2.4	
Lash and Aschengrau (1999)	Total Study	Never active/passive	40/139	-	Referent	A, AL, BMI, EC, FH, HB, HR,
United States, 1983-1986		Ever active	137/338	2.0	1.1-3.6	P
Case Source = general population						
Controls = population		Active only before 1st pregnancy	7/6	5.6	1.5-21.0	A, BMI, EC, FH, HB, HR, P
		Active only after 1st pregnancy	63/110	2.1	1.1-4.0	
		Active before & after 1st pregnancy	57/175	1.1	0.6-2.0	
Delfino *et al.* (2000)	Total Study	No active/passive	33/96	-	Referent	A, FH, M
United States		Former	40/99	0.94	0.53-1.68	*Risk estimates w/ all controls
Years Diagnosis = DNS		Current	5/24	0.55	0.18-1.67	
Case Source = Clinic/Breast Centers						
Controls = Clinic/Breast Centers						

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Johnson *et al.* (2000)	Premenopausal cancer	No active/passive	14/35	-	Referent	A, AF, AH, AL, AM,
Canada, 1994-1997		Former	182/150	2.6	1.3-5.3	BMI, E, P, PH, RE
Case Source = population registry		Current	116/133	1.9	0.9-3.8	
Controls = population		Ex- or Current	298/282	2.3	1.2-4.5	
		Former - adult only	21/23	1.6	0.6-4.2	BMI, E, P, PH, RE
		Former - child & adult	160/124	2.6	1.3-5.3	
		Current - adult only	10/21	1.0	0.3-2.8	BMI, E, P, PH, RE
		Current - child & adult	106/112	2.1	1.0-4.4	
	Postmenopausal cancer	No active/passive	52/92	-	Referent	A, AF, AH, AL, AM,
		Former	307/324	1.4	0.9-2.1	BMI, E, P, PH, RE
		Current	202/190	1.6	1.0-2.5	
		Ex- or Current	509/514	1.5	1.0-2.3	
		Former - adult only	49/36	1.8	1.0-3.4	BMI, E, P, PH, RE
		Former - child & adult	257/288	1.3	0.8-2.0	
		Current - adult only	28/27	1.6	0.8-3.2	BMI, E, P, PH, RE
		Current - child & adult	174/162	1.8	1.1-2.9	
Morabia *et al.* (2000)	Pre- and postmenopausal combined	Never active/never passive	160/162	-	referent	A, E, FH
Switzerland						
Case source: population		Active		3.3	1.7-6.5	
Controls: general population						
Kropp and Chang-Claude (2002)	Premenopausal cancer	No active/passive	44/144	-	Referent	Al, BF, BMI, ED FH, MS
Germany, 1992-1995		Former	113/299	1.15	0.76-1.74	
Case source = population registry		Current	158/334	1.47	0.99-2.20	
Controls = population						

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Marcus *et al.* (2000)		**Age at start (years)**				
United States, 1993-1996	Current smokers	Never	445/423	1.0	Referent	A
Case source = cancer registry		10-14	34/15	2.1	1.2-3.4	
Controls = population (vehicle reg)		15-19	103/90	1.0	0.7-1.4	
		≥ 20	82/71	1.2	0.8-1.6	
Rookus *et al*. (2000)	Premenopausal	Never active/ passive		1.0	Referent	PH
Netherlands		Current active		1.2	0.8-1.6	
		Former active		1.4	1.0-2.0	
Band *et al.* (2002)	Premenopausal	Smoking initiation (y)				AF, AL, AM, AMP, BF, BMI,
Canada, 1988-1989	Ever Pregnant	< 5 before menarche	104/83	1.69	1.13-2.51	E, FH, HB, HU, MS, M, OC, R
Case source = cancer registry		≥ 5 before menarche	58/70	1.05	0.67-1.65	
Controls = population (voter list)		Before 1st pregnancy	148/131	1.47	1.02-2.10	
		After 1st pregnancy	11/18	0.83	0.37-1.85	
		Before full term preg	113/105	1.37	0.93-2.01	
		After full term preg	7/15	0.67	0.26-1.73	
	Postmenopausal	Ever pregnant	334/343	0.93	0.74-1.17	
		Nulliparous	46/37	1.26	0.66-2.41	
Egan *et al.* (2002)	Full study	Never	1359	1.0	Referent	A, AF, AL, AM, AMP, FH,
United States, 1982-1996		Current active	573	1.04	0.94-1.15	HB, HU, MS, WT
Case & control source: Nurses		Former active	1208	1.09	1.00-1.18	
Health Study						
Terry *et al.* (2002)	Full study	Never		1.00	Referent	A, AL, AM, BMI, E, FH,
Canada, 1980, 1985		Current active		1.14	1.03-1.27	HB, HU, M, P
		Former active		0.99	0.90-1.09	
Lash and Aschengrau (2002)	Full study	Never active/ passive	80/53	1.0	Referent	AF, AL, BMI, FH, HB, HR, P
United States, 1987-1993		Ever active	361/366	0.72	0.55-0.95	
Reynolds *et al*. (2004)	Full study	Never active/ passive	316	1.00	Referent	A, AF, AL, AM, BMI, E, FH,
United States, 1995-2000		Current active	141	1.25	1.02-1.53	HB, HU, M, P, PH, R
California Teachers Study		Former active	690	1.03	0.89-1.18	
		Ever active*	831	1.06	0.92-1.21	

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Gammon *et al*. (2004)	Full study	Never active/ passive	155/170	1.0	Referent	A, BMI, FH, HB, M, P#, WT
United States, 1996-1997		Ever active	127/131	1.06	0.76-1.48	
Case source: population		Ever active + passive	631/625	1.15	0.90-1.48	
Controls: general population		Before+after 1st preg	551/563	1.08	0.82-1.43	
Hanaoka *et al.* (2005)		Never	162	1.0	Referent	A, AL, AM, E, ES, FH, HB,
Japan, 1990-1999	Full study	Current active	14	1.9	1.0-3.6	HU, MS, P
Case source: population	Premenopausal	Ever	11	3.9	1.5-9.9	
Controls: general population	Postmenopausal	Ever	7	1.1	0.5-2.5	
Gram *et al.* (2005)	Full study	Never		1.0	Referent	A, AL, FB, HU, MS, P
Norway/Sweden, 1991-2000		Current active	130	1.17	0.95-1.45	
Case source: population		Ever active	245	1.0	0.98-1.50	
Controls: general population	Premenopausal	Active 20+ years	276	1.21	0.91-1.61	
	Postmenopausal	Active 20+ years	198	1.31	0.92-1.88	

*Reynolds pers. Comm. To M. Miller. Former and current smokers combined with passive smokers excluded from reference group

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
		Studies included in Cal/EPA, 1997				
Morabia *et al.* (1996)	Total Study	No current or passive	28/241	-	Referent	A, AF, AL, AM, BMI, E, FH,
Switzerland, 1992-1993		Ever active 1-9 cpd	31/131	2.2	1.0-4.4	HB, OC, SF
		Current 1-9 cpd	10/78	1.5	0.6-3.9	
		Current <20 pack yrs	23/129	2.1	1.0-4.5	
		Studies included in this update				
Millikan *et al.* (1998)	Total Study	**Packs/day**				
Carolina Breast Cancer Study		Never	248/253	--	Referent	A, AF, AL, AM, FH, HB, P, R
United States, 1993-1996		< ½	85/82	1.1	0.8-1.6	
		½ -1	91/71	1.3	0.9-1.9	
Case Source = population registry		> 1	72/66	1.1	0.7-1.7	
Controls = population	Premenopausal	Never	123/110	--	Referent	A, AF, AL, AM, FH, HB, P, R
		< ½	41/42	1.0	0.6-1.7	
		½ -1	46/34	1.2	0.7-2.1	
		> 1	30/30	0.9	0.5-1.7	
	Postmenopausal	Never	125/143	--	Referent	A, AF, AL, AM, FH, HB, P, R
		< ½	44/40	1.3	0.8-2.2	
		½ -1	45/37	1.4	0.8-2.4	
		> 1	42/36	1.4	0.8-2.5	
	Total Study	**Duration (yrs)**				
		Never	248/253	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 10	63/62	1.0	0.7-1.5	
		11-20	57/68	0.8	0.5-1.2	
		> 20	129/89	1.6	1.1-2.3	
	Premenopausal	Never	123/110	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤10	48/45	1.0	0.6-1.7	
		11-20	35/37	0.8	0.6-1.4	
		>20	35/24	1.4	0.8-2.6	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity; PAS = previous active smoking; PH = Physical Activity; R = Race; RE = Residence, RH = reproductive history; WT = adult weight

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Millikan *et al.* (1998) (continued)	Postmenopausal	Never	125/143	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 10	15/17	1.1	0.5-2.4	
		11-20	22/31	0.8	0.4-1.5	
		> 20	94/65	1.7	1.1-2.6	
		Time since cessation (yrs)				
	Former Smokers	Never	248/253	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 3	49/19	2.2	1.2-4.0	
		4-9	41/24	1.7	1.0-3.0	
		10-19	31/44	0.8	0.5-1.4	
		≥ 20	36/40	1.1	0.7-1.9	
	Premenopausal	Never	123/110	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 3	23/11	1.3	0.6-2.9	
		4-9	15/14	0.9	0.4-2.1	
		10-19	20/24	0.9	0.4-1.8	
		≥ 20	14/13	1.3	0.5-3.1	
	Postmenopausal	Never	125/143	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 3	26/8	3.4	1.4-8.1	
		4-9	26/10	3.0	1.3-6.7	
		10-19	11/20	0.6	0.3-1.4	
		≥ 20	22/27	1.1	0.6-2.2	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Lash and Aschengrau (1999)		**Cigarettes/day**				
		Never	40/139	--	Referent	A, BMI, EC, FH, HB, HR, P*
United States, 1983-1986		<20	84/160	2.1	1.0-4.6	*Plus duration smoking
		>20	16/42	1.6	0.6-4.3	
		Duration Years				
Case Source = general population		0-19	34/54	2.6	1.2-5.5	A, BMI, EC, FH, HB, HR, P*
Controls = population		20-39	46/117	1.5	0.7-3.2	*Plus cigarettes per day
		>40	54/147	2.4	1.1-5.5	
		Years since cessation before index year				
		<5 or current	22/75	2.3	0.8-6.8	A, BMI, EC, FH, HB, HR, P*
		5-15	33/54	3.9	1.4-10.0	*Plus cigarettes per day
		>15	82/209	2.2	1.0-4.9	and duration active smoking
		Age Initiated Smoking				
		<17	28/75	2.4	0.8-7.2	A, BMI, EC, FH, HB, HR, P*
		17-20	60/138	2.3	1.0-5.5	*Plus cigarettes per day
		>21	47/106	2.4	1.0-5.7	and duration active smoking
Delfino *et al.* (2000)		**Duration Smoking**				A, FH, M
		Never/No Passive	33/96	1.00	Referent	*Risk estimates w/ all controls
United States		<13 years	14/42	0.94	0.43-2.03	
(time period not specified)		13-26 years	10/42	0.70	0.30-1.62	
Case Source = clinic/breast centers		>26 years	20/38	0.74	0.34-1.61	
Controls = clinic/breast centers		**Cigarettes per Day**				
		None	33/96	1.00	Referent	A, FH, M
		< 8 per day	19/45	1.04	0.50-2.13	*Risk estimates w/ all controls
		8-25 per day	18/46	0.75	0.35-1.58	
		>25 per day	7/31	0.51	0.19-1.35	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Johnson *et al.* (2000)	Premenopausal	**Age initiated smoking**				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
Canada, 1994-1997		> 20 years	38/33	2.1	0.9-4.8	P, PH, RE
Case Source = population registry		16-19 years	138/123	2.4	1.2-4.9	
Controls = population		< 15 years	121/126	2.1	1.0-4.3	
					P trend=0.63	
		Cigarettes per day				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
		< 10 cpd	91/75	2.5	1.2-5.2	P, PH, RE
		10-19 cpd	101/100	2.3	1.1-4.6	
		> 20 cpd	102/104	2	1.0-4.0	
					P trend=0.99	
		Duration Active Smoking				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
		1-11 years	109/91	2.7	1.2-6.1	
		11-20 years	72/90	1.9	0.8-4.5	
		> 21 years	114/98	2.1	0.9-4.7	
					P trend=0.91	
		1-10 pack-years	161/151	2.4	1.2-4.7	
		11-20 pack-years	81/74	2.3	1.1-4.7	
		12-30 pack-years	38/40	1.7	0.8-3.9	
		> 30 pack-years	10/11	1.5	0.4-5.9	
					P trend=0.92	
		Years since Cessation				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
		> 20 years	42/34	2	0.9-4.6	P ,PH, RE
		11-20 years	76/58	2.9	1.3-6.1	
		< 10 years	64/58	2.5	1.2-5.5	
					P trend=0.08	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Johnson *et al.* (2000) (continued)	Postmenopausal	**Age initiated smoking**				
		No active/passive	52/92	1.0	Referent	A, AF, AH, AL, AM, BMI,
		> 20 years	167/173	1.4	0.9-2.3	E, P, PH, RE
		16-19 years	230/209	1.5	1.0-2.4	
		< 15 years	110/129	1.2	0.7-1.9	
				P trend = 0.19		
		Cigarettes per day				
		No active/passive	52/92	1.0	Referent	A, AF, AH, AL, AM, BMI,
		< 10 cpd	120/132	1.4	0.8-2.2	E, P, PH, RE
		10-19 cpd	182/183	1.5	0.9-2.3	
		> 20 cpd	203/194	1.4	0.9-2.1	
				P trend = 0.08		
		Duration				
		No active/passive	52/92	--	Referent	A, AF, AH, AL, AM, BMI,
		1-20 years	160/179	1.2	0.8-1.9	E, P, PH, RE
		21-35 years	154/159	1.3	0.8-2.1	
		> 35 years	194/165	1.7	1.1-2.7	
				P trend = 0.003		
		1-10 pack-years	166/176	1.4	0.9-2.1	
		11-20 pack-years	110/139	1.2	0.7-1.9	
		12-30 pack-years	109/84	1.9	1.1-3.1	
		> 30 pack-years	118/99	1.6	1.0-2.6	
				P trend = 0.01		
		Years since Cessation				
		No active/passive	52/92	--	Referent	A, AF, AH, AL, AM, BMI,
		> 20 years	110/138	1.1	0.7-1.8	E, P, PH, RE
		11-20 years	93/105	1.3	0.8-2.1	
		< 10 years	104/81	1.8	1.1-3.0	
				P trend = 0.03		

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Marcus *et al.* (2000)		**Age initiated smoking**				
Carolina Breast Cancer Study	Former smokers	Never	445/423	--	Referent	A, R
United States, 1993-1996		10-14 years	10/12	0.7	0.3-1.8	
		15-19 years	114/106	1.0	0.8-1.4	
Case Source = population registry		≥ 20 years	74/69	1.1	0.8-1.6	
Controls = population	Current smokers	Never	445/423	1.0	Referent	A, R
		10-14 years	34/15	2.1	1.2-3.4	
		15-19 years	103/90	1.0	0.7-1.4	
		≥ 20 years	82/71	1.2	0.8-1.6	
	Smoked < 20 yrs	Never	445/423	--	Referent	A, R
		10-14 years	34/15	2.1	1.2-3.4	
		15-19 years	103/90	1.0	0.7-1.4	
		≥ 20 years	82/71	1.2	0.8-1.6	
	Smoker >20 years	Never	445/423	1.0	Referent	A, R
		10-14 years	11/5	2.0	0.7-6.7	
		15-19 years	67/68	0.9	0.6-1.3	
		≥ 20 years	63/57	1.2	0.8-1.7	
	Smoked < 1 pk/day	Never	445/423	1.0	Referent	A, R
		10-14 years	11/5	2.0	0.7-6.7	
		15-19 years	67/68	0.9	0.6-1.3	
		≥ 20 years	63/57	1.2	0.8-1.7	
	Smoked ≥ 1 pk/day	Never	445/423	1.0	Referent	A, R
		10-14 years	32/22	1.4	0.8-2.4	
		15-19 years	149/128	1.1	0.9-1.5	
		≥ 20 years	92/82	1.2	0.8-1.6	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Egan *et al.*, (2002)		Never active	1,359	1.0	Referent	A, AF, AH, AL, AM, AMP, FH,
United States, 1982-1996		Current	573	1.04	0.94-1.15	HB, HU, M, PAS, WT
		Ex-smokers	1,208	1.09	1.00-1.18	
		Ex- <5 yrs	189	1.17	1.01-1.40	
		No active/passive		1.0	Referent	
		Current	573	1.15	0.98-1.34	
		Ex-smokers	1,208	1.17	1.01-1.34	
	Parous smokers	Started age <16	218	1.31	1.07-1.61	
		Started age >16	1,288	1.12	0.96-1.31	
	Preparous smoking	0 yrs	1,340	1.0	Referent	
		< 5 yrs	563	1.10	0.96-1.26	
		≥ 5 yrs	943	1.13	0.99-1.30	
		< 1 pk/day		1.12	0.95-1.31	
		≥ 1 pk/day		1.21	0.98-1.51	
				P for trend = 0.05		
Band *et al.* (2002)	**Premenopausal**	Never	114/138	--	Referent	AM, AL, E, R, FH, HB, BMI,
	Ever pregnant	Ever	164/153	1.42	1.00-2.00	MS, AMP, RH, MB, OC
Canada, 1988-1989		**Cigarettes per day**			P=0.05	
		< 20	87/86	1.36	0.91-2.05	P= 0.14
Cases : cancer registry		≥ 20	72/66	1.39	0.91-2.14	P= 0.13
Controls: general population		**Years of smoking**				
		< 20	75/84	1.24	0.81-1.89	P= 0.32
		≥ 20	84/69	1.50	0.98-2.28	P= 0.06
		Pack-years				
		< 20	93/101	1.25	0.84-1.86	P= 0.27
		≥ 20	61/51	1.46	0.92-2.32	P= 0.11

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Band *et al.* (2002)		**Smoking initiation from onset of menarche**				
(continued)		< 5 years	104/83	1.69	1.13-2.51	P= 0.01
		≥ 5 years	58/70	1.05	0.67-1.65	P= 0.83
		Smoking initiation in relation to 1st pregnancy				
		before	146/131	1.47	1.02-2.10	P= 0.04
		after	11/18	0.83	0.37-1.85	P= 0.64
	Nulliparous	never	14/28	--	Referent	--
		ever	25/21	2.09	0.78-5.59	P= 0.14
		Cigarettes per day				
		< 20	14/17	1.45	0.49-4.29	P= 0.50
		≥ 20	11/4	7.08	1.63-30.8	P= 0.009
		Years of smoking				
		< 20	13/10	3.55	0.97-13.0	P= 0.06
		≥ 20	12/10	2.27	0.72-7.13	P= 0.16
		Cigarette pack-years				
		< 20	14/16	1.67	0.55-5.04	P= 0.37
		≥ 20	11/4	7.48	1.59-35.2	P= 0.01
Kropp and Chang-Claude (2002)		**Never**	44/144	--	Referent	
Germany, 1992-1995		**Duration (yrs)**				
		1-9	47/153	0.99	0.61-1.60	AL, E, FH, M, BMI, MB
		10-19	91/202	1.40	0.90-2.16	
		≥ 20 years	133/278	1.45	0.96-2.19	P=0.047
		Age (yrs) at initiation of active smoking				
		9-15	46/128	1.02	0.62-1.68	AL, E, FH, M, BMI, MB
		16-18	134/321	1.29	0.86-1.94	
		≥ 19	91/184	1.54	0.99-2.37	P= 0.015

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Lash and Aschengrau (2002)		Never	80/53	--	Referent	
United States, 1987-1995		Ever	361/366	0.72	0.55-0.95	AF, AL, BMI, EC, FH, HB, P
		Duration (yrs)				
		0-20	71/77	0.69	0.48-1.0	AF, AL, BMI, EC, FH, HB, P
		20-< 40	145/139	0.87	0.74-1.0	
		≥ 40	117/117	0.90	0.80-1.0	
	Pregnancy demarcated					
	All before first		21/20	.73	0.42-1.3	AF, AL, BMI, EC, FH, HB, P
	Before and after first		196/205	.69	0.49-0.96	
	All after first		59/70	.66	0.42-1.0	
	Never gave birth		78/65	.82	0.48-1.4	
Terry *et al.*, 2002		**Cigarettes/day**				
Unites States.		Never	1,306/498,516	1.0	Referent	A,AL,AM,E,
		1-9	265/102,182	0.97	0.85; 1.11	FH,HB,HU,M,OC,P,
		10-19	317/120,688	0.98	0.86; 1.11	
		20-29	483/166,846	1.10	0.99; 1.23	
		30-39	72/29,414	0.90	0.71; 1.16	
		40+	79/23,194	1.34	1.06; 1.69	
			P for trend	0.05		
		Years smoked				
		Never	1,306/498,516	1.0	Referent	
		1-9	204/84,398	0.93	0.80; 1.09	
		10-19	279/113,276	0.97	0.85; 1.11	
		20-29	426/156,621	1.06	0.94; 1.19	
		30-39	268/79,907	1.14	0.99; 1.31	
		40+	46/8,966	1.61	1.19; 2.19	
			P for trend	0.009		

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Terry *et al*., 2002		**Pack-years**				
***(continued)*.**		Never	1,306/498,516	1.0	Referent	
		1-9	396/156,089	0.98	0.87; 1.10	
		10-19	251/98,989	0.97	0.85; 1.12	
		20-29	204/76,188	1.08	0.93; 1.25	
		30-39	191/58,288	1.21	1.04; 1.42	
		40+	151/42,986	1.37	1.15; 1.62	
			P for trend	0.003		
Gammon *et al.* (2004)		**Cigarettes/day**				
United States, 1997-1997		Never	155/170	1.0	Referent	A, BMI, HB,MS,P#
		Ever 1-9	210/216	1.10	0.82-1.47	
		10-19	172/160	1.24	0.91-1.70	
		20+	369/373	1.13	0.86-1.48	
		Current 1-9 cpd	49/44	1.38	0.86-2.23	
		10-19	63/59	1.30	0.84-2.00	
		20+	150/141	1.31	0.94-1.82	
		Current Pack-yrs				
		<20	91/88	1.41	0.95-2.08	
		20+	168/151	1.33	0.97-1.83	
Gram *et al*. (2005)	Current smokers	Cigarettes per day				A, AF, AL, BMI, OC
Norway/Sweden, 1991-2000		Never	137	1.0	Referent	
		Current 1-9	135	0.96	0.74-1.25	
		10+	225	1.28	1.01-1.63	
					P trend = 0.03	
		Years smoked				
		1-19	68	0.93	0.68-1.28	
		20-24	96	1.09	0.81-1.45	
		25+	196	1.26	0.98-1.63	
					P trend = 0.05	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)	Factors Adjusted
Gram *et al.* (2005)		**Pack-years**			
(continued)		0-14	162	0.95 0.74-1.20	
		15-19	90	1.28 0.96-1.72	
		20+	108	1.48 1.14-1.96	
				P trend = 0.001	
		Latency			
		1-19	48	0.75 0.52-1.08	
		20-24	116	1.20 0.91-1.58	
		25+	196	1.27 0.98-1.64	
				P trend = 0.02	
Reynolds *et al.* (2004)	Full study	**Cigarettes per day**			
United States, 1995-2000		Never	1174	1.00 Referent	A,AF, AL, AM, BMI, FH, HU, MS,
		< 10	343	1.04 0.92-1.18	P, PH, menstrual status,
		10-19	260	1.14 0.99-1.30	
		≥ 20	209	1.22 1.05-1.42	
				P trend =0.004	
		Smoking years			
		≤ 10	176	0.99 0.85-1.17	
t		11-20	193	1.17 1.00-1.37	
		21-30	163	1.17 0.99-1.38	
		≥ 30	251	1.15 1.00-1.33	
				P trend =0.009	
		Pack-years			
		≤ 10	338	1.02 0.91-1.16	
		11-20	165	1.24 1.05-1.46	
		21-30	94	1.12 0.91-1.39	
		≥ 30	173	1.25 1.06-1.47	
				P trend =0.002	
		Age smoking start			

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Reynolds *et al.* (2004)		≥ 20	285	1.03	0.90-1.17	
(continued)		< 20	507	1.17	1.05-1.30	
		Smoking and 1st preg				
		Pre-partum < 5 yr	110	0.99	0.80-1.21	
		Pre-partum ≥ 5 yr	406	1.13	1.00-1.28	
		Post-partum only	42	0.89	0.65-1.21	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure		Genotype				Factors Adjusted
Millikan *et al.* (1998)			NAT1*10		NAT1-non*10		
	PREMENOPAUSAL Former Smokers:						
	Years since cessation:	Never smoker	1.0	Referent	1.0	Referent	A,R
		≤ 3	1.6	0.6-4.5	2.1	0.6-7.2	
		4-9	0.8	0.2-3.0	0.8	0.3-2.2	
		10-19	0.9	0.4-2.3	1.0	0.4-2.7	
		≥ 20	0.6	0.2-1.9	1.7	0.5-6.2	
	POSTMENOPAUSAL Former Smokers:						
	Years since cessation:	Never smoker	1.0	Referent	1.0	Referent	A, R
		≤ 3	9.0	1.9-41.8	2.5	0.9-7.2	
		4-9	7.0	2.0-25.2	1.5	0.5-4.5	
		10-19	0.6	0.2-1.9	0.6	0.2-1.8	
		≥ 20	0.6	0.2-1.5	1.7	0.7-4.3	
			NAT2 fast		NAT2 slow		
	PREMENOPAUSAL	Quit ≤ 3 years	1.5	0.6-4.0	1.9	0.5-7.9	
		Current Smokers	1.1	0.5-2.3	0.8	0.4-1.6	
	POSTMENOPAUSAL	Quit ≤ 3 years	7.4	1.6-32.6	2.8	0.4-8.0	
		Current Smokers	1.4	0.7-2.8	1.1	0.6-2.2	
Morabia *et al.* (2000)			NAT2 slow		NAT2 fast		
	PREMENOPAUSAL	no active/passive	1.0	Referent	1.0	Referent	
		ever passive	3.2	0.9-11.5	3.3	0.7-15.7	A, E, FH
		ever active	2.9	0.8-10.3	3.0	0.7-11.8	
	POSTMENOPAUSAL:	no active/passive	1.0	Referent	1.0	Referent	
		ever passive	1.1	0.3-4.3	11.6	2.2-62.2	A, E, FH
		ever active	2.9	0.8-11.2	8.2	1.4-46.0	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure		Genotype				Factors Adjusted
Delfino *et al.* (2000)			NAT2 slow				
	PREMENOPAUSAL		1.15	0.49-2.77			A, FH, HB, MS
	POSTMENOPAUSAL		1.29	0.74-2.27			
Krajinovic *et al.* (2001)			NAT2	rapid vs slow			
	PRE-, POSTMENOPAUSAL	Never	1.0	Referent			
		Ever	2.6	1.1-6.3			
Chang-Claude *et al.* (2002)	PRE-, POSTMENOPAUSAL		NAT2 fast		NAT2 slow		A, AF, AL, E, FH, M, MB,
			1.22	0.59-2.54	1.67	0.67-2.89	
Zheng *et al*. (2002)	Smoking started <18 years of age		GSTT1 null		GSTT1 positive		A, AF, FH, M, MB
	PRE-, POSTMENOPAUSAL		1.7	0.8-3.7	1.0	0.7-1.6	
	POSTMENOPAUSAL		2.9	1.0-8.8	1.1	0.6-1.9	
	Current smokers						
	PRE-, POSTMENOPAUSAL		1.1	0.4-2.7	1.1	0.6-1.9	
	POSTMENOPAUSAL		2.3	0.6-8.9	1.1	0.6-2.1	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure		Genotype				Factors Adjusted
Saintot *et al*. (2003)			CYP1B1 high/low		SULT1A1 low/high		AF, AM, AMP, BP, FH,
	All		1.72	0.67-4.42	0.54	0.22-1.33	
	PREMENOPAUSAL	≤ 5 cig/day	3.09	0.61-15.60	0.67	0.19-2.31	HB, HU
	POSTMENOPAUSAL		1.37	0.39-4.82	0.40	0.10-1.67	
	All		2.32	1.28-4.21	1.65	0.97-2.80	
	PREMENOPAUSAL	> 5 cig/day	2.00	0.87-4.57	2.11	1.00-4.46	
	POSTMENOPAUSAL		3.56	1.40-9.02	1.50	0.67-3.39	
	All		2.37	1.24-4.51	1.71	0.97-3.03	
	PREMENOPAUSAL	>20YRS DURATION	2.79	1.06-7.33	2.83	1.23-6.54	
	POSTMENOPAUSAL		2.23	0.90-5.52	1.17	0.49-2.76	
	All		2.01	0.97-4.15	1.00	0.53-1.92	
	PREMENOPAUSAL	≤ 10 pack-years	2.03	0.70-5.87	1.44	0.58-3.54	
	POSTMENOPAUSAL		2.05	0.74-5.73	0.70	0.25-1.93	
	All		2.38	1.23-4.63	1.68	0.93-3.04	
	PREMENOPAUSAL	> 10 pack-years	2.22	0.86-5.70	1.89	0.83-4.30	
	POSTMENOPAUSAL		2.81	1.07-7.43	1.59	0.65-3.85	
	All		2.81	1.46-5.41	1.49	0.85-2.60	
	PREMENOPAUSAL	start ≤ 20 years old	3.25	1.28-8.25	1.91	0.91-4.04	
	POSTMENOPAUSAL		2.67	1.00-7.18	1.31	0.50-3.39	
	All		1.45	0.67-3.15	1.07	0.52-2.22	
	PREMENOPAUSAL	start >20 years old	0.89	0.26-3.03	1.14	0.35-3.66	
	POSTMENOPAUSAL		2.25	0.79-6.43	0.98	0.38-2.57	
			COMT high/low				
	PRE-, POSTMENOPAUSAL		1.42	0.65-3.13			

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure	Genotype				Factors Adjusted
Cohort						
Couch *et al.* (2001)	Ever smoking in relatives of BC patient	High BC risk		Highest BC risk*		AF, AL, AM, BC, BMI
	1st degree relatives (sisters, daughters)	1.8	1.2-2.7	5.8	1.4-23.9	
	2nd degree relatives	1.1	0.8-1.5	1.6	0.8-3.2	
	Marry-ins	1.2	0.9-1.6	1.2	0.8-1.9	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.8. In Utero exposure to tobacco smoke and breast cancer.

Case-control Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted[a]
Sanderson *et al.* (1996)		Perinatal				
	Women ages 21-45	No	447/580	--	Ref	A, M
United States, 1983-1990		Yes	257/325	1.1	0.9-1.3	
Case Source = population registry		Missing	42/55			
Controls = population	Women ages 50-64	No	336/376	--	Ref	A, M
		Yes	46/40	1.3	0.9-2.1	
		Missing	19/23			
	Women < age 30	No	DNS[2]	--	Ref	DNS[2b]
		Yes	DNS[2]	1.9	1.0-3.4	
		Missing	DNS[2]			
Weiss *et al.* (1997)		Perinatal				
	Women ages 20-44	No	352/331	--	Ref	A, AF, AL, AM, BMI, FH,
United States, 1990-1992		Yes	170/153	1.06	0.8-1.4	MAM, PA, PB
Case Source = population registry		Cigarettes/trimester				
Controls = population		<10	109/84	1.19	0.9-1.7	A, AF, AL, AM, BMI, FH,
		>10	55/58	0.98	0.6-1.5	MAM, PA, PB
		Other[3c]	5/11	0.41	0.1-1.3	

[a] Factors adjusted for: A=Age, AF=Age first childbirth, AL=Alcohol consumption, AM=Age menarche, BMI=Body mass index, FH=Family history breast, M=Menopausal status, MAM=Number mammograms previous, PA=Combination parity & full term births, PB=Previous breast biopsy;

[b] DNS = Data not presented in original publication.

[c] These women did not smoke the same number of cigarettes/trimester.

Appendix 7B:
Lung Cancer Deaths Attributable to Environmental Tobacco Smoke

In order to assess the impact of ETS on population mortality, we estimate the number of lung-cancer deaths attributable to ETS in a single year. The calculation, based on the equations of U.S. EPA (1992c), apportions the overall number of lung-cancer deaths into four categories: (1) deaths in mainstream smokers and former smokers, (2) ETS-attributable deaths in nonsmokers exposed to spousal smoking, (3) ETS-attributable deaths in non-smokers not exposed to spousal smoking, (4) deaths not related to tobacco smoke.

7.ApB.1 Methods

The equations, which require algebraic manipulation to derive, use the assumption that risk is linear in dose, as specified in the NRC model for relative risk in epidemiology studies: $R(d_E) = (1 + Z * ßd_N)/(1 + ßd_N)$ where $R(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS). Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N. ß is the amount of increased risk per unit dose.

Algebraic manipulations then derive risks relative to deaths not related to tobacco smoke from two kinds of relative risks obtained from epidemiological studies:

R1, risks for smokers relative to non-smokers, and
R2, risks for non-smoking spouses of smokers relative to non-smoking spouses who were not so exposed.

Also needed for the calculations are
P1, the proportion of smokers in the population,
P2, the proportion of non-smokers exposed to spousal ETS, and
Z, as defined above.

The equations giving risks relative to other baselines are

$R01 = R1(P2*R02 + (1 – P2)R02/R2)$ where R01 is the risk of ever-smokers relative to never-smokers with no background.

$R02 = (Z – 1)/(Z/R2 – 1)$ where R02 is the passive risk relative to no background.

$R03 = R02/R2$ where R03 is the risk for never-smokers with background ETS only relative to no background ETS.

$R11 = R1(P2\ R2 + 1 – P2)$ where R11 is the risk of ever-smokers with spousal ETS relative to never-smokers with only background ETS.

Z: exposure ratio between spousal exposure plus background and background alone determined by cotinine measurements in nonsmoking with and without spousal ETS exposure (Wells, pers. comm.).

Using the three risks relative to the zero-ETS baseline permits calculation of the proportions of lung cancer deaths into the four smoking categories, each with its indicated numerator:

Table 7.ApB.1 Numerators for Attributable Risk Equations

Category	Numerator
Ever smokers	P1(R01-1)
Never smokers exposed to spousal ETS	(1-P1)P2(R02-1)
Never smoker not exposed to spousal ETS	(1-P1)(1-P2)(R03-1)
Not related to tobacco smoke	1

The denominator for each proportion is the sum of the four numerators. Multiplication of each resulting proportion by the overall lung cancer deaths in the population provides the estimate of lung cancer deaths attributable to that category.

7.ApB.2 Results

Separate estimates are made for males and females reflecting the gender differences in exposure prevalence to active and passive smoking and hence, lung cancer risk. Two adjusted ORs are used from Fontham *et al*. (1994) to provide a range of probable attributable deaths. These include 1.29 (95% CI 1.04; 1.60) for the risk of all lung carcinomas among nonsmoking women with spousal exposure, and 1.74 (95% CI 1.14; 2.65) for lung cancer among nonsmoking women with ≥ 48 adult smoke-years of exposure to spousal ETS.

Table 7.ApB.2 Input Parameters for Lung Cancer Attributable Risk Estimates

Input	Females	Males	Source
R2 low	1.29	1.29	Fontham, 1994
R2 high	1.74	1.74	Fontham, 1994
R1	8.27	13.54	Thun, 2000
P1 former	0.228	0.231	Wells pers com
P1 current	0.187	0.343	Wells pers com
P1 ever	0.42	0.57	Wells pers com
P2	0.56	0.22	Wells pers com
Z	3.14	2.02	Wells pers com
U.S. Pop 2004	78,857,000	70,235,000	Census Bureau
U.S. LC deaths 2003	68,800	88,400	NCI - SEER

The methodology used here is based on that used by the U.S. EPA (1992c), and is applied to the population 35 years old and older to reflect the low incidence of lung cancer before age 35. It applies to males the R2 values determined for females since the data from which to calculate R2 for males are lacking. Values for P1 and P2 were derived by Wells from data provided by Dr. Schoenborn of the National Center for Health Statistics (pers. comm.). The value of Z was estimated by Wells based on several studies. It is lower for males than for females reflecting the smaller proportion of males, versus females, who are never-smokers exposed to spousal smoking. The method also takes into account smokers who have quit smoking for five or more

years, the proportion of which is estimated to be 80%, based on studies by Lash *et al*. (1999) and Johnson *et al*. (2000). This value is used for both genders.

Table 7.ApB.3 National ETS-Attributable Lung Cancer Deaths

	Eversmokers	Spouse ETS	Background ETS	Non-tobacco smoke	Total from ETS
R2=1.29					
Female	53523	2048	512	12717	2560
Male	78780	408	455	8758	863
Both				**Total**	3423
R2 = 1.74					
Female	55522	4294	1074	7909	5368
Male	82330	1271	2227	2572	3498
Both				**Total**	8866

We estimate that for the nation in 2003, the number of ETS-attributable lung cancer deaths associated with spousal smoking and background ETS exposure for both genders combined is in the range of 3423 to 8866. The deaths among males are lower than among females reflecting the lower proportion of non-smoking males with spousal exposure. On the other hand, this analysis does not address ETS exposure at work or in other venues that may be generally higher for males than for females.

The number of ETS-attributable lung cancer deaths in Californian may be crudely estimated by taking California's population as 12% of the national population, and assuming the same rates of exposure to active and spousal smoking. This would result in estimates for females and males, respectively, of 307 and 104 deaths when R2 = 1.29, and 644 and 420 for R2=1.74. The total ETS attributable lung cancer deaths in California would thus be expected to be in the range of 411-1064.

Table ETS-Attributable Lung Cancer Deaths in California in 1999

	R=1.29	R=1.74
Female	307	644
Male	104	420
Both	411	1064

California deaths may be somewhat lower than these estimates because it is expected that the rates of smoking cessation and the number of homes with smoking restrictions may be higher in California than in the rest of the country. However, California-specific estimates of the rate of smoking cessation for five or more years among individuals 35 and older were not available. By presenting a range of estimates based on high and low risk values, it is likely that the true number of deaths is included. In addition, OEHHA calculated a slightly higher summary OR of 7.8 based on more recent studies that included occupational exposure. However, this higher estimate included studies that were not specific to the U.S., while the estimate used here was thought to be more representative of the U.S. population.

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7.6.1. *IARC Monographs on the Evaluation of carcinogenic risks to humans* cited in this chapter

Pages	Compound or topic
IARC (1972). Volume 1. *Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds, and Natural Products*. 1972; 184 pages	
40-50	lead, arsenic
74-79	4-aminobiphenyl
95-124	N'-nitrosodimethylamine, N-nitrosodiethylamine
IARC (1973a). Volume 2. *Some Inorganic and Organometallic Compounds* . 1973; 181 pages.	
48-149	arsenic, lead, cadmium, chromium VI, nickel
IARC (1973b). Volume 3. *Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds* . 1973; 271 pages.	
45-48	benz[a]anthracene
69-196	benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, benzo[e]pyrene, chrysene, dibenz[a,h]anthracene
201-237	dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, dibenzo[a,l]pyrene, indeno[1,2,3-cd]pyrene
241-268	benz[c]acridine, dibenz[a,h]acridine, dibenz[a,j]acridine, 7H dibenzo[c,g]carbazole
IARC (1974a). Volume 4. *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. 1974; 286 pages.	
27-39	aniline
87-111	1-naphthylamine, 2-naphthylamine
127-143	hydrazine, 1,1-dimethylhydrazine
173-179	maleic hydrazide
197-210	N-nitrosodi-n-butylamine
IARC (1974b). Volume 5. *Some Organochlorine Pesticides*. 1974; 241 pages.	
83-124	DDT
157-166	endrin
IARC (1974c). Volume 7. *Some Anti-Thyroid and Related Substances, Nitrofurans and Industrial Chemicals*. 1974; 326 pages.	
111-140	urethane
197-221	acetamide, benzene
291-318	vinyl chloride
IARC (1975). Volume 9. *Some Aziridines, N-, S- and O-Mustards and Selenium*. 1975; 268 pages.	
245-260	selenium
IARC (1976a). Volume 10. *Some Naturally Occurring Substances*. 1976; 353 pages.	
99-119	coumarin, cholesterol
IARC (1976b). Volume 11. *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics.* 1976; 306 pages.	
39-112	cadmium, nickel
157-167	ethylene oxide
191-199	propylene oxide
231-240	γ-butyrolactone
IARC (1977). Volume 15. *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* 1977; 354 pages.	
155-175	catechol, hydroquinone, resorcinol
265-271	succinic anhydride

Pages	Compound or topic
IARC (1978a). Volume 16. *Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals.* 1978; 400 pages.	
325-341	N-phenyl-2-naphthylamine
349-366	*ortho*-toluidine
IARC (1978b). Volume 17. *Some N-Nitroso Compounds.* 1978; 365 pages.	
51-189	N-nitrosodi-n-butylamine, N-nitrosodiethanolamine, N-nitrosodiethylamine, N'-nitrosodimethylamine, N-nitrosodi-n-propylamine
221-226	N-Nitroso-N-methylethylamine
281-301	N'-nitrosonornicotine, N-nitrosopiperidine
313-326	N-nitrosopyrrolidine
IARC (1979). Volume 19. *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein.* 1979; 513 pages.	
52	methyl acrylate
73-113	acrylonitrile
157-186	ethylene
213-274	propylene, styrene
377-438	vinyl chloride
479-494	acrolein
IARC (1980). Volume 23. *Some Metals and Metallic Compounds*. 1980; 438 pages.	
39-141	arsenic, lead
205-415	chromium VI, lead
IARC (1982a). Volume 27. *Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking Water and Dental Preparations.* 1982; 341 pages.	
39-80	aniline, *ortho*-anisidine
155-175	*ortho*-toluidine
IARC (1982b). Volume 29. *Some Industrial Chemicals and Dyestuffs.* 1982; 416 pages.	
93-148	benzene
331-397	2-nitropropane, formaldehyde, benzene
IARC (1983a). Volume 30. *Miscellaneous Pesticides.* 1983; 424 pages.	
103-129	malathion
295-318	captan
IARC (1983b). Volume 31. *Some Food Additives, Feed Additives and Naturally Occurring Substances*. 1983; 314 pages.	
95-132	cholesterol
247-263	3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)
IARC (1983c). Volume 32. *Polynuclear Aromatic Compounds, Part 1: Chemical, Environmental and Experimental Data*. 1983; 477 pages.	
95-268	anthracene, benz[a]acridine, benz[c]acridine, benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[ghi]fluoranthene, benzo[a]fluorene, benzo[b]fluorene, benzo[c]fluorene, benzo[ghi]perylene, benzo[c]phenanthrene, benzo[a]pyrene, benzo[e]pyrene, carbazole, chrysene, coronene
277-451	dibenz[a,h]acridine, dibenz[a,j]acridine, dibenz[a,c]anthracene, dibenz[a,h]anthracene, dibenz[a,j]anthracene, 7H dibenzo[c,g]carbazole, dibenzo[a,e]fluoranthene, dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, dibenzo[a,l]pyrene, 1,4-dimethylphenanthrene, fluoranthene, fluorene, indeno[1,2,3-cd]pyrene, 1-methylchrysene, 2-methylchrysene, 3-methylchrysene, 4-methylchrysene, 5-methylchrysene, 6-methylchrysene, 2-methylfluoranthene, 3-methylfluoranthene, 1-methylphenanthrene, perylene, phenanthrene, pyrene , triphenylene

Pages	Compound or topic
IARC (1985a). Volume 36. *Allyl Compounds, Aldehydes, Epoxides and Peroxides.* 1985; 369 pages.	
75-161	eugenol, acetaldehyde, acrolein
189-243	ethylene oxide, propylene oxide
IARC (1985b). Volume 37. *Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines.* 1985; 291 pages.	
209-261	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanabasine, N'-nitrosoanatabine, N'-nitrosonornicotine
IARC (1986a). Volume 38. *Tobacco Smoking.* 1986; 421 pages.	
83-126	Tobacco smoke; chemistry and analysis
194-198	Tobacco smoke; Summary, biological data
309-314	Tobacco smoke carcinogenicity: conclusions and evaluations
387-394	Appendix 2 (compounds in tobaco smoke previously evaluated in the IARC Monograph series).
IARC (1986b). Volume 39. *Some Chemicals Used in Plastics and Elastomers.* 1986; 403 pages.	
99-112	methyl acrylate
155-179	butadiene
IARC (1986c). Volume 40. *Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation.* 1986; 444 pages.	
223-273	2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) , 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2), 2-amino-9H-pyrido[2,3-b] indole (A-α-C), 2-amino-3-methyl-9H-pyrido [2,3-b]indole (MeA-α-C), 2-amino-3-methyl-3H-imidazo(4,5-f)quinoline (IQ)
IARC (1990). Volume 49. *Chromium, Nickel and Welding.* 1990; 677 pages.	
49-445	chromium VI, nickel
IARC (1991a). Volume 51. *Coffee, Tea, Mate, Methylxanthines and Methylglyoxal.* 1991; 513 pages.	
483	chromium VI (correction)
IARC (1991b). Volume 53. *Occupational Exposures in Insecticide Application, and Some Pesticides.* 1991; 612 pages.	
179-249	DDT
IARC (1992). Volume 54. *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals.* 1992; 336 pages.	
237-285	butadiene
IARC (1993a). Volume 56. *Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins.* 1993; 599 pages.	
115-129	caffeic acid
165-195	2-amino-3-methyl-3H-imidazo(4,5-f)quinoline (IQ)
229-242	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)
IARC (1993b). Volume 57. *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines.* 1993; 427 pages.	
323-335	2,6-dimethylaniline
IARC (1994a). Volume 58. *Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry.* 1994; 444 pages.	
119-237	cadmium

Pages	Compound or topic
IARC (1994b). Volume 60. *Some Industrial Chemicals.* 1994; 560 pages.	
45-213	ethylene, ethylene oxide, propylene, propylene oxide
233-319	styrene
389-433	acrylamide
IARC (1995a). Volume 62. *Wood dust and Formaldehyde.* 1995; 405 pages.	
217-362	formaldehyde
IARC (1995b). Volume 63. *Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals.* 1995; 558 pages.	
337-407	acrolein, crotonaldehyde, furan
431-441	benzofuran
IARC (1996a). Volume 65. *Printing Processes and Printing Inks, Carbon Black and Some Nitrocompounds.* 1996; 578 pages.	
381-408	nitrobenzene
549	acrolein (correction), formaldehyde (correction)
IARC (1996b). Volume 66. *Some Pharmaceutical Drugs.* 1996; 514 pages.	
485	formaldehyde (correction)
IARC (1996c). Volume 67. *Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses.* 1996; 424 pages.	
395	nickel (correction)
IARC (1999a). Volume 71. *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide.* 1999; 1589 pages.	
43-225	acrylonitrile, butadiene
319-335	acetaldehyde
367-382	γ-butyrolactone
433-451	catechol
691-719	hydroquinone
991-1013	hydrazine
1079-1094	2-nitropropane
1119-1131	resorcinol
1211-1221	acetamide
1319-1323	carbazole
1425-1436	1,1-dimethylhydrazine
1489-1496	methyl acrylate
IARC (1999b). Volume 73. *Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents, and Some Other Substances.* 1999; 674 pages.	
49-58	*ortho*-anisidine
IARC (2000). Volume 77. *Some Industrial Chemicals.* 2000; 564 pages.	
193-225	coumarin
267-322	*ortho*-toluidine
403-438	N-nitrosodiethanolamine
487-501	nitromethane
IARC (2001). Volume 78. *Some Internally Deposited Radionuclides.* 2001; 596 pages.	
465-477	α-emitting radionuclides
IARC (2002). Volume 82. *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene.* 2002; 590 pages.	
367-550	naphthalene, styrene

Pages	Compound or topic
IARC (2004a). Volume 83. *Tobacco Smoke and Involuntary Smoking.* 2004; 1452 pages.	
59-94	Tobacco smoke - composition
1180-1188	Active smoking – summary of overall effects
1189-1203	Environmental tobacco smoke - composition
1409-1413	Lung cancer
1271- 1283	Breast cancer
IARC (2004b). Volume 84. *Some Drinking-water Disinfectants and Contaminants, including Arsenic.* 2004; 512 pages.	
39-267	arsenic
IARC (2005). Volume 87. *Inorganic and organic lead compounds (In preparation): see http://www-cie.iarc.fr/htdocs/announcements/vol87.htm for summary*	
	lead
IARC (1982c). Supplement No. 4. *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29).* 1982; 292 pages.	
25-27	acrylonitrile
37-38	4-aminobiphenyl
50-51	arsenic
56	benzene
71-73	cadmium
91-93	chromium VI
105-108	DDT
131-132	formaldehyde
136-138	hydrazine
149-150	lead
164-170	1-naphthylamine, 2-naphthylamine, nickel
213-215	N-phenyl-2-naphthylamine
227-233	benzo[a]pyrene, styrene
245-246	*ortho*-toluidine
260-262	vinyl chloride
IARC (1987a). Supplement No. 6. *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42.* 1987; 729 pages.	
21-23	acrolein
27-31	acrylonitrile
60-63	4-aminobiphenyl
68-76	aniline, arsenic
91-95	benzene
132-135	cadmium
168-175	chromium VI
212-215	DDT
321-324	formaldehyde
341-343	hydrazine
351-354	lead
406-414	1-naphthylamine, 2-naphthylamine
417-420	nickel
461-462	N-phenyl-2-naphthylamine
523-527	*ortho*-toluidine
566-569	vinyl chloride

Pages	Compound or topic
IARC (1987b). Supplement No. 7. *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42.* 1987; 440 pages.	
56-74	(Table of all listings for Volumes 1 - 42)
77-80	acetaldehyde, acrolein, acrylonitrile
91-92	4-aminobiphenyl
99-106	aniline arsenic
120-122	benzene
136	butadiene
139-142	cadmium
161-168	cholesterol, chromium VI
186-189	DDT
205-207	ethylene oxide
211-216	formaldehyde
223-224	hydrazine
230-232	Lead
260-269	1-naphthylamine, 2-naphthylamine, ortho-toluidine, nickel
318-319	N-phenyl-2-naphthylamine
328-329	propylene oxide
345-347	styrene
373-376	vinyl chloride
389-390	acetamide

Chapter 8. Cardiovascular Health Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and cardiovascular effects from the 1997 OEHHA report (Cal/EPA, 1997) and this update are provided below. Table 8.01 presents conclusions regarding the cardiovascular outcomes of coronary heart disease (CHD) and stroke. The conclusions in Table 8.02 relate to changes in the cardiovascular system that contribute to the outcomes in Table 8.01. These conclusions are based on a weight of evidence approach. In summary, there is evidence that exposure to ETS causes coronary heart disease and pathophysiological changes. In addition, there is evidence suggestive of an association between ETS exposure and stroke, and exercise tolerance.

Table 8.01 ETS and Cardiovascular Outcomes: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Findings: OEHHA 1997 Evidence of causal association?	Findings: Update Evidence of causal association?
CHD	18	6 (3 meta[a])	Conclusive	Conclusive
Stroke	0	3	Not assessed	Suggestive

[a]meta= meta-analyses, – not included in counts of studies. Including aortic distensibility and reactivity, intima-media thickness, lesion formation, platelet aggregation, and altered blood lipids.

Table 8.02 ETS and Acute Cardiovascular Effects: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Findings: OEHHA 1997 Evidence of causal association?	Findings: Update Evidence of causal association?
Impaired vascular and platelet function[a]	6	10[b]	Suggestive	Conclusive
Exercise tolerance	4	0	Suggestive	Suggestive

[b]Includes eight epidemiological and two animal studies

8.0. Introduction

The association between coronary heart disease (CHD) and exposure to environmental tobacco smoke (ETS) was examined in OEHHA's 1997 report (Cal EPA, 1997). The following is from the conclusion presented in that report:

> "In summary, the epidemiological 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."

This chapter reviews the relationship between cardiovascular disease and ETS exposure in light of the epidemiological studies, meta-analyses and related research published since the 1997 report. Various contributing conditions and endpoints of cardiovascular disease were measured in the studies reviewed below, including myocardial infarction (MI), ischemic stroke, coronary flow velocity reserve (CFVR), flow-mediated dilatation (FMD), aortic responsiveness and elasticity, arterial intima-media thickness (IMT), and high and low density lipoprotein-cholesterol (HDL-C, LDL-C).

ETS has been associated with a number of measurable physiological and biochemical changes in exposed individuals. These include increases in blood levels of atherogenic lipids and arterial wall thickness, decreases in aortic elasticity, endothelial responsiveness, blood levels of HDL-C and exercise endurance. It has also been associated with platelet activation and enhanced plaque growth. These effects are thought to be responsible, at least in part, for the increased risks of CHD, ischemic stroke and sudden death associated with exposure to cigarette smoke.

8.1. Description of Recent Studies

This section begins with a review of three meta-analyses relating the risks of CHD to ETS exposure in the home and/or workplace (He *et al.*, 1999; Law *et al.*, 1997; Wells, 1998c). MI is the endpoint in the subsequent three studies by Rosenlund *et al.* (2001), Ciruzzi *et al.* (1998) and Sargent *et al*. (2004), while CHD is addressed by prospective studies by Enstrom and Kabat (2003) and Whincup *et al*. (2004). The possible role of ETS exposure in stroke is addressed by Zhang *et al*. (2005), Bonita *et al*. (1999) and You *et al*. (1999). These are followed by studies of the atherogenic effects of ETS in adults (Moffatt *et al.*, 2004), children (Moskowitz *et al.*, 1999), and mice (Gairola *et al.*, 2001). A series of studies of the relationship between endothelial properties and function, and cardiovascular risk provide a theoretical mechanistic basis to explain some of the associations between ETS exposure and CHD outcomes.

8.1.1. Coronary Heart Disease – Meta-analyses

Table 8.10 Summary of Cited Studies: Coronary Heart Disease – Meta-analyses

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments
He *et al.,* 1999	Meta-analysis of 18 epidemiological studies of nonsmokers' risk of CHD from ETS 10 Cohort, 8 Case-control	 Men Women Cohort Case-control Work Home 1-19 cig/d > 20 cig/d	CHD incidence 1.22 (1.10-1.35) 1.24 (1.15-1.34) 1.21 (1.14-1.30) 1.51 (1.26-1.81) 1.11 (1.00-1.23) 1.17 (1.11-1.24) 1.23 (1.13-1.34) 1.31 (1.21-1.42)	Inconsistent confounder control. All controlled for age and sex. 6 cohort studies controlled for b.p./hypertension, weight/BMI, cholesterol or hyperlipidemia. In 10 studies with control for CHD risk factors, RR = 1.26 (1.16-1.38; p<0.001). Dose-exposure increase in risk.
Wells 1998c	Meta-analysis of workplace ETS and CHD in 8 studies 1,699 cases Appendix: Update of 1994 home exposure	Workplace Top 3 studies + next 4 + ACS All adult Tier 1 All studies Tier 1 All studies	RR for CHD 1.50 (1.12-2.01) 1.35 (1.09-1.67) 1.18 (1.04-1.34) Morbidity 1.86 (1.20-2.88) 1.49 (1.29-1.78) Mortality 1.87 (0.56-6.20) 1.23 (1.14-1.32) Both 1.28 (1.20-1.37)	Ranked studies by quality of ETS exposure data, then by control for confounders. Am. Cancer Society Study.
Law *et al*., 1997	Meta-analysis of 19 studies of ischemic heart disease in never- smokers living with vs. without smoker. N=6,600 events	Men and Women + ETS Adjusted for diet	Ischemic heart disease risk 1.30 (1.22-1.38) 1.23 (1.14-1.33)	Estimated that diet alone of nonsmokers living with smokers increased risk 6%. Thus RR adjusted for diet is 1.30/1.06 = 1.23

He et al. (1999) conducted a meta-analysis of 18 epidemiological studies (10 prospective cohort, 8 case-control) relating ETS exposure and coronary heart disease (CHD). From these studies, overall nonsmokers exposed to ETS had a pooled relative risk (RR) of CHD of 1.25 (95% CI 1.17-1.32; p<0.001) compared to nonexposed nonsmokers. The cohort studies included Hirayama, 1990; Garland *et al.,* 1985; Svendsen *et al.,* 1987; Butler, 1988 (includes two separate studies); Sandler *et al.,* 1989; Hole *et al.,* 1989; Humble *et al.,* 1990; Steenland *et al.,* 1996; and Kawachi *et al.,* 1997. The analysis by He *et al.* (1999) excluded three potentially relevant studies: Tunstall-Pedoe *et al.* (1995), because it was a cross-sectional survey; Layard (1995), as it did not provide valid data on passive smoking, and the case and control groups were not

comparable; and LeVois and Layard (1995), the results of which conflicted with a "more careful" study by Steenland *et al.* (1996) of many of the same data from the American Cancer Society Cancer Prevention Study II (ACS-CPS-II).

In the cohort studies the outcome measure was MI or death due to CHD and the pooled RR for these outcomes was 1.21 (95% CI 1.14-1.30), with mean follow-up periods ranging from 6 to 20 years. The case-control studies included four that assessed ETS exposure from spouse and/or children (Lee *et al.,* 1986; He, 1989; La Vecchia *et al.,* 1993; Ciruzzi *et al.,* 1998) and another four that also included ETS exposure from work (Jackson, 1989; Dobson *et al.,* 1991; He *et al.,* 1994; Muscat & Wynder, 1995). In the case-control studies, the pooled estimated risk (odds ratio; OR) for diagnosis of CHD was higher at 1.51 (95% CI 1.26-1.81) than in the cohort studies. The RR was similar in men, 1.22 (95% CI 1.10-1.35), and women, 1.24 (95% CI 1.15-1.34). There was no significant difference between those exposed to ETS at home (1.17; 95% CI 1.11-1.24), or in the workplace (1.11; 95% CI 1.00-1.23). A dose effect was also suggested with the pooled RR for nonsmokers exposed to 1-19 cigarettes/day of 1.23 (95% CI 1.13-1.34), increasing to 1.31 (95% CI 1.21-1.42) with exposure to ETS from >20 cigarettes/day.

The main limitation of this work is that control for confounders and effect modifiers was inconsistent across studies. Age and sex were controlled in all cohort studies, but only six controlled for blood pressure or hypertension, weight or BMI, serum cholesterol or hyperlipidemia. However, the pooled risk estimate calculated from the 10 studies, case-control and cohort, that controlled for important CHD risk factors, was not much different (1.26; 95% CI 1.16-1.38; $p<0.001$), suggesting that the effects of confounding factors were minimal. In addition, He *et al.* found that different combinations of studies, which included only peer-reviewed studies or used death or MI as the outcome measure, or which eliminated an outlier study, gave similar pooled RRs in the range of 1.24-1.26. In all cases the ETS effect was significant ($p<0.001$).

Wells, 1998c. Most studies of passive smoke exposure focus on the home environment. However, for many people, the workplace is a significant source of exposure. Wells (1998c) evaluated seven studies that addressed the pooled relative risks (RR) of CHD from workplace ETS exposure primarily on the quality of the passive smoking history (duration, intensity and frequency) and secondarily on the extent of adjustment for various confounders. The top three studies were He *et al.* (1994); Kawachi *et al.* (1997); and Butler (1988), from which Wells estimated a RR for CHD of 1.50 (95% CI 1.12-2.01) for both sexes combined. The next four studies had less extensive control for confounders, and less information on data sources (surrogates vs. direct interviews) and smoking history. Inclusion of these studies brought the RR down to 1.35 (95% CI 1.09-1.67). Inclusion of the study by Steenland *et al*. (1996), with its relatively poor workplace exposure data, brought the combined RR to 1.18 (95% CI 1.04-1.34). Even at this level, there was a statistically significant risk of CHD from workplace ETS exposure that is similar to the RRs reported for home ETS exposure, a similarity also observed by He *et al.* (1999). Thus, using the studies with better quality exposure estimates resulted in an increased RR reported for ETS exposure and CHD. This effect is reflected in the appendix to Wells' paper which included seven more-recent studies not used in the original analysis. From the combined studies, the pooled risk for CHD morbidity for all adult exposure was 1.49 (95% CI 1.29-1.78). This estimate increased to 1.86 (95% CI 1.20-2.88) when only tier 1 studies were used.

Similarly for CHD mortality, the estimate from all studies was 1.23 (95% CI 1.14-1.32), and 1.87 (95% CI 0.56-6.20) for tier 1 only studies.

The potential for confounding by diet is diminished in workplace exposure studies as coworkers are less likely to share the same dietary habits as are people living in the same household. The similarity in the RRs associated with home and work ETS exposure thus suggests that while dietary effects cannot be excluded, dietary effects alone cannot explain the excess CHD risk.

This analysis excluded LeVois and Layard's (1995) study of ACS CPS-I data due to uncertainty about the selection of subjects in favor of the "more detailed analysis" by Steenland *et al* (1996) of the ACS CPS-II data. Layard's 1995 study based on the National Mortality Followback Survey was also excluded as it contained a disproportionate number of blacks, Native Americans and young people who had died of ischemic heart disease. ETS exposure was reported by spouses or surrogates on mailed questionnaires rather than from direct interviews. With the inclusion of Layard's data, the combined RR for mortality dropped from 1.23 to 1.17 (95% CI 1.10-1.25). For combined morbidity and mortality, the risk dropped from 1.28 to 1.22 (95% CI 1.15-1.29); however it is not clear how these numbers were derived. Brown (1998) and Glantz and Parmley (1996) pointed out a number of other reasons for excluding the analysis by LeVois and Layard (1995), in favor of the analysis by Steenland *et al*. (1996) of the updated data.

Law et al. (1997) conducted a meta-analysis of 19 published studies of the risk of ischemic heart disease in never-smokers living with smokers versus with nonsmokers. Also included were five large prospective studies of active smoking and ischemic heart disease, studies of smoking and platelet aggregation, and studies relating smoking and diet. They derived a relative risk of ischemic heart disease at age 65 for ETS exposure of 1.30 (95% CI 1.22-1.38), similar to the extrapolated risk at age 65 from smoking one cigarette a day: 1.39 (95% CI 1.18-1.64). From cohort studies in which diet was evaluated, dietary differences between nonsmokers who lived with a smoker versus those who did not were estimated to account for an excess ischemic risk of 1-2%. Thus, adjusted for diet, specifically a lower consumption of fruits and vegetables in smoking households, the passive smoker's risk of developing ischemic heart disease dropped to 1.23 (95% CI 1.08-1.40). Summary estimates were similar for men and women in both cohort and case-control studies.

Platelet aggregation has been suggested as a plausible mechanism to account for the disproportionate risks of CHD associated with ETS versus active smoking. Law *et al.* (1997) reviewed data from the Caerphilly collaborative heart disease study (Elwood *et al.,* 1991) and found a linear association between the risk of ischemic heart disease and platelet aggregation. It was estimated that an increase of one standard deviation (SD) in platelet aggregation (as measured by an increase in optical density) was associated with a relative risk of 1.33 (95% CI 1.19-1.48). From another series of studies comparing platelet aggregation in non-, passive- and active-smokers, ETS exposure resulted in an increase in platelet aggregation of 1.03 SD while active smoking caused an increase of 1.25 SD. Based on the linear relationship mentioned above this translates into an associated immediate relative risk of ischemic heart disease of 1.34 (95% CI 1.19-1.50) for passive smokers and 1.43 (95% CI 1.24-1.63) for active smokers. While smoke exposure alters platelet sensitivity to aggregation-inducing or inhibiting compounds, and altered platelet aggregation is associated with an immediate risk of IHD, platelet aggregation *per se* does not appear predictive of long-term ischemic risk (Elwood *et al.,* 2001).

This meta-analysis excluded a study by Layard (1995), which found no increased risk of ETS from spousal smoking. However Layard included ever-smoking versus using only current-smoking spouses. In the larger studies, risk estimates from exposure to current-smoking spouses tend to be higher than from ever-smokers as the latter group includes ex-smokers. Based on these studies of ETS, and also on parallel observations in active smokers (Benowitz, 2003), it appears that the adverse cardiovascular impacts of tobacco smoke exposure are considerably (although not necessarily completely) reversed within a few years of cessation of exposure, so the cessation of exposure to ETS in the spouses of ex-smokers reduces their risk. These three meta-analyses analyzed substantially the same set of studies and derived similar overall statistically significant estimates of risk for CHD from ETS exposure of 1.23-1.26. Subanalyses of the studies deemed to have better confounder control and/or ascertainment of exposure resulted in higher risk estimates.

8.1.2. Coronary Heart Disease – Primary Studies

Table 8.11 Summary of Cited Studies: Coronary Heart Disease – Primary Studies

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Whincup *et al.*, 2004 Britain	Prospective study of serum cotinine and risk of CHD and stroke n = 4729	Cotinine ≤ 0.7 ng/ml 0.8-1.4 “ 1.5-2.7 “ 2.8-14.0 “ Smoker 1-9 cig/day ≤ 0.7 ng/ml 0.8-1.4 “ 1.5-2.7 “ 2.8-14.0 “ Smoker 1-9 cig/day	CHD HR all men 1.0 1.45 (1.01-2.08) 1.49 (1.03-2.14) 1.57 (1.08-2.28) Trend p = 0.001 1.66 (1.04-2.68) Never smokers 1.0 1.54 (0.88-2.69) 1.89 (1.05-3.99) 1.67 (0.91-3.07) Trend p = 0.001 2.05 (1.14-3.69)	Significant risk of CHD with increasing cotinine for all men (including former smokers). Trend still significant after elimination of former smokers. Risk of stroke not significantly associated with cotinine levels.
Chen *et al.*, 2004	Cross-sectional study of ETS and CHD based on questionnaires n = 1,854 adults	Passive by self-report	Trend with ETS Angina p < 0.01 Undiag CHD p < 0.05 Diag CHD p < 0.01	Self-report ETS exposure associated with significant trends in increasing angina, diagnosed and undiagnosed CHD. Serum cotinine not well correlated.
Sargent *et al.*, 2004	Observational case study of effect of smoking ban on AMI incidence	Public ETS During ban Other years OR difference	Average #AMI 24 40 -16 (-31.7--0.3)	AMI incidence was significantly lower during 6 month smoking ban vs. before or after.

Table 8.11 Summary of Cited Studies: Coronary Heart Disease – Primary Studies

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Enstrom and Kabat 2003	Prospective cohort study of ETS and CHD deaths in CPS-I. 35,561 never smokers	Spousal ETS ever ETS Cig/day 1-9 10-19 20 21-39 ≥ 40	CHD death 0.94 (0.85-1.05) Male CHD death 0.98 (0.78-1.24) 0.82 (0.66-1.02) 0.89 (0.70-1.13) 1.13 (0.76-1.68) 1.24 (0.70-2.19)	Suggestion of exposure-response for death by CHD in men but not women. Effect not statistically significant for either gender.
Rosenlund *et al.,* 2001 Sweden	Rated risk of MI from ETS at work and/or from spouse in 45-70 yr olds. 344 nonfatal MI, 677 pop controls	Spouse < 20 cig ≥ 20 cig wrk+spouse 0-17 hr-yr 18-41 hr-yr 42-89 hr-yr > 90 hr-yr after ETS stop > 16 yr 7-16 yr 1 - 6 yr < 1 yr	OR for MI 1.02 (0.73-1.42) 1.58 (0.97-2.56) 0.70 (0.43-1.15) 1.22 (0.80-1.88) 1.27 (0.83-1.95) 1.55 (1.02-2.34) 0.92 (0.58-1.44) 1.11 (0.70-1.74) 1.30 (0.85-1.98) 1.39 (0.91-2.10)	ETS exposure associated with MI. Risk increased with dose (# cigs) from spouse and with duration (hr-yrs) from work and spouse. Increased time since cessation of ETS exposure reduced risk. Adjusted for age, BMI, sex, SES, job strain, hypertension, diabetes, diet. Inclusion of previous smokers as never smokers may explain lack of statistical significance.
Ciruzzi *et al*., 1998 Argentina	Case-control study of home ETS and acute MI. 336 never smokers with first MI vs. 446 never smokers without.	1 relative smoked men women both	OR for AMI 1.89 (1.13-3.18) 1.54 (0.95-2.51) 1.68 (1.20-2.37)	Compared ETS of nonsmokers hospitalized for 1st MI vs. those hospitalized for non-cardiac disease.

*Abbreviations: AMI – acute myocardial infarction; BMI – body mass index; CHD – coronary heart disease; OR – odds ratio; SES – socioeconomic status.

Whincup et al. (2004) conducted a population-based prospective study of the effects of passive smoking on the risks of coronary heart disease (CHD) and stroke. Questionnaires administered at baseline in 1978-80 provided data on current and past smoking habits, alcohol intake, physical activity, and medical history. At baseline, blood pressure was recorded and blood taken for determination of total and HDL cholesterol, and serum cotinine. Cotinine levels were determined by gas-liquid chromatography with a detection limit of 0.1 ng/ml. Questionnaire data and blood analyses were available for 4,729 men. During the 20-year follow-up, all cause mortality and cardiovascular morbidity were recorded. At baseline, men who reported that they did not smoke tobacco products and who had serum cotinine levels < 14.1 ng/ml were considered current nonsmokers. Among these, those who reported never smoking tobacco products were

considered lifelong non-smokers. Light active smokers were those reporting smoking 1-9 cigarettes per day irrespective of cotinine levels. Smoking habits were assessed again at five and twelve years after baseline by postal questionnaire.

Cox proportional hazard models were used to assess the association between serum cotinine and cardiovascular disease risk. The relative hazard estimates were stratified by town of residence and adjusted for age, BMI, height, systolic and diastolic blood pressure, serum total and HDL cholesterol, white cell count, FEV_1, triglyceride levels, physical activity, alcohol intake, social class, diabetes, pre-existing CHD, and cigarette smoking history. As shown in Table 8.12, among all participants, cotinine levels were significantly associated with CHD risk. These risk estimates were only slightly affected by adjustment for the risk factors listed above compared to adjustment for age alone. There was also a significant dose-response association between increasing cotinine levels and increasing risk of CHD. After exclusion of former smokers, risk estimates were still elevated, but with wider confidence intervals; in two of the four categories the effect was not statistically significant. There was no statistically significant association between cotinine levels and incidence of stroke.

Table 8.12 Serum Cotinine and Cardiovascular Disease Risk (hazard ratio) (Whincup *et al.*, 2004)

	Cotinine (ng/ml) HR (95% CI)				**Smokers**	**Trend**
CHD	≤ 0.7	0.8-1.4	1.5-2.7	2.8-14.0	1-9/day	P
All men[a]	1.0	1.50 (1.06-2.12)	1.56 (1.11-2.20)	1.61 (1.15-2.27)	1.65 (1.08-2.54)	0.001
All men[b]	1.0	1.45 (1.01-2.08)	1.49 (1.03-2.14)	1.57 (1.08-2.28)	1.66 (1.04-2.68)	0.001
No former smokers[a]	1.0	1.32 (0.78-2.25)	1.44 (0.83-2.50)	1.55 (0.90-2.69)	1.17 (1.07-2.96)	0.006
No former smokers[b]	1.0	1.54 (0.88-2.69)	1.89 (1.05-3.99)	1.67 (0.91-3.07)	2.05 (1.14-3.69)	0.001
Stroke						
All men[a]	1.0	0.76 (0.44-1.31)	0.83 (0.50-1.40)	0.87 (0.52-1.47)	1.48 (0.81-2.69)	0.73
All men[b]	1.0	0.83 (0.46-1.47)	0.94 (0.54-1.64)	0.77 (0.42-1.41)	1.45 (0.71-2.96)	0.99
No former smokers[a]	1.0	1.01 (0.43-2.35)	0.66 (0.25-1.78)	1.25 (0.54-2.89)	1.95 (0.90-4.22)	0.52
No former smokers[b]	1.0	1.34 (0.53-3.40)	1.39 (0.48-4.04)	2.16 (0.80-5.80)	2.69 (1.07-6.75)	0.11

[a] Stratified by town and adjusted for age. [b] Stratified by town and adjusted for all covariates.

Risk estimates were calculated for consecutive five-year intervals of the follow-up. As shown in Table 8.13, there appears to be an attenuation of CHD risk over time. Since cotinine levels were only determined for baseline, it is uncertain what the true ETS exposures were after baseline. It is likely that this decline is in part a reflection of the general decline in smoking in Britain during the follow-up period. This suggests that basing risk estimates on the baseline ETS exposures may underestimate the risk if subsequent exposures are lower.

Table 8.13 Change in CHD Risk Over Study Period (Whincup *et al.*, 2004)

	Follow-up Period (years) HR (95% CI)			
Exposure	**0-4**	**5-9**	**10-14**	**15-20**
Passive	3.73 (1.32-10.58)	1.95 (1.09-3.48)	1.13 (0.63-2.04)	1.04 (0.62-1.76)
Active	3.32 (0.87-12.64)	1.66 (0.66-4.18)	1.71 (0.71-4.10)	1.34 (1.23-1.47)

The follow-up questionnaires at five and twelve years indicated that non-smokers at baseline continued to report a non-smoking status. When former smokers were excluded from the analysis, the risk estimates, while still elevated, included no effect. This is likely due in part to the reduced size of the remaining group. It may also reflect a residual higher risk for CHD among former smokers versus never-smokers, a risk possibly exacerbated by ETS exposure. Overall, this study supports a significant association between ETS exposure and CHD.

Chen et al., 2004. In this cross-sectional study, data from the Scottish MONICA surveys in 1986, 1989, 1992, and 1995 were analyzed to determine whether prevalent heart disease (CHD) was independently associated with ETS exposure as measured by self-report, serum cotinine, and the two measures combined. Data on sociodemographics, personal health, diet and exposure to tobacco smoke were collected by questionnaire for 1,854 subjects. Electrocardiograms (ECG) and blood samples for cotinine levels and other biochemical assays were collected during clinical examinations. The study examined the effects in nonsmokers defined by self-report and serum cotinine levels below 17.50 ng/ml. Probable angina and undiagnosed CHD were apparently determined from responses to the questionnaires.

The prevalence of angina showed a dose-response with increasing self-reported exposure to ETS (p for trend < 0.01). The 300 cases of undiagnosed CHD further showed a dose-response relationship with ETS exposure (p for trend < 0.05) with a significant OR only at the highest exposure level (1.6, 95% CI 1.0-2.5). When all CHD categories (angina, undiagnosed CHD and diagnosed CHD) were combined, there was a significant dose-response trend ($p < 0.01$). However, serum cotinine did not completely corroborate self-report. For example, there was a higher prevalence of angina, undiagnosed CHD and all CHD in subjects with no detectable cotinine compared to those with cotinine levels >0-1.05 ng/ml. (However, the prevalence of diagnosed CHD was lowest in the group with no detectable cotinine.) This unexpected result may reflect active avoidance of ETS exposure by individuals who are aware of their CHD condition. Alternatively, since the lower limit of detection of the assay for cotinine was not specified, a lack of sensitivity in the assay may have limited the ability to associate cotinine levels with CHD outcomes. The serum cotinine level of 17.50 ng/ml used to distinguish active from passive smokers is higher than in most other studies, so some light active smokers may have been included in the nonsmoking group. Among those with detectable cotinine, there was a dose-response in the categories of questionnaire angina, undiagnosed CHD, and all CHD.

Given the apparent limitations of the cotinine assay and the high cotinine level used to separate nonsmokers from smokers, the results of this study are viewed as suggestive of an association between ETS exposure and CHD.

Sargent et al. (2004) studied the effects of a six-month smoke-free policy in public and work places on the incidence of hospital admissions for acute myocardial infarction (AMI) in Helena, Montana. Data on AMI were derived from discharge records of the only hospital that provided

cardiology services to Helena and the surrounding area. Diagnoses were made or confirmed by physicians blinded to the study, and included both primary and secondary diagnoses of AMI. Overall, 304 cases were included. Admissions during the six months the ban was in effect were compared with those during the same six months of the previous and following years, and from within versus outside of Helena, where the smoking ban was not in force.

During the ban, the number of admissions for AMI compared to the previous and subsequent years was significantly lower (24 vs. an average of 40). At the same time, there was a non-significant increase in the number of admissions from outside the area of the ban (18 vs. an average of 12.4). Admissions from within the area of the smoking ban were thus significantly lower than from the area without the ban.

Table 8.14 Effect on Admissions for Acute Myocardial Infarction (Sargent *et al.*, 2004)

	Helena	**Outside Helena**
Ban year (2002)	24	18
Other years (average)	40	12.4
Difference (95% CI)	-16 (-31.7--0.3)	5.6 (-5.2-16.4)
Difference Helena vs. outside	-21.6 (-40.6--2.6)	

The implementation of this ban created a geographically and temporally isolated experiment on the effects of smoke exposure on cardiovascular disease, the results of which indicate a significant adverse effect. However the study population was small and the number of AMI cases correspondingly low thus limiting the statistical power of the study and the ability to generalize the results. In addition, the non-randomized nature of the study leaves open the possibility of undetected systematic bias or confounding. Of the AMI cases, 38% were current smokers, 29% were former-smokers, and 33% were never-smokers. Thus it is not clear what proportion of the decrease in AMI admissions represents decreased smoking among active smokers versus curtailment of passive exposure among non-smokers. However, it does appear that cessation of smoke exposure had a positive effect on cardiovascular health.

Enstrom and Kabat (2003) examined ETS exposure and long-term mortality from CHD, lung cancer and chronic obstructive pulmonary disease (COPD) in a prospective cohort study of adult Californians enrolled in 1959 in the American Cancer Society's Cancer Prevention Study (CPS-I). Never smokers married to current or former smokers were compared to never smokers married to never smokers, with the former group subdivided based on the smoking status of the spouse (1-9, 10-19, 20, 21-39, ≥ 40 cigarettes per day). Former smokers were considered in a separate category. The relative risk of death was calculated as a function of the spouse's smoking status and adjusted for age and seven potential confounders at baseline: race, education, exercise, BMI, urbanization, fruit or fruit juice intake, and health status (good, fair, poor, sick).

For CHD among males, there was a suggestion of an exposure response based on ETS from increasing numbers of cigarettes smoked per day by the spouse but the confidence intervals included no effect (Table 8.11). Among women there was no evidence of an effect of spousal smoking as the reported risks were generally below unity.

There are several concerns with this study which are described in the review of Enstrom and Kabat in Section 7.3.2.1. There is potential misclassification of smoke exposure due to the high prevalence of cigarette smoking and thus extensive ETS exposure regardless of spousal smoking status at the start of CPS-I. Defining ETS exposure based solely on spousal smoking during the first third of the study period seriously biases the results towards the null. As a result, the control group, defined as non-ETS-exposed based on the absence of spousal smoking, would include individuals with extensive ETS exposure outside the home, at work and elsewhere.

Analyses were adjusted for the factors listed above at baseline; while exercise, weight, height, and fruit intake reportedly changed little over time, changes in health status or in other lifestyle factors that could affect survival were not included in the adjustment. There was, for example, a large increase between 1959 and 1999 in the proportion of the population using vitamin pills (38.3% and 81.2%, respectively) that may have mitigated the effects of smoke exposure. Finally, the category of current smokers may include intermittent smokers and those who started smoking relatively recently, potentially leading to wide variations in the duration of ETS exposure among never smokers, and a dilution of effects. Thus, while this study does not appear to support a causal role for ETS in CHD mortality, the problems noted above lead to difficulty in interpretation of the results.

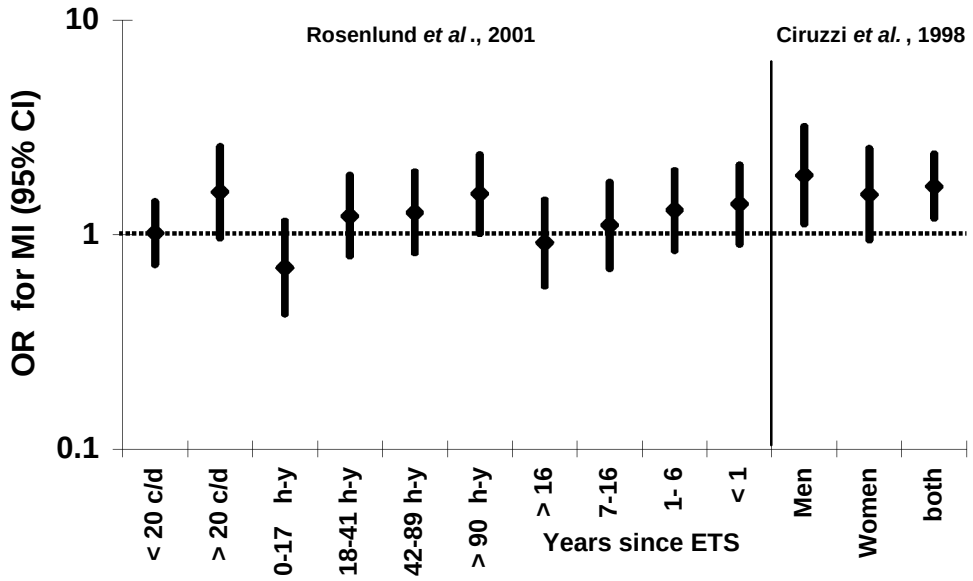
Rosenlund et al. (2001) evaluated the risk of myocardial infarction (MI) associated with ETS exposure at work and/or from spousal smoking among participants in the Stockholm Heart Epidemiology Program (SHEEP). Data from 334 non-fatal never-smoking MI cases and 677 population controls ages 45-70 yrs (average 62.6 ± 6.6 yrs) in Sweden were collected by postal questionnaire and telephone follow-up. The collected data included ETS exposure, age, gender, body mass index (BMI), socioeconomic status, job strain, hypertension, diet and diabetes. The odds ratios (OR) for MI after adjustment for these factors (sexes combined) showed an exposure-response relationship with the number of cigarettes smoked by the spouse. The risk of MI from combined ETS exposure from work and spouse, expressed in hour-years, also showed an exposure-response relationship. (1 hour-year = 365 hrs or the equivalent exposure duration of one hr/d for one year.) In addition, there was a higher risk from recent exposure, which decreased with increasing years since last exposure at home or work (Fig. 8.01).

Except at the highest exposure duration, the confidence intervals reported include no effect. However, this study defined never smokers as "…subjects who had never smoked regularly for at least a year…". As a result, the control group may have included previous smokers and people who smoke intermittently, the inclusion of whom might tend to diminish any apparent effects due to ETS exposure and make the OR estimates artificially low.

The participation rate in the SHEEP study was relatively high (≥ 70%) thus minimizing bias due to nonparticipation and differential reporting. Exposure misclassification is also expected to be minor based on data from population validation studies of reported smoking that indicate about 5% misclassification of ever-smokers in the never-smoking category, mainly of light or long-term ex-smokers. The misclassification rate was even lower in case-control studies in which 1.25% of "never-smokers" were reported by next of kin to be former regular smokers (Nyberg et *al.,* 1997; 1998b). In the Rosenlund *et al.* study, recall bias on the part of proxies was further minimized by excluding fatal MI cases.

It has been argued that the association between ETS exposure and CHD may be explained by differences in the diets of smoking versus nonsmoking families (Forastiere *et al.,* 2000). To address this concern, Rosenlund *et al.* (2001) adjusted for dietary intake of fat and fiber. This adjustment reportedly did not affect the results. Similarly, dietary cholesterol and blood lipids were considered and reportedly had little or no effect on the analysis.

Figure 8.01 Two Studies of the Risk of Myocardial Infarction in Relation to ETS Exposure



Ciruzzi et al. (1998) conducted a case-control study in Argentina from 1991-1994 of the association between exposure to ETS in the home and the risk of acute myocardial infarction (AMI). Cases included 336 never-smokers (median age 66) admitted to hospitals for first episodes of AMI. Those with a history of ischemic heart disease, valvular disease, cardiomyopathy or cardiac surgery were excluded. Controls comprised 446 never-smokers, with a median age of 65, admitted to the same hospitals for acute conditions unrelated to known or suspected risk factors for AMI. Data were collected during interviews on age, gender, education, diet, alcohol and coffee consumption, socioeconomic status, BMI, presence of diabetes and hypertension, family history of MI, and smoking habits of spouse and children. Serum cholesterol was determined following hospital admission. Odds ratios were calculated for AMI from multiple logistic regression analyses adjusted for these factors. For men, the OR for AMI when at least one person in the household smoked was 1.89 (95% CI 1.13-3.18), for women 1.54 (95% CI 0.95-2.51), and for both sexes, 1.68 (95% CI 1.20-2.37) (Fig. 8.01). For women, an exposure-response trend with spousal smoking was suggested. An OR of 0.90 (95% CI 0.28-2.86) for spousal smoking of 1-20 cigarettes per day increased to 3.31 (95% CI 0.77-14.17) at >20 cigarettes per day.

The participation rate was high (96%) with good comparability of the recruitment areas for cases and controls. However, while the median ages of both groups were similar, a higher percentage of the cases was over 75 years of age compared to the control group (28.6% vs. 17.7%), which

may have exaggerated the ETS effect. Since the cases and controls for this study were admitted to hospitals for AMI or other conditions, the applicability of these results to an otherwise healthy population may be limited. Indeed, the authors found evidence that interaction between ETS exposure and chronic conditions may influence risk for CHD and AMI. The OR for AMI when at least one relative smoked rose from 1.51 (95% CI 1.04-2.19) in the absence of diabetes, to 5.26 (95% CI 2.44-11.36) in its presence. Similarly, hypertension increased the OR associated with ETS from 1.65 (95% CI 1.03-2.65) to 3.28 (95% CI 2.02-5.34), while with hypercholesterolemia the OR went from 1.60 (95% CI 1.08-2.34) to 4.01 (95% CI 2.17-7.40). A family history of MI was found to enhance the ETS effect with ORs increasing from 1.71 (95% CI 1.16-2.53) to 4.08 (95% CI 2.16-7.70). This study thus suggests that individuals with other risk factors for AMI may be especially susceptible to the effects of ETS exposure.

8.1.3. Stroke

Few studies address the possible association of passive smoking with stroke. The three studies described below all demonstrated significant elevations in risk of stroke and two of the studies provide evidence for a dose-response. In addition, one of the studies demonstrated a stronger odds ratio for stroke in active smokers when passive smokers are removed from the referent group. Taken together these studies provide evidence suggesting a role for ETS in stroke. Limitations in the studies are described below. Further investigation is warranted to clearly elucidate the role of ETS exposure in stroke.

Table 8.15 Summary of Cited Studies: Stroke

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Zhang *et al*., 2005 China	Population-based cross-sectional study of stroke in women with spousal ETS. n = 22,982	Amount 1-9 cig/d 10-19 cig/d ≥ 20 cig/d Duration ≤ 17 yrs > 17 yrs Pack-years ≤ 13 pk-yrs > 13 pk-yrs	Stroke OR 1.28 (0.92-1.77) 1.32 (1.01-1.72) 1.62 (1.28-2.05) trend p=0.0002 1.13 (0.70-1.82) 1.47 (1.22-1.78) trend p=0.0004 1.12 (0.82-1.54) 1.55 (1.27-1.90) trend p<0.0001	Adjusted for age, education, SES, alcohol, BMI, medical history, menopausal status. Significant risk and dose response trends. Study limited to women 40-70 yrs old.
Bonita *et al.,* 1999 New Zealand	Population-based, case-control study of stroke vs. smoking status. Stroke: men 279, women 242. Ctrl: 1,851. 35-74 yr.	Status: Non (ns) Men ns Women ns Smoker vs. ns +/-ETS ns-ETS	Stroke OR 1.82 (1.34-2.49) 2.10 (1.33-3.32) 1.66 (1.07-2.57) 4.14 (3.04-5.63) 6.33 (4.50-8.91)	Adjusted for age, sex, heart disease, hypertension (not diet). Source of ETS not delineated. Higher OR for stroke in men. Exclusion of ETS-exposed non-smokers (ns) in reference group increases smokers' OR.
You *et al*., 1999 Australia	Case-control study of ischemic stroke in ex, never, current smokers living with vs. without smoker n = 452	Spouse: Ever 1-20 cig/d ≥ 20 cig/d Ever 1-20 cig/d ≥ 20 cig/d	OR: NS group 1.70 (0.98-2.92) 1.55 (0.83-2.88) 1.91 (0.94-3.88) Whole group 2.03 (1.33-3.10) 1.72 (1.07-2.77) 2.59 (1.51-4.47)	452 cases of first time ischemic stroke vs. age-, sex-matched ctrl. Incl. current, ex, never smokers, parental & spousal exposure. Adjusted for smoking status, heart disease, hypertension, diabetes, education.

Zhang et al. (2005) examined the prevalence of stroke among non-smoking Chinese women exposed to spousal smoking. This cross-sectional study used baseline data from The Shanghai Women's Health Study, a population-based cohort study in China. Data on demographics, lifestyle, medical history, and husband's smoking habits were collected by structured interview on 60,377 women, 40-70 years of age. Multivariate analyses were adjusted for age, education, occupation, income, alcohol consumption, BMI, exercise, menopausal status, diabetes, hormone therapy and medication use. No distinction was made between ischemic and hemorrhagic stroke.

As seen in Table 8.16, the adjusted OR for stroke was elevated by ETS exposure, significantly so with higher or longer exposures. There were also significant exposure-response trends for both degree and duration of exposure (Fig. 8.02).

Table 8.16 Spousal ETS and Stroke Risk (Zhang *et al*., 2005)

Exposure	Cases/total	OR (95% CI)	P for trend
Cigarettes/day			
1-9	46/6,736	1.28 (0.92-1.77)	
10-19	77/11,233	1.32 (1.01-1.72	
≥ 20	116/14,316	1.62 (1.28-2.05	0.0002
Duration (yrs)			
≤ 17	25/16,245	1.13 (0.70-1.82)	
> 17	214/16,042	1.47 (1.22-1.78)	0.0004
Pack-years			
≤ 13	54/16,512	1.12 (0.82-1.54)	
> 13	185/15,772	1.55 (1.27-1.90)	<0.0001

Exposure was based on living with a smoking husband and so missed other sources of ETS exposure. In addition, the exposure assessment was only made at baseline and so does not reflect any subsequent changes in smoking habits. These two effects would be expected to lead to an underestimate of the association with passive smoking. In addition to being population-based, this study had the advantages of large sample size and high participation rate (92.7%). The elevated risk estimates and dose-response trends indicate a significant association between exposure to ETS and stroke in women.

Bonita et al. (1999) conducted a population-based case-control study of smoking status versus stroke incidence in first-time stroke victims (279 men, 242 women) compared with 1,851 controls. Cases were taken from the Auckland stroke study, which documented stroke events among the Auckland population in 1991-1992. Trained nurse interviewers administered questionnaires to the stroke victims, or to next-of-kin if the patient had died, to assess age, gender, history of smoke exposure, heart disease, hypertension and diabetes. The risks for stroke among active smokers were derived from comparisons with never-smokers with and without ETS exposure and with never-smokers with no ETS exposure. Active smokers were separated into three groups for analysis based on the number of cigarettes smoked per day (≤ 5, 6-14, ≥ 15). Ex-smokers were included and grouped according to the time elapsed since quitting (< 2, 2-10, >10 yrs). A person was classified as ETS-exposed if a household member had regularly smoked cigarettes in their presence or if a co-worker smoked in their presence for more than one year during the prior ten years.

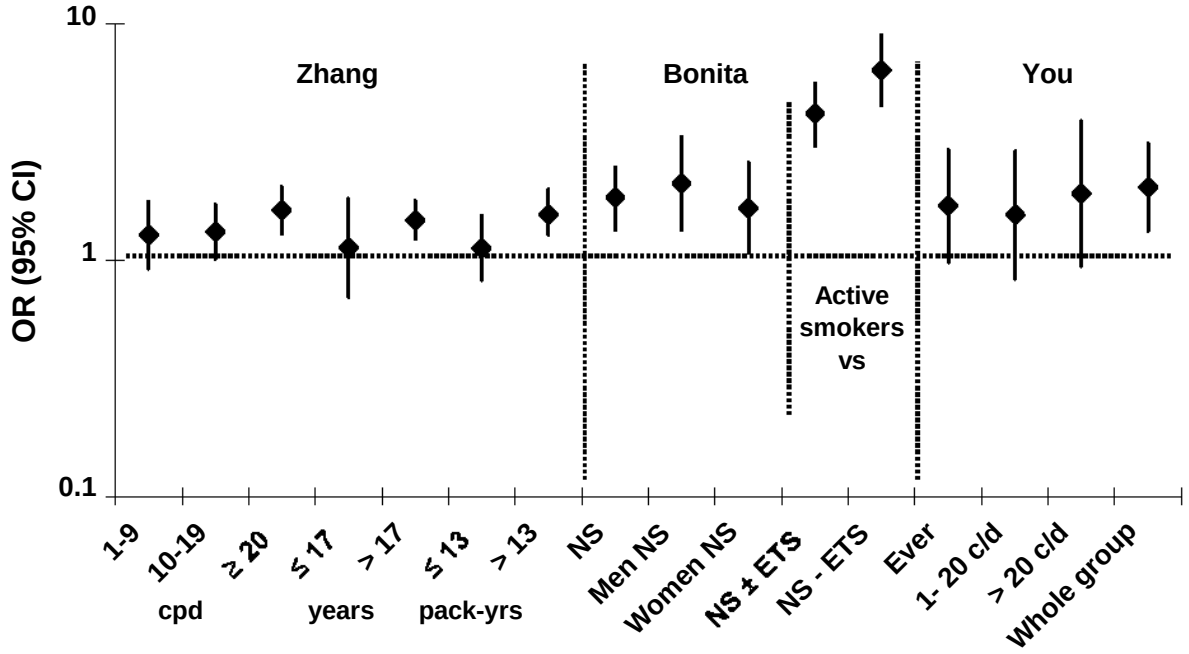
After adjustment for heart disease, hypertension, diabetes, age and sex, ETS exposure among never-smokers was associated with an elevated risk of stroke (OR 1.82; 95% CI 1.34-2.49), which was higher in men (OR 2.10; 95% CI 1.33-3.32) than in women (OR 1.66; 95% CI 1.07-2.57). Compared to all nonsmokers, the risk of stroke for active smokers was high (OR 4.14; 95% CI 3.04-5.63). More importantly, when the reference group included only nonsmokers with no ETS exposure, the OR for stroke among active smokers increased to 6.33 (95% CI 4.50-8.91).

This additionally supports an ETS effect in stroke and underscores the importance of reference group selection (Fig. 8.02).

One of the strengths of this study is that all strokes in the Auckland population, fatal and nonfatal, were identified, though there was no differentiation of stroke type or severity in the analysis. The decision to include all nonfatal and fatal cases is important, as passive smoke exposure may be associated with strokes of varying severity from mild to fatal. On the other hand, it limits the study's ability to discern whether ETS exposure is associated with stroke severity.

Limitations of this study include the lack of control for diet. Reporting bias may have resulted from the fact that cases and controls were interviewed in separate years, allowing for exposure to other factors in the intervening time. Also controls were interviewed directly while data for some cases were obtained from a caregiver or next-of-kin. Data on education and socioeconomic status were not included, as 60% of the patients with acute stroke were past retirement age (65-74 yrs). The authors attempted to reduce confounding due to socioeconomic factors by excluding Maoris and Pacific Islanders who tend to be of lower socioeconomic status, and have higher smoking and stroke rates than those of European descent. There may have been incomplete control for age in this study since more than half the cases, but only about half of the controls were 55 and older. The reliability of self-reported ETS exposure was not verified biochemically, so it is possible that stroke victims and healthy controls reported smoking consumption differently. To mitigate this potential bias, questions regarding smoke exposure were embedded among a large number of other questions.

Figure 8.02 Three Studies of the Risk of Stroke and ETS Exposure



You et al. (1999) conducted a case-control study in Australia of ischemic stroke in 452 never, former, and current smokers living with smokers compared with a similar number of age and sex-matched neighborhood controls not exposed to ETS. The study group was 59.5% male with a mean age of 59 (SD ± 14.8) years. Parental and spousal smoking were examined but the former had no effect on stroke risk. Among never-smokers exposed to spousal ETS, the odds ratios adjusted for age, gender, hypertension, ischemic heart disease, diabetes, personal smoking and education, were elevated and suggested an exposure-response, but the 95% CIs included unity, consistent with an estimate of no increased risk. However, since ETS exposure was only assessed as exposure to a smoking spouse, the reference group likely included individuals with ETS exposure from other sources, thus weakening the apparent association. On the other hand, the risk for ischemic stroke from spousal smoking for the entire group, including smokers as well as nonsmokers, was significantly elevated with an adjusted OR of 2.03 (95% CI 1.33-3.10) (Fig 8.02). This suggests that smokers may also be susceptible to ETS. Indeed, when the data for active smokers were stratified according to smoking by the spouse, the OR for stroke for active smokers exposed to spouse's ETS was 1.91 (95% CI 0.90-4.04) (data not plotted).

Because this was a hospital-based study, selection bias is a concern, especially since the controls were recruited from the community rather than from the hospital. In addition, recruitment occurred in two phases, from 1985 to 1988, and from 1988 to 1992. The latter group contained patients ≤ 55 years of age. Recognizing these weaknesses, the authors suggest that these results, although indicating an association between ETS and stroke, should be regarded as hypothesis generating.

8.1.4. Impaired Vascular Function and Other Pathophysiological Effects in Humans

Studies examining the pathophysiological effects of ETS exposure on the vascular system and blood in humans are described below. The changes described lead to chronic heart disease and can precipitate or aggravate an acute event (e.g., myocardial infarction).

Table 8.17a Summary of Cited Studies: Vascular Pathophysiological Effects- Humans.

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Mack *et al.,* 2003	Cross-sectional study of passive smoking and arterial stiffness n = 227 adults	Passive BMI >27.1 Age ≥ 55 IMT > 0.707 BMI >27.1 IMT > 0.707	Stiffness increase w/#ETS sources trend p = 0.048 trend p = 0.09 trend p = 0.05 w/ hours of ETS trend p = 0.04 trend p = 0.04	Significant trends of increasing arterial stiffness with number of sources and number of hours of ETS exposure among persons with high BMI, larger IMT, and older age.

Table 8.17a Summary of Cited Studies: Vascular Pathophysiological Effects- Humans.

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Otsuka *et al.,* 2001 Japan	Measured CFVR (coronary flow velocity reserve) by Doppler echocardiography in active and passive smokers before and after 30 min passive smoke.	Nonsmokers Smokers Nonsmokers Smokers	Mean CFVR Before ETS 4.4 ± 0.91 3.6 ± 0.88 p = 0.02 After 30 min ETS 3.4 ± 0.73 p < 0.001 3.3 ± 0.74 p = 0.83	Passive smoke sig. reduced CFVR in nonsmokers and to same level as in active smokers. No significant differences between groups in age, heart rate, b.p., cholesterol, triglycerides and HDL. 15 smokers, 15 non-smokers, men, 27± 4 yrs
Pope *et al*., 2001	Measure heart rate variability (HRV) with ETS.16 adults.	2 hr ETS in smoking room	SDNN negatively correlated with ETS ($p < 0.05$)	Short exposure to ETS decreased HRV, a risk factor for chronic heart disease.
Woo *et al.,* 2000 China Australia	Tested vascular reactivity of brachial arteries by ultrasound in 20 casino workers exposed to ETS >8 hr/d, 6 d/wk, 9.2 ± 6.1 yr vs. 20 Ctrls	Controls Workers Mean diff	Flow-mediated dilatation (FMD) 10.6 ± 2.3% 6.6 ± 3.4% 4% CI 3-5.4% p < 0.001	Gender and age matched. BP, medical history, BMI, lipid and cholesterol levels (HDL, LDL). Passive smoking strongest predictor of impaired FMD $R^2 = 0.75$, $F = 6.1$, $p = 0.0001$
Raitakari *et al*., 1999 Australia	Cross-sectional study of effects of current and past ETS on flow-mediated dilation (FMD) in 3 x 20 adults 15-39 yr	Status: Never Past ETS ETS	FMD (%) 8.9 ± 3.2 5.1 ± 4.1 p < 0.01 2.3 ± 2.1 p < 0.01	ETS exposure decreased FMD (p<0.001). Quitting ETS improved FMD vs. current ETS (p<0.01) but still worse than never ETS (p<0.01). Control for bp, dyslipidemia, heart disease, diabetes, age and sex. No gender differences.
Stefanadis *et al*., 1998	Measured aortic distensibility in men during cardiac catheterization for chest pain	Smokers: 16 passive 16 active 16 sham	Decrease in distensibility 21% p<0.001 27% p<0.001 0	5 min smoke exposure caused significant reduction in aortic elasticity in both passive and active smokers vs. sham. Recovery seen in passive group 15 min after cessation.

Table 8.17a Summary of Cited Studies: Vascular Pathophysiological Effects- Humans.

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Sumida *et al*., 1998	Measured diameters of coronary arteries after ACh by angiography in women hospitalized for atypical chest pain. 11 never smokers 8 active smokers 19 ETS exposed	Status: Never Active ETS Never Active ETS	% diameter change Distal LAD 13.7 ± 3.4 p<0.05 -27.2 ± 6.0 p<0.01 -22.3 ± 4.1 p<0.01 Distal LCX 9.7 ± 3.4 p<0.05 -22.4 ± 4.0 p<0.01 -17.3 ± 2.9 p<0.01	ACh caused dilation of distal segments of left descending and left circumflex arteries in never smokers but constriction in ETS and active smokers. In all groups, NTG increased diameter. Suggests active and passive smoke exposure damages endothelium.
Howard *et al.,* 1998 U.S.	Longitudinal study of current, past and passive smokers and change in Intima-Media Thickness (IMT) over 3 yrs. n = 10,914 adults	Smokers: never-ETS never + ETS Past – ETS Past + ETS Current	Progression rate 25.9 ± 2.1 µm/3 yr 31.6 ± 2.0 “ 32.8 ± 2.7 “ 38.8 ± 2.3 “ 43.0 ± 1.9 “	After adjusting for cardiovascular risk factors, lifestyle and demographics, ETS increased progression by 5.9 µm/3yr. No relationship between IMT progression and number of hours exposed.

*Abbreviations: ACh – acetylcholine; AMI – acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilatation; IMT – intima-media thickness; LAD – left anterior descending artery; LCX – left circumflex artery; MI – myocardial infarction; NTG – nitroglycerin; OR – odds ratio; SDNN – standard deviation of normal-to-normal beast interval; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke

Mack et al. 2003. The effects of ETS exposure on arterial stiffness were evaluated in 227 adult nonsmokers participating in the Vitamin E Atherosclerosis Prevention Study. Intima-media thickness (IMT) and maximum and minimum arterial diameters of the common carotid artery were obtained by B-mode ultrasonography. The percentage change in carotid arterial diameter between maximum and minimum dilation was used to calculate the carotid stiffness index beta. Exposures to passive smoking at home, work, and other sites were ascertained by questionnaire. Home ETS exposures were quantified by number of smokers and number and number of hours per day of exposure to each smoker's smoking, while exposures at work and other places were recorded as the number of hours of exposure per day. Other measures collected included BMI, total, LDL and HDL cholesterol, total triglycerides, and serum glucose. Subjects exposed to ETS from any source were, on average, significantly older than those not exposed.

Increasing values of age, BMI, IMT, and glucose were significantly associated with increased beta (β), the carotid stiffness index. After adjusting for age, BMI and IMT, the value of β among females increased as the number of ETS sources increased, but not significantly (p for trend = 0.07). There was no evidence of an association in males (p for trend = 0.10). However, when the data were stratified by BMI, β increased with the number of ETS exposures for individuals with BMI >27.1 kg/m^2 (p for trend = 0.048) but not in those with lower BMIs. Similarly, when

stratified by age (≥ 55 years), or IMT (≥ 0.707 mm), the trends for increasing β with increasing numbers of ETS sources had *p* values of 0.09 and 0.05, respectively. In contrast to the analysis by number of ETS sources, the carotid stiffness index was not associated with hours of ETS exposure in either gender. However, after stratification by BMI >27.1 kg/m^2 or IMT ≥ 0.707 mm, there were significant associations between increasing hours of ETS exposure and arterial stiffness (p for each trend = 0.04).

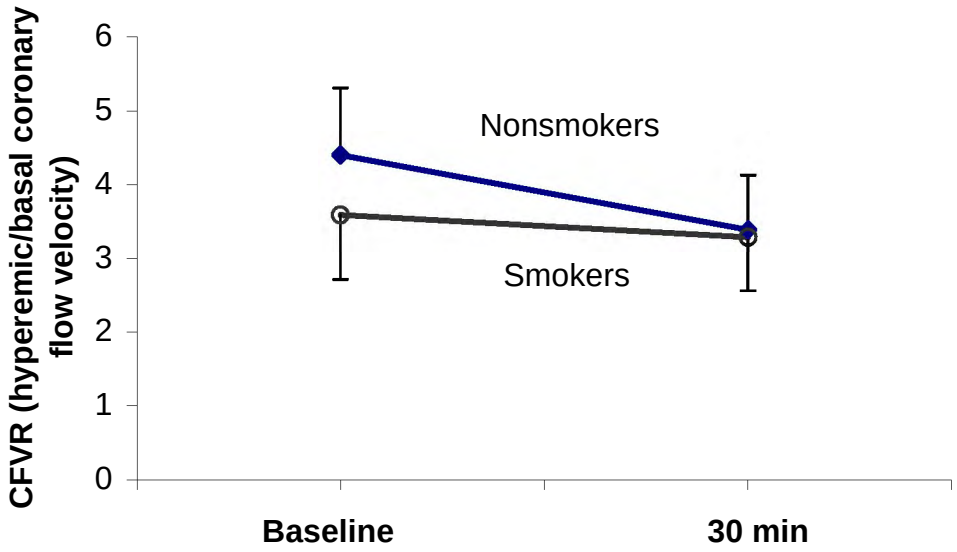
This study was limited by its small size and crude measures of ETS exposure intensity. The results of this study are thus taken to be suggestive that individuals with elevated BMI and IMT values are at greater risk of increased arterial stiffness with chronic ETS exposure. Put another way, individuals with elevated values of BMI and/or IMT have a predisposition to CHD that is exacerbated by ETS exposure.

Otsuka et al., 2001. As a gauge of endothelial function in coronary circulation, coronary flow velocity reserve (CFVR) was measured with transthoracic Doppler echocardiography of the left anterior descending coronary artery. Unlike flow mediated dilatation (see below), which is a measure of endothelial function typically made in brachial arteries, CFVR was based on echocardiographic imaging of coronary arteries to provide an integrated measure of both coronary vascular endothelial function and smooth muscle relaxation. Narrowing of the coronary arteries, or stenosis, was reported by Claeys *et al.* (1996) to be the main determinant of CFVR in patients with myocardial infarction (MI), while Hozumi *et al* (1998) found a CFVR < 2 to be a highly sensitive (92%) and specific (86%) predictor of significant stenosis in the left anterior descending coronary artery. For patients with angina, a CFVR of < 2 was a significant predictor of cardiac events (MI, death, or coronary revascularization) in the year following testing (Chamuleau *et al.*, 2002). Thus decreases in CFVR reflect impaired function in the large epicardial arteries and decreased microcirculation, resulting in a diminished ability of the heart to respond to physiological demands. In the study by Otsuka *et al.*, CFVR was calculated as the ratio of hyperemic velocity (induced by ATP infusion) to basal coronary flow velocity, and reflects the capacity of the arteries to accommodate increased blood flow. Measurements were made in 15 active smoking and 15 nonsmoking males (mean age 27 ± 4 yr) before and after 30 min passive smoke exposure. Smoke exposure occurred in a smoking room with mean CO levels of 6.02 ppm. Carboxyhemoglobin (COHb) levels were measured before and after exposure. During exposure, mean COHb levels (± SD) in nonsmokers rose from 0.40 ± 0.21% to 1.57 ± 0.32%. COHb levels in active smokers before and after exposure were 2.49 ± 1.78% and 2.67 ± 1.79%, respectively. Prior to passive smoke exposure, mean CFVR was significantly higher in non-smokers vs. active smokers (4.4 ± 0.91 vs. 3.6 ± 0.88, p = 0.02), suggesting compromised endothelial function in the latter group. However, after exposure CFVR was not different between nonsmokers and active smokers (p = 0.83). This result may, in part, be due to small sample size. Passive smoking significantly reduced CFVR in nonsmokers (4.4 ± 0.91 to 3.4 ± 0.73, p<0.001) but not in smokers (3.6 ± 0.91 to 3.3 ± 0.74); in both cases there was no change in heart rate or blood pressure (Fig. 8.03). These data suggest that even a single transient exposure to passive smoke may compromise coronary artery function. No significant differences were seen between groups for age, heart rate, blood pressure, total cholesterol, triglycerides and HDL levels.

The design of the study by Otsuka *et al.* did not allow for an assessment of the long-term effects of passive smoke on CFVR nor a determination of the duration of the effects after exposure

cessation. Nevertheless, these results suggest that among healthy young adults, ETS exposure may cause endothelial dysfunction of the coronary circulation, an early step in the development of atherosclerosis.

Figure 8.03 Coronary Flow Velocity Reserve after 30 min ETS



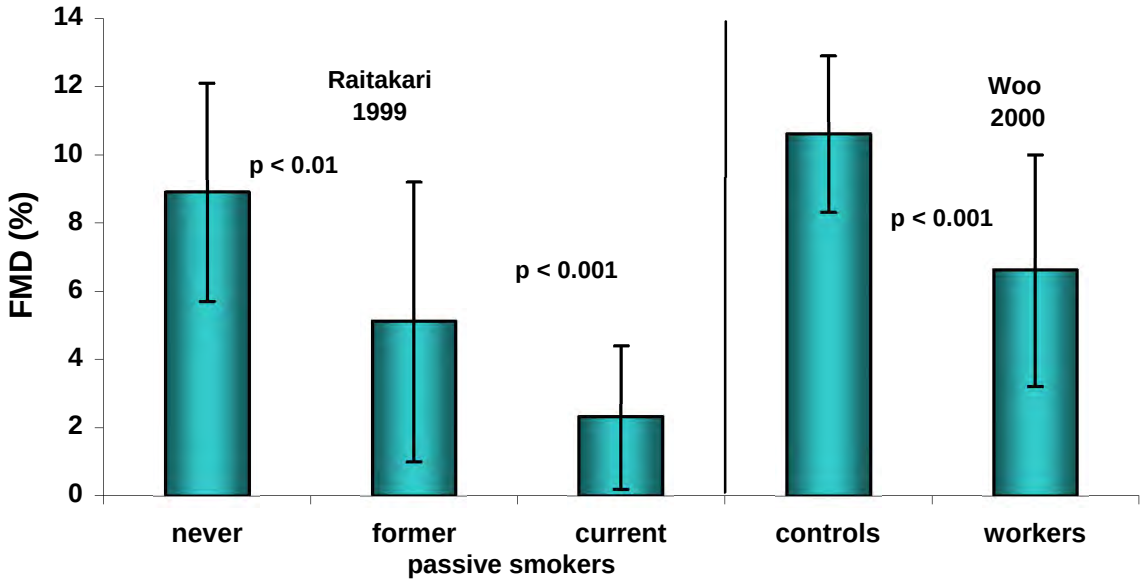
Adapted from Otsuka *et al.*, 2001

Pope et al., 2001. A characteristic of a healthy cardiovascular system and the associated autonomic nervous system is a high level of heart rate variability (HRV). Measures of decreased HRV have been associated with increased risk of chronic heart failure (Nolan *et al.,* 1998). Pope *et al.* examined changes in both time- and frequency-domain measures of HRV in 16 adults (21-76 yrs) during alternating two-hour periods of exposure to ETS or room air in an airport's smoking and nonsmoking areas. Both areas were monitored for numbers of lit cigarettes, air nicotine, respirable suspended particulates (RSP; > 3μm), and CO. Ambulatory electrocardiograph monitors collected data on all participants during the eight hour experiment for analysis of HRV. Over the eight hour period, nicotine and RSP levels were in the ranges 21-53 $\mu g/m^3$ and 41-166 $\mu g/m^3$, respectively, in the smoking area, and 0-2 $\mu g/m^3$ and 12-43 $\mu g/m^3$, respectively, in the nonsmoking area.

One measure, the standard deviation of normal-to-normal beat intervals (SDNN), correlated most highly with overall measures of HRV and so was used to examine the effect of ETS exposure on HRV. Among six models controlling for various covariates, all ETS exposure variables were negatively and significantly ($p<0.05$) correlated with SDNN. Thus the overall effect of ETS exposure in this study was a decrease in cardiac autonomic function, as measured by HRV that reversed upon cessation of exposure. This study was small and of short duration so it is not known whether chronic ETS exposure would result in chronic depression of HRV. However, the acute effects of ETS on HRV could put susceptible individuals at higher risk of a cardiovascular event.

Woo et al., 2000. Flow mediated dilatation (FMD) is an endothelium-dependent response to sheer stress caused by increased blood flow. It is largely mediated by the endothelial release of nitric oxide and prostacyclin which cause the relaxation of the underlying smooth muscle. Since an intact endothelium is required for this response, decreases in FMD reflect decrements in vascular endothelial function and reactivity. In this study, Woo *et al.* evaluated FMD in brachial arteries by ultrasonography in 20 non-smoking casino workers (mean age 36.6 ± 7.0 yr) exposed to ETS for over 8 hr/day, 6 day/wk for 2-24 years (mean 9.2 ± 6.1 yrs). FMD was measured following reactive hyperemia caused by pressure cuff release while endothelium-independent dilatation was measured following nitroglycerin administration. Twenty non-exposed controls were matched for age and gender. Age, gender, active smoking, duration of exposure to ETS, blood pressure, BMI, total serum cholesterol (C), HDL-C, LDL-C, degree of hyperemia and vessel size were included as independent variables in the multivariate analyses. In the nonexposed controls, FMD was 10.6 ± 2.3% compared to 6.6 ± 3.4% in passive smokers (mean difference 4%; 95% CI 3-5.4%; p<0.001) (Fig. 8.04). In contrast, nitroglycerin-induced responses were similar in the two groups suggesting that the dysfunction was at the level of the endothelium. Passive smoke exposure was thus associated with impaired FMD which in turn has been related to the extent of coronary disease (1-, 2- or 3-vessel disease) in both CHD and non-CHD patients (Neunteufl *et al.,* 1997). No effect of duration of passive smoking on FMD was seen (p=0.63), however the heavy exposure to ETS, >8 hr/d for over 2 years, may have resulted in a maximal response which would mask a dose-response relationship. After multivariate analysis, passive smoking was the strongest predictor of impaired FMD (ß = -0.59, p = 0.0001), independent of age, gender and other measured variables (model R^2 = 0.75; F value = 6.1, p = 0.0001).

Figure 8.04 Impairment of Flow-Mediated Dilatation with ETS Exposure



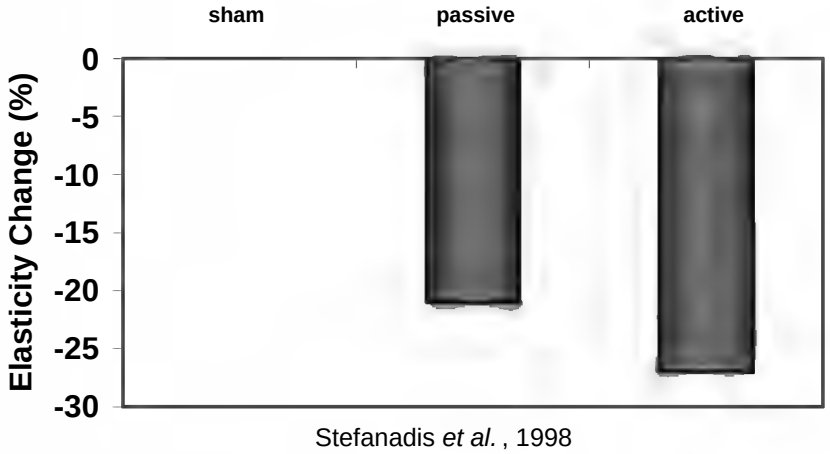
Raitakari et al., 1999. The effects of ETS exposure on vascular reactivity and the potential for recovery following exposure cessation were studied in this cross-sectional study. Reactive hyperemia was induced by pressure cuff release, and endothelium-dependent flow-mediated

dilatation (FMD) and endothelium-independent (nitroglycerin-induced) dilatation were measured by ultrasonography. The study included 60 young adults (age 15-39 yrs): 20 with no exposure to active or passive smoking (controls), 20 nonsmokers with passive smoke exposure for ≥ 1 hr/d, for ≥ 2 yr, and 20 former passive smokers. Smoke exposure was self-assessed by questionnaire with recent exposure verified by measurement of salivary cotinine. The study controlled for age, sex, dyslipidemia, blood pressure, diabetes, and history of heart disease. Among never smokers, the mean (± SD) FMD was 8.9 ± 3.2%. In former passive-smokers this value was 5.1 ± 4.1%, which dropped to 2.3 ± 2.1% ($p<0.001$) in current passive-smokers (Fig. 8.04). After administration of nitroglycerin, no significant difference was seen among groups for endothelium-independent dilatation. There were also no significant gender differences. In the former passive-smoking group, FMD was most impaired in recent quitters (< 2 yrs; FMD 1.2 ± 1.7%) versus those quitting more than two years previously (FMD 5.8 ± 4.0%; $p \leq 0.05$). Thus ETS exposure was seen to significantly impair vascular responsiveness as measured by FMD and, consistent with other studies, the tissue most adversely affected by ETS exposure was the vascular endothelium. These effects appeared to be at least partially reversible following cessation of smoke exposure. Although limited by its small size and cross-sectional nature, the inverse relationship between ETS exposure and FMD is consistent with a causal role of ETS in CHD.

Stefanadis et al., 1998. Loss of arterial flexibility is associated with increased risk of CHD. Stefanadis *et al.* studied the association between passive smoking and the elastic properties of the aorta via measurement of instantaneous diameters and pressures in the descending thoracic aorta during and after active, sham and passive smoking. All participants in this study were males (mean 48 ± 10 yr) undergoing diagnostic cardiac catheterization for evaluation of chest pain. The study included 16 nonsmokers (for passive smoke exposure) and 32 current, long-term smokers (≥ 1 pack/d, ≥ 1 yr). For this study the latter group was divided into 16 active and 16 sham smokers. Passive smokers were exposed to ETS in an exposure chamber with CO levels of 30 ppm for 5 min. Active smokers smoked one filtered cigarette (1 mg nicotine) in 5 min while sham smokers "smoked" one unlighted cigarette for 5 min. Arterial measurements were made at baseline and 1, 2, 3, 4, 5, 10, 15 and 20 min after the start of smoke exposure. Aortic distensibility, which measures vessel diameter as a function of vessel pressure, was used as a gauge of aortic elasticity. Large distensibility values represent healthy aortic elasticity while low values indicate deteriorated properties. In this context both passive and active smoking caused decrements in aortic distensibility. Whereas sham smoking did not change distensibility, passive smoking caused a significant 21% decrease from 2.02×10^{-6} to 1.59×10^{-6} cm^2/dyne during the 5 minutes of passive smoke exposure ($p<0.001$) with gradual recovery over the subsequent 15 min to near sham values. Active smoking decreased mean distensibility 27% (from 2.08 to 1.51×10^{-6} cm^2/dyne), and did so more rapidly than did passive smoking, with no recovery during the subsequent 15 min (compared to sham, $p<0.001$) (Fig. 8.05). This study suggests that both active and passive smoking can cause acute deterioration of elastic properties of the aorta and thereby compromise aortic function.

All participants in this study were men, most of whom had CHD, which limits the generalizability of these results. It is unknown whether women, those without CHD, or (since the aorta loses elasticity with age) younger individuals would respond in the same way. However, these data suggest that people with CHD may be especially at risk from ETS exposure.

Figure 8.05 Loss of Aortic Elasticity with Active and Passive Smoking.

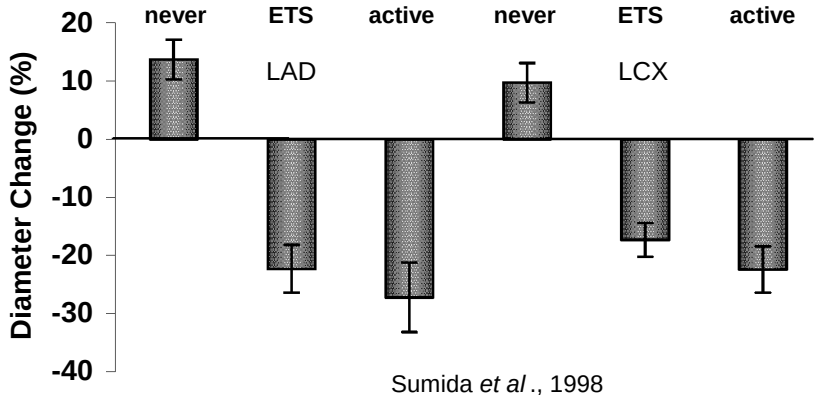


Stefanadis *et al.* , 1998

Sumida et al. (1998) used quantitative coronary angiography to measure diameters of the epicardial coronary artery in response to intracoronary injection of acetylcholine (ACh). The subjects of this study were 38 women admitted to a hospital in Japan for diagnostic cardiac catheterization for evaluation of atypical chest pain. Included were 11 never-smokers not exposed to ETS, 19 passive smokers, and 8 active smokers, all of similar age. The passive smoking group included life-long nonsmokers with a self-reported history of exposure to ETS at home, work or both for ≥ 1 hr/day for ≥ 10 years. Active smokers were those who smoked ≥ 20 cigarettes per day for > 10 years. Urinary cotinine levels, measured at hospital admission, were not detectable in nonsmokers not exposed to ETS (<5.0 ng/ml). These levels were 9.1 ± 0.5 ng/ml in passive smokers, and 1,350 ± 60 ng/ml in active smokers. All patients were reportedly free of important coronary risk factors, and there were no significant differences among groups with respect to age, blood pressure, total cholesterol, LDL-C and HDL-C.

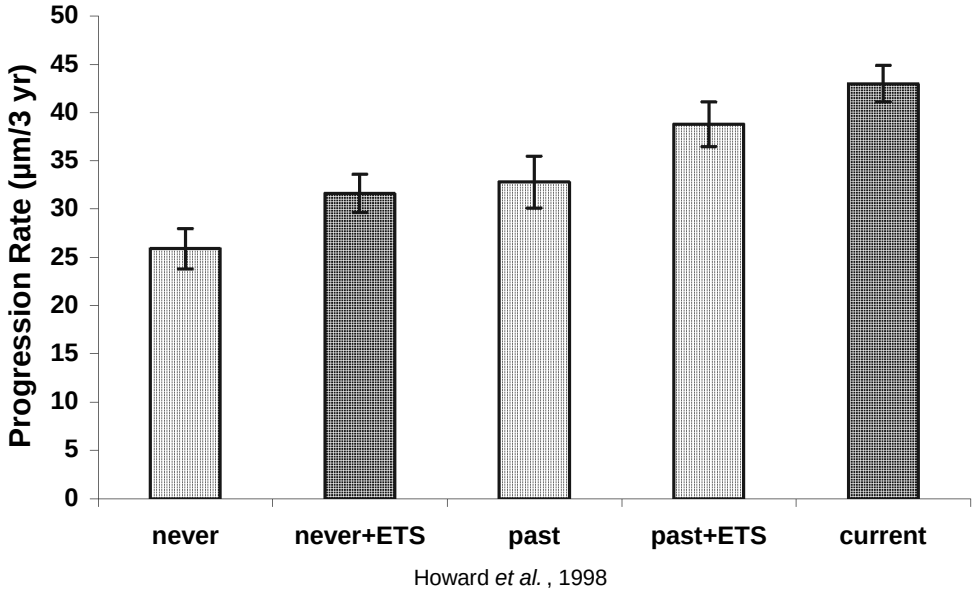
Lumen diameters were measured at the proximal, middle and distal segments of the left anterior descending (LAD) and the left circumflex (LCx) coronary arteries by computer-assisted angiography at baseline and after administration of acetylcholine (ACh) and nitroglycerin (NTG). The response to treatment was expressed as the percent change in coronary diameter from baseline. In the nonsmokers, ACh significantly dilated the distal segment of the LAD but not the proximal and middle segments. In the LCx, ACh significantly dilated the middle and distal but not the proximal segments. By contrast, in the passive smokers, ACh significantly constricted all segments of the left coronary artery (Fig. 8.06). The degree of constriction in passive smokers was similar to that seen in active smokers. No significant differences were found in ACh-induced constriction between those with light passive smoke exposure (3.7 ± 1.4 hr/day) versus heavy (7.8 ± 2.6 hr/day). There were also no significant differences in response to NTG among active, passive and nonsmokers.

Figure 8.06 Smoke Exposure and Modified Arterial Response to Acetylcholine



In the absence of underlying disease, vasodilation is the normal arterial response to ACh. This effect is mediated by the endothelium mainly through the release of nitric oxide (NO). On the other hand, ACh causes vascular smooth muscle to constrict. Thus the arterial response to ACh is a result of the balance between the dilator action of endothelium-derived substances, including nitric oxide, and a direct constrictor action of ACh on smooth muscle. The constriction of all segments of the coronary arteries in response to ACh among the patients exposed to smoke, either passively or actively, sharply contrasts with the dilatory response seen in nonsmokers and suggests that the coronary endothelium may have been damaged by smoke exposure. Endothelial damage is further supported by the similarity among all exposure groups to the dilatory effects of NTG, a non-endothelium-dependent response. However, the subjects were admitted to a hospital because of chest pains, so it is possible that undetected pre-existing conditions other than smoke exposure may have distinguished the smokers from nonsmokers. This study found no significant differences in arterial diameter changes between light and heavy ETS exposure. Although the small study size precludes a definitive conclusion regarding the exposure-response relationship, these results suggest that the observed effects of ETS on arterial dilatation may saturate at a relatively low exposure level.

Figure 8.07 Progression of Arterial Intima Media Thickness with Smoke Exposure



Howard et al. (1998) used data from the Atherosclerosis Risk in Communities Study (ARIC) in a longitudinal assessment of the effects of active and passive smoking on the progression of atherosclerosis over three years. This population based study included 10,914 middle-aged adults (average age 54 yr). The intima-media thickness (IMT) of carotid arteries was measured by ultrasound at baseline and three years later. Smoking history and ETS exposure were self-assessed by questionnaire. Covariates included blood pressure, LDL-cholesterol, diabetes, fat intake, leisure time activity, education, alcohol use, and BMI. The group was divided into 2,956 current smokers, 1,849 past-smokers with ETS exposure (past+ETS), 1,344 past-smokers without ETS exposure (past–ETS), 2,449 never-smokers with ETS (never+ETS), and 2,316 never-smokers with no ETS exposure (never–ETS).

Using smoking category as the primary independent variable, there was a significant progressive increase in wall thickness from never smokers (never-ETS), through those exposed to ETS, to current smokers (Fig. 8.07). In the model with all adjustments, ETS increased progression by 5.9 µm over three years ($p = 0.01$). Current smoking versus never-exposed increased progression by 17.1 µm/3 yrs (43-25.9=17.1), 34.5% (5.9 µm/17.1) of which was attributable to ETS exposure.

8.1.5. Vascular Pathophysiological Effects – Experimental Animals

Table 8.17b Summary of Cited Studies: Vascular Pathophysiological Effects - Experimental Animals

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Knight-Lozano *et al*., 2002	Laboratory exposure of atherosclerosis-prone mice to SHS. Mitochondrial damage and lesions measured in aorta.	$ApoE^{-/-}$ mice 30 mg/m^3 21d " 42d Mitochondrial lesions 1 mg/m^3 42d 30 mg/m^3 42d	Aortic lesion area +76% vs no SHS +156% " Lesions/16 kilo-bases 1.3 6.0 $p<0.001$	Significant increase in aorta lesion area ($p<0.05$), and in mitochondrial DNA damage after SHS exposure. Hypercholesterolemia increased SHS damage to mitochondria and aorta wall.
Gairola *et al*., 2001	Laboratory exposure of atherosclerosis-prone mice to side stream smoke (SS). Lesions and lipids measured in aorta.	 SS Control SS Control	Lesion area 33 ± 11% 10 ± 8% Cholesterol 7 wk 718 ± 61 mg/dl 553 ± 26 mg/dl	Significant increase in area of aorta covered by lesion after SS exposure ($p<0.001$). Transient increase in plasma cholesterol at 7 wks in SS mice but back to control levels by 14 wks.

Knight-Lozano et al., 2002. $ApoE^{-/-}$ mice lack apolipoprotein E, a high-affinity ligand for lipoprotein receptors, and as a result have elevated levels of serum LDL-C and triglycerides, and develop atherosclerotic plaques in a manner similar to humans. $ApoE^{-/-}$ mice and the normocholesterolemic mouse strain, C57BL/6, were compared in this study of the effects of hypercholesterolemia and smoke exposure on atherosclerotic lesion formation and mitochondrial damage in cardiovascular tissue. Mice were exposed to second hand smoke (SHS; a surrogate for ETS) at 1 and 30 mg/m^3 total suspended particulates (TSP) or filtered air 6 hr/d, 5 d/wk for 42 days, or to air for 21 days followed by 21 days of SHS. Examination of the aortas of SHS-exposed (30 mg/m^3) compared to non-exposed $ApoE^{-/-}$ mice revealed a mean increase in lesion size of 76% at 21 days and 156% at 42 days. In contrast, no lesions were observed in the aortic sinus region of C57BL/6 mice in any exposure group. However, comparison of lipid staining with oil red O (which is used to visualize atherosclerotic lesions) in entire aortas from SHS-exposed vs. non-exposed mice revealed a 4.5-fold increase in stained area for $ApoE^{-/-}$ mice ($p<0.05$), and 2.1- and 3.7-fold increases for C57BL/6 mice at 21 and 42 days, respectively.

Quantitative polymerase chain reaction was used to assess damage to aortic mitochondrial DNA. At both high (30 mg/m^3) and low (1 mg/m^3) TSP, significant mitochondrial DNA damage was observed for both mouse strains. This effect was more pronounced in the $ApoE^{-/-}$ than the C57BL/6 mice, suggesting an interaction between hypercholesterolemia and SHS exposure ($p<0.001$). While higher or longer exposures caused substantially more mitochondrial damage ($p<0.001$), even the more environmentally relevant dose (1 mg/m^3) resulted in statistically

significant damage ($p<0.001$). Mitochondrial damage could affect cardiovascular cell function through the increased formation of reactive nitrogen and oxygen species. These radicals can in turn oxidize LDL, which enhances its uptake into atherosclerotic plaques, and damage mitochondrial proteins, thereby disrupting energy production and intracellular signaling. These results are consistent with the view that oxidative stress mediates the link between ETS and cardiovascular disease.

Gairola et al., 2001. As described above, $ApoE^{-/-}$ mice develop atherosclerotic lesions very similar to those seen in human disease, including the formation of fatty streaks and fibrolipid lesions. In this study, female $ApoE^{-/-}$ mice (8-9 wks old) were fed a modified diet containing 21% w/w saturated fat and 0.15% w/w cholesterol, and then divided into control and sidestream smoke (SS) exposed groups. Animals were exposed to SS at 25 mg/m^3 particulates for 6 h/d, 5d/wk for 7, 10 or 14 weeks. Upon sacrifice the intimal surfaces along the arch, thoracic and abdominal sections of the aortas were examined microscopically for lesions. The lipid content of aortic tissues was also measured. Atherosclerotic lesions covered greater areas in SS-exposed mice compared to controls starting at the earliest time (7 weeks) with a significantly more rapid increase in size through 14 weeks. This was especially pronounced in the thoracic region of the aorta, which is not normally a lesion-susceptible area. In SS-exposed animals, 33 ± 11% of the intima was covered by lesions versus 10 ± 8% in controls ($P<0.001$). The lesions were also thicker in the SS mice as verified by an increase in esterified and unesterified cholesterol in these tissues. Macrophages were the predominant cellular component of the lesions. Exposure to SS was also associated with a modest, but statistically significant, transient increase in plasma cholesterol levels at 7 weeks (SS, 718 ± 61 vs. Ctrl, 553 ± 26 mg/dl; $p=0.027$) that was not evident at the later time points. This transient increase may have been related to the increase in atherosclerosis in the SS-exposed group.

There are differences between the exposure conditions in this study and realistic human ETS exposures. The mice were exposed to levels of smoke constituents roughly ten times the respirable particulates in a smoky bar (Anderson *et al.,* 1991). However, the most prolonged exposure was for only approximately 10% of their normal life span; the dose-time integrals for the lower exposure groups may thus be relatively realistic. Although the cardiovascular consequences of briefer but more intensive ETS exposure may differ from those associated with chronic lower level exposure, in this animal model ETS exposure was clearly associated with promotion of atherosclerosis.

8.1.6. Hematological Effects

Table 8.28 Summary of Cited Studies: Hematological Effects

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Moffatt *et al.,* 2004	Measured HDL and total cholesterol before and after 6 hr ETS. 12 male nonsmokers.	6 hr ETS Post ETS 8 hr 16 hr 24 hr Post ETS 8 hr 16 hr 24 hr	HDLC decrease 37% 31% 28% Total HDLC pre- vs. post ETS 4.1 vs. 4.9 4.2 vs. 5.0 4.2 vs. 4.9	Single, long-duration ETS exposure lowered HDLC in healthy adult males for over 24 hours post-exposure.
Moskowitz *et al*., 1999	Cross-sectional study of CHD risk factors in pubertal children vs. ETS, race, sex in 408 twin pairs 11-15 yr	Family ETS exposure ETS No ETS ETS No ETS ETS + family history CHD No CHD	Level (mmol/ml) HDLC 1.19 ± 0.22 1.26 ± 0.28 $HDLC_2$ 0.30 ± 0.16 0.35 ± 0.20 HDLC 1.18 ± 0.23 1.25 ± 0.23	Lower levels of HDL-C and subfraction 2 (HDL_2-C) in kids from smoking families ($p \leq 0.01$, $p \leq 0.001$, resp). Even lower HDL-C in smoking families with CHD history ($p<0.001$).
Valkonen & Kuusi, 1998	Measured HDL-C, and antioxidants before and after ETS	30 min ETS Post ETS 6 hr	Blood changes Vit C -25% SH -21% Oxidized LDL	30 min ETS exposure lowered blood antioxidant capacity up to 6 hr post-exposure.

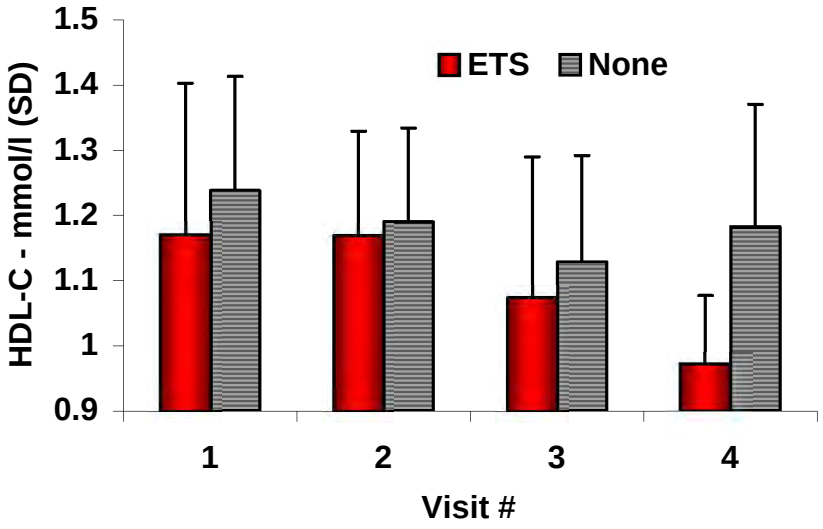
Moffatt et al., 2004. Active smoking has been associated with a decrease in plasma high-density lipoprotein cholesterol (HDL-C). To address whether ETS has similar effects, Moffat *et al*. examined the effects of 6 hours of exposure to ETS on blood levels of HDL-C and its subfractions, HDL_2-C and HDL_3-C, in 12 male non-smokers. Subjects were 21-31 years of age and reportedly free from diseases known to alter lipid profiles. During the first of three consecutive days, baseline data were collected prior to ETS exposure. At 6 am, 2 pm and 10 pm, respiratory carbon monoxide (CO) and HDL-C levels were determined. ETS exposure occurred on the second day for 6 continuous hours during which levels of CO and nicotine were monitored to maintain levels comparable to establishments in which smoking was permitted (12 ppm and 16.0 $\mu g/m^3$, respectively). Respiratory CO levels and blood samples were again taken at 8, 16, and 24 hours post ETS exposure. Dietary records were obtained for the three days prior to, during, and following exposure.

HDL-C levels were significantly reduced at 8 hrs (18%), 16 hrs (14%), and 24 hrs (13%) post-ETS exposure. Similarly, following ETS exposure, the subfraction HDL_2-C was also significantly reduced: 8 hrs (37%), 16 hrs (31%), and 24 hrs (28%). By contrast, total

cholesterol levels were not different between pre- and post-ETS exposures. As a result, the ratio between total cholesterol and HDL-C significantly increased following exposure: 8 hrs (4.9 vs. 4.1), 16 hrs (5.0 vs. 4.2), 24 hrs (4.9 vs. 4.2). The ratio between HDL_2-C and HDL_3-C decreased between pre- and post-ETS exposure: 8 hrs (0.31 vs. 0.45), 16 hrs (0.36 vs. 0.53), 24 hrs (0.36 vs. 0.48). Pre- and post-exposure respiratory CO levels were not different, but during exposure CO increased from 3.61 ± 0.21 to 7.31 ± 0.51 ppm.

This study was small and the ETS exposure of long duration. How the results apply to individuals with shorter and/or more frequent exposures to ETS is not known. However, the study did find that a single ETS exposure of long duration significantly altered the plasma lipid profiles in healthy males, and that these changes required more than 24 hours to reverse following cessation of ETS exposure. The depression of HDL-C, but not total cholesterol levels, following exposure suggests a mechanism by which ETS exposure may promote atherosclerosis.

Figure 8.08 ETS Exposure and HDL-C Levels in Children

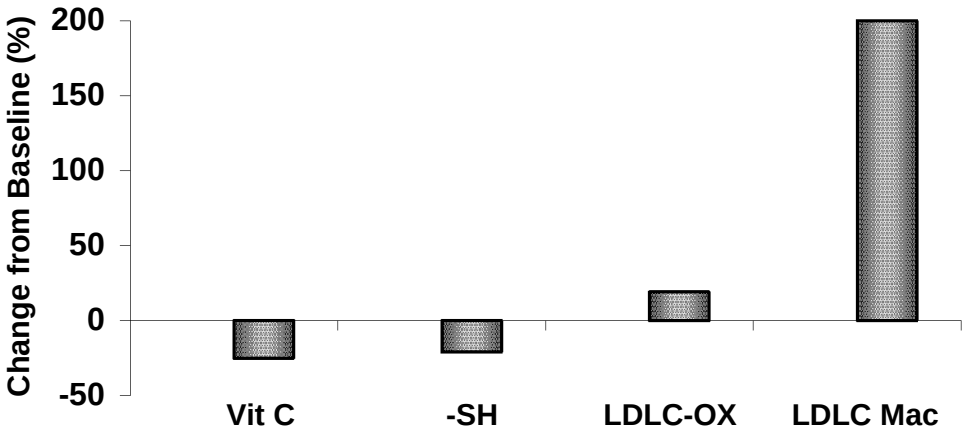


Adapted from: Moskowitz *et al.*, 1999

Moskowitz et al,. 1999. Most investigations of the association between CHD and ETS focus on adults. In this study, Moskowitz *et al.* examined how CHD risk factors, passive smoking, gender and race are related in pubertal children. Data were collected during four visits at 18-month intervals from 113 twin pairs from 11-15.5 years of age. Information on family and health histories, smoking, alcohol use, blood pressure, and anthropometrics was collected by questionnaire and during interview. Biochemical assays provided data on blood HDL-cholesterol (HDL-C), LDL-C, and cotinine. HDL-C subfraction 2 (HDL_2-C) was also assessed as most of the variation in HDL-C is due to this subfraction and others have shown that CHD deaths occur more frequently in families with low levels of HDL_2-C (Bodurtha *et al.,* 1987). At the first visit, children with long-term passive smoke exposure had significantly lower HDL-C (visit 1: 1.19 ± 0.22 vs. 1.26 ± 0.28 mmol/L; $p \leq 0.01$) and HDL_2-C (0.30 ± 0.16 vs. 0.35 ± 0.20 mmol/L, $p \leq 0.01$) than kids from nonsmoking families. In addition, over the course of the four

visits, HDL-C significantly decreased among children exposed to ETS compared to children in nonsmoking families ($p \leq 0.001$ for trend; Fig 8.08). The negative effects of passive smoke exposure on HDL-C levels were more pronounced in children of families with a history of cardiac disease versus those without (visit 1: 1.18 ± 0.23 vs. 1.25 ± 0.23 mmol/mL; visit 4: 0.98 ± 0.10 vs. 1.19 ± 0.18 mmol/mL; $p<0.001$). This study indicated that in children also, ETS exposure has a deleterious effect on HDL-C levels, a risk factor for CHD. In addition there appeared to be differences in susceptibility to ETS effects related to race, gender and familial history of cardiac disease.

Figure 8.09 Effect of ETS Exposure on Blood Anti-oxidants, Lipid Oxidation and Accumulation in Macrophages



From Valkonen and Kuusi, 1998
Vit C – ascorbic acid; -SH – protein sulfhydryls; LDL-OX – oxidized LDL

Valkonen and Kuusi (1998) examined the blood of nonsmokers prior to, and 1.5 and 6 hours after starting a 30-min exposure to ETS. They measured serum cholesterol, HDL-C, triglycerides and LDL-C levels, lipid- and aqueous-soluble antioxidants, and the combined ability of all antioxidants to resist artificially induced LDL-C peroxidation. Acute exposure to ETS resulted in a 25% decrease in serum ascorbic acid starting at 1.5 hrs after exposure and lasting 6 hrs ($p<0.001$), and a gradual decrease in sulfhydryls by 21% from baseline by 6 hrs ($p<0.063$) signifying a loss of antioxidant defenses. There was a concomitant 19% decrease in the resistance of LDL-C to Cu^{2+}-initiated oxidation. Uptake by cultured macrophages of LDL-C isolated following ETS exposure was found to be 1.6-2.3 times higher than that of unexposed LDL-C (Fig 8.09). Thus, ETS exposure enhanced peroxidation of LDL-C and its accumulation in macrophages, both of which occur during the formation of atherosclerotic plaques. In a subsequent study, peroxidation of LDL-C after ETS exposure was ameliorated by ascorbic acid administration (Valkonen & Kuusi, 2000), consistent with the role of peroxidation in plaque formation.

8.2. Other Pathophysiological Evidence

The 1997 report described evidence for pathophysiological mechanisms that may mediate the cardiovascular effects of ETS. Additional pathophysiological evidence is reviewed below.

8.2.1. Internal Carotid Artery Intima-Media Thickness (IMT)

Results from the British Regional Heart Study (Ebrahim *et al.,* 1999) suggest that IMT of the common carotid artery is strongly associated with risk factors for stroke, while IMT of the bifurcation was more directly associated with plaque and ischemic heart disease. It appeared that the presence of plaques rather than IMT *per se* was the more important predictor of disease risk. The presence of plaques was in turn significantly associated with increasing levels of fibrinogen in men ($p<0.01$ for trend), and to a lesser extent in women. ETS exposure was not evaluated in this study; however, Iso *et al.* (1996) found an association between fibrinogen levels and ETS exposure in women (see below).

The studies by Chambless *et al*. (1997, 2000) were not specifically designed to examine the effects of smoke exposure on vascular disease; however, these studies are included here as they substantiate the importance of arterial wall thickness as a risk factor for cardiovascular disease. Thickening of arterial walls is associated with increased risk of CHD, stroke and death (Bots *et al.,* 1999).

Chambless et al. (1997) related the mean carotid IMT, measured by ultrasonography, to CHD incidence during a 4-7 year follow-up among 7,289 women and 5,552 men (45-64 yr). CHD incidents included myocardial infarction (MI), CHD death, and probable CHD. Hazard rate ratios (HRR) were calculated for incident CHD as a function of IMT. After adjusting for age, race, diabetes, cholesterol (C), LDL-C, HDL-C, blood pressure, smoking (pack-years), and alcohol use, an increase in IMT of 0.19 mm ($\approx$ 1 SD) was associated with a HRR for CHD of 1.42 (95% CI 1.24-1.64) in women and 1.18 (95% CI 1.06-1.32) in men. In women, current vs. ever smoking had an associated HRR of 3.64 (95% CI 2.30-5.76) while in men this HRR was 2.27 (95% CI 1.53-3.35). Smoking cessation was associated with dramatically decreased HRRs. In female ex-smokers versus never smokers, the HRR was 1.20 (95% CI 0.64-2.27), and the similar comparison for men gave a HRR of 1.17 (95% CI 0.79-1.73). Interestingly, the risk for CHD with increasing IMT increased more rapidly at low IMT values than at higher IMT suggesting a higher sensitivity to smoke in arteries with smaller IMTs at baseline.

The prospective nature of this study made it possible to link IMT measured at baseline with subsequent CHD, and so directly examine the risk of CHD incidents as a function of IMT. A limitation of this study was the basing of mean IMTs on a single assessment. Incomplete sets of ultrasound data necessitated exclusion of some participants and imputation of some IMT measurements for most others using maximum likelihood techniques. This study controlled for most major CHD risk factors; however, diet and socioeconomic status were not included. While this study was not designed to specifically examine the effects of smoke exposure on IMT, active smoking was seen to increase the risk of CHD, a relationship that is already well known. The association between IMT and CHD incidence is important in the context of increases in IMT associated with passive smoke exposure reported in other studies (see Howard *et al.*, 1998).

Chambless et al. (2000) conducted a prospective study of ischemic stroke. The mean carotid intima-media thickness (IMT) was measured by ultrasonography and was related to stroke incidence during a 6-9 year follow-up among 7,865 women and 6,349 men (45-64 yr). Hazard rate ratios (HRR) were calculated for incident ischemic stroke as a function of IMT relative to the reference category of 0.6 mm. The HRRs for mean IMT $\geq$ 1 mm compared to $\leq$ 0.6 mm were 8.5 for women (95% CI 3.5-20.7) and 3.6 for men (95% CI 1.5-9.2). A graded increase in the event rate or hazard rate ratio was seen in both men and women. After adjusting for HDL-C, LDL-C, smoking, hypertension, body mass index (BMI), sports activity, diabetes, fibrinogen levels, left ventricular hypertrophy and white blood count, at low IMT, a 0.18 mm increase in IMT gave a HRR for stroke of 1.21 (95% CI 1.05-1.39) in men and 1.36 (95% CI 1.16-1.59) in women. These results suggest that mean IMT is predictive for subsequent ischemic stroke. As in the study on CHD, the stroke risk reflected in the HRR increased more rapidly at low IMT than at higher IMT. It should be noted that although increased carotid wall thickness played a role in the etiology of stroke, the thickening of the carotid wall as measured in this study was not assumed to be the sole cause of ischemic stroke. Rather it was a surrogate marker for the existence of etiologically significant lesions elsewhere. Whereas CHD is due almost exclusively to atherosclerosis, stroke has a mixed etiology that includes degeneration of intracerebral arteries as well as atherosclerosis of the carotid and basilar arteries, and the large arteries of the brain.

This study shares the limitations reported above for the ARIC CHD study, including basing of IMTs on single assessments, incomplete sets of ultrasound data requiring imputation of some IMT measurements, and no control for some potential confounders such as diet and socioeconomic status. As with the report above, the effects of smoke exposure on IMT were not addressed; however, these results complement the longitudinal study by Howard *et al.* (1998) that specifically looks at passive smoking in the context of the ARIC IMT data.

8.2.2. Endothelial Function

Several recent studies in humans and animals continue to document that ETS exposure damages vascular endothelium. This is usually manifested as impaired endothelium-dependent dilatation of coronary arteries. Woo *et al.* (2000) found significantly ($p<0.001$) diminished flow-mediated dilatation (FMD) in casino workers extensively exposed to ETS compared to unexposed controls. FMD was also observed by Raitakari *et al.* (1999) to be significantly reduced in former passive ($P<0.01$) and current passive ($P<0.001$) smokers compared with unexposed nonsmokers. In a study by Sumida *et al.* (1998), acetylcholine (ACh) induced coronary artery dilatation in nonsmoking women but caused significant arterial constriction in women passively or actively exposed to smoke ($p<0.01$). Yet another measure of endothelial function, coronary flow velocity reserve, was found by Otsuka *et al.* (2001) to be significantly diminished ($p<0.001$) in young men following a 30 min exposure to passive smoke. In studies of atherogenesis in rabbits, secondhand smoke increased intimal lesion size in the aorta and inhibited ACh-induced relaxation of isolated aortic rings (Hutchison *et al.,* 1999). This effect may be mediated by ETS's ability to inhibit nitric oxide synthase and decrease endothelial arginine (Hutchison *et al.,* 2001). In both the human and animal studies, similar aortic responses in exposed and unexposed groups to endothelium-independent (nitroglycerin-induced) dilatation indicated that the endothelium is adversely affected by ETS exposure.

8.2.3. Exercise Tolerance

The deleterious effects of exposure to smoke and CO on oxygen transport and usage during exercise were recently reviewed by McDonough and Moffat (1999), but no data beyond those included in the 1997 report were identified by OEHHA staff. The OEHHA report (Cal/EPA, 1997) found suggestive evidence that ETS exposure impairs exercise tolerance, especially in patients with existing CHD but also to a lesser extent in healthy individuals.

8.2.4. Oxidative Effects

Oxidative stress results when levels of reactive oxygen species (ROS) from endogenous and exogenous sources exceed the capacity of the body's antioxidant defenses. ETS exposure results in an increase in ROS and a depletion of circulating antioxidants (Sobczak *et al*., 2004; Dietrich *et al*., 2003; Barnoya and Glantz, 2004; Giordano, 2005). The circulating oxygen free radicals may damage vascular endothelium and cardiac tissue directly, and indirectly through the formation of peroxidized lipids (see Sec. 8.2.5). Among non-smokers exposed to ETS, increased oxidative stress has been reflected in elevated blood levels of the antioxidant enzymes superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase. In addition, 8-hydroxy-2-deoxyguanosine, a marker of oxidative DNA damage, was also significantly elevated in the ETS-exposed group relative to controls (Howard *et al*., 1998). While ROS exposure from ETS was associated with elevated antioxidant enzymes in blood, in other tissues smoke exposure compromised protective enzymes. In mouse aortic tissue, exposure to secondhand smoke decreased the activity of the mitochondrial antioxidant enzyme, superoxide dismutase 2, and the adenine nucleotide translocator, an enzyme involved in mitochondrial ATP production (Knight-Lorzano *et al*., 2002). There was also evidence of damage to mitochondrial DNA in aortas of smoke-exposed mice. Because mitochondria are critical to multiple cellular processes, including energy production, apoptosis, and signaling, the compromise of mitochondrial function is likely a significant contributor to the negative cardiovascular effects associated with ETS exposure (Barnoya and Glantz, 2004). Indeed, apoptosis in cardiac cells following ischemia and reperfusion is thought to be mediated by ROS. This is supported by the finding that exposure to ROS induced apoptosis in cardiomyocytes in culture. The involvement of damage to mitochondria was indicated by the appearance of cytochrome c in the cytosol of the apoptotic cells (von Harsdorf *et al*., 1999).

As reviewed by Giordano (2005), ROS may also adversely affect cardiac function by altering ion flux through calcium channels in the sarcolemma and by decreasing the sensitivity of myofilaments to calcium, with the net effect of reducing cardiac contractility. Contractility is also controlled by NO. However, ROS may interact with NO and alter the nitroso-redox balance thereby disturbing NO control of contractility and other essential cellular processes. The role of ETS-derived ROS in compromising cardiovascular function is both varied and complex.

8.2.5. Lipid Profile

The growth of atherosclerotic plaques is associated with the accumulation of LDL-cholesterol (LDL-C) by macrophages, the precursors to foam cells in atherosclerotic lesions. Peroxidation of LDL-C also enhances its penetration of the arterial intima, binding to the extracellular matrix of intimal cells (Wang *et al.,* 2001), and uptake by macrophages. Valkonen and Kuusi (1998)

documented the loss of antioxidants as well as a decreased resistance of LDL-C to oxidation in the blood of nonsmokers exposed to ETS. In addition, the uptake of LDL-C from ETS-exposed subjects by cultured macrophages was substantially enhanced. Thus, ETS exposure enhanced peroxidation of LDL-C and its accumulation in macrophages, both of which occur during the formation of atherosclerotic plaques. In a subsequent study, peroxidation of LDL-C after ETS exposure was ameliorated by ascorbic acid administration (Valkonen & Kuusi, 2000), consistent with the role of peroxidation in plaque formation.

Whereas LDL-C promotes atherogenesis, HDL-C is protective and low HDL-C levels are considered a risk factor for CHD. In the study by Moskowitz *et al.* (1999), HDL-C levels in children with long-term passive smoke exposure were lower than in children from nonsmoking families (1.21 ± 0.26 vs. 1.31 ± 0.26 mmol/L; $p \leq 0.01$). This difference was especially pronounced for the subfraction HDL_2-C (0.31 ± 0.18 vs. 0.41 ± 0.19 mmol/L, trend $p \leq 0.001$). This subfraction accounts for most of the variation in HDL-C and, in families with low levels of HDL_2-C, is associated with more frequent CHD death (Bodurtha *et al.*, 1987). Decreases in HDL-C and its subfractions were also observed in adults after ETS by Moffatt *et al*. (2004).

8.2.6. Platelet Aggregation and Endothelial Damage

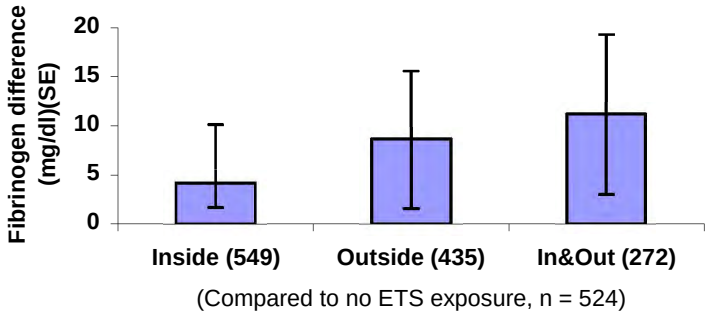
Activation of platelets is associated with damage to the lining of coronary arteries, and with the synthesis and secretion of thromboxanes, which in turn promote vasoconstriction and platelet aggregation. Levels of thromboxane in the blood are thus a measure of platelet activation and signal an increased likelihood of thrombus formation. The formation of thrombi may elevate the risk of an ischemic event such as myocardial infarction. Schmid *et al.* (1996) examined malondialdehyde (MDA), plasma and serum thromboxane B_2 (TXB_2), 11-dehydrothromboxane B_2, and conversion of exogenous arachidonic acid to TXB_2 and to hydroxy-5,8,10-heptadecatrienoic acid in 12 active smokers and 12 nonsmokers following exposure to ETS. For both groups, both single 60-min exposures and exposures repeated on 5 successive days resulted in significant increases ($p<0.05$) in all parameters except serum TXB_2. Whereas prior to acute smoke exposure, the levels of all six compounds were significantly lower ($p<0.05$) in nonsmokers than in smokers, after 4 days of ETS exposures, the MDA and serum TXB_2 levels in nonsmokers rose and became similar to those of active smokers. Among nonsmokers, levels of MDA and plasma TXB_2 remained elevated 6 hours after exposure. Thus the acute effects of ETS on platelet activation were more pronounced in nonsmokers than in smokers, possibly due to chronic activation of platelets in the latter group, and repeated ETS exposure that made nonsmokers more like smokers in this respect. The effect was also observed in studies by Sinzinger and Kefalides (1982) and Burghuber *et al.* (1986). These studies, described in Cal/EPA (1997), document a significant decrease in platelet sensitivity to the anti-aggregatory effects of PGI_2 among nonsmokers but not active smokers following acute smoke exposure.

8.2.7. Fibrinogen Levels

Elevated plasma fibrinogen is an important coronary risk factor associated with both active and passive smoking. In a cross-sectional study of 1,780 Japanese women, Iso *et al.* (1996) reported that in women exposed to ETS outside the home, mean fibrinogen levels were 8.6 (95% CI 1.6-15.6) mg/dl higher than among non-exposed women. For ETS exposure in the home only, fibrinogen levels were 4.2 mg/dl (95% CI 1.7-10.1) higher, while in women exposed both in and

outside the home, fibrinogen levels were 11.2 (95% CI 3.0-19.3) mg/dl higher than in non-exposed women (Fig. 8.10).

Figure 8.10 Increased Plasma Fibrinogen in Women Exposed to ETS Inside and/or Outside the Home



Adapted from Iso *et al.*, 1996

8.2.8. In vitro Studies

Wong et al., 2004. This study examined the responses of fibroblasts exposed to solutions containing whole sidestream smoke or whole mainstream smoke in vitro. As such it bears more on the differential effects of ETS versus mainstream smoke that may be important in various disease outcomes, not just CHD. In this study, fibroblasts were exposed for four hours to media containing sidestream smoke at nicotine concentrations (~2 µg/ml) adjusted to reflect typical tissue nicotine levels in nonsmokers following 78 minutes of exposure to ETS in a smoky room, or to a similar preparation of mainstream smoke. Cells were examined microscopically following staining with DIOC6, a stain used to label the endoplasmic reticulum (ER). In control cells not exposed, the ER was well developed, and concentrated around the nucleus but spread throughout the cytosol. By comparison, the ER in cells in sidestream smoke-containing media showed punctate staining reflecting the fragmentation and coalescence of the ER around the nucleus, whereas the ER in cells exposed to the mainstream smoke solution looked more like that of the control cells. Similarly, sidestream smoke had a differential negative effect on the integrity of Golgi vesicles and the distribution of the chemokine cIL-8 compared to control and mainstream smoke-exposed cells. These data suggest that ETS and mainstream smoke have different cellular effects, possibly indicating different mechanisms of action.

8.3. Chapter Summary and Conclusions

The growing body of evidence continues to support the observation in the 1997 Cal/EPA document that chronic ETS exposure is causally associated with an increased risk for cardiovascular disease in the range of 20-50%. Ultimately, cardiovascular disease is the result of multiple, interrelated changes in the cardiovascular system that manifest primarily as atherosclerosis, the main pathogenic process underlying CHD. Endothelial dysfunction contributes to atherosclerosis (Chilton, 2004; Ross, 1999). The ability of ETS to damage the arterial endothelium is seen in the loss of arterial elasticity and decreased endothelial responsiveness to endogenous signals. Among the causes of vascular damage and the resulting

endothelial dysfunction are elevated and oxidized LDL, and circulating free radicals, such as are found in the blood after exposure to tobacco smoke. Vascular damage leads to the uptake and further oxidation of LDL by macrophages at the site of injury, and to plaque formation. The ability of ETS to promote plaque growth is evident from both human and animal studies. A mechanistic basis for ETS's atherogenic effects is provided by observations of ETS-associated decreases in HDL-C, increases in peroxidized LDL, compromised antioxidant defenses, and mitochondrial damage after ETS exposure. In addition, ETS is associated with platelet activation and elevated fibrinogen levels that in turn are associated with endothelial damage and plaque formation, respectively.

As a result of the loss of endothelial responsiveness associated with ETS exposure, the coronary arteries are not as responsive to increased tissue demands for oxygen by dilating. This problem is further exacerbated in arteries remodeled by atherosclerotic plaques and carrying blood whose oxygen carrying capacity is decreased by the binding of carbon monoxide from ETS. The elevation of fibrinogen levels and the activation of platelets increase the blood's viscosity, further diminishing the delivery of oxygen to tissues. When the transport of oxygen is compromised, transient or permanent ischemic damage to cardiac and peripheral tissues is more likely. In individuals with vulnerable plaques, these effects may lead to plaque disruption and the formation of thrombi that in turn may precipitate an ischemic event such as MI or stroke. Indeed, there is some evidence that ETS also contributes to stroke, the etiology of which includes atherosclerosis of the carotid and large arteries of the brain, and degeneration of intracerebral arteries. Research in this area suggests that chronic ETS exposure increases the risk of stroke by about 82% (Bonita *et al.*, 1999).

The deleterious effects of ETS on cardiovascular functioning parallel those observed for other forms of air pollution and for active smoking (US DHHS, 2004d). In humans, long term exposure to particulate air pollution has been associated with increased mortality due to AMI, coronary atherosclerosis, and other ischemic heart disease (Pope *et al*., 2004). In vitro, experiments with rat aortic rings exposed to solutions of diesel exhaust particulates showed inhibition of relaxation (Ikeda *et al*., 1995) similar to that reported for rabbit aortic rings exposed to second hand smoke (Hutchison *et al.*, 1999). While the similarities in the biological responses to these various forms of air pollution are not surprising, there are likely to be subtle differences in the mechanisms of action.

In attempts to understand the plausible mechanisms of action of ETS in cardiovascular and other disease endpoints, comparisons with active smoking are often made, frequently with the erroneous assumption that ETS is essentially diluted mainstream smoke. There are, however, significant differences in the chemical composition of ETS and mainstream smoke, some of which are germane to CHD, such as higher levels of CO and nicotine in ETS. That cellular responses are different with ETS versus mainstream smoke exposure was supported by Wong *et al.* (2004) above. In addition, as suggested by Law and Wald (2003), the response of ischemic heart disease to smoke exposure appears to be non-linear with a strong response at low smoke levels that tends to plateau at higher levels.

8.3.1. Cardiovascular Disease Deaths Attributable to ETS Exposure.

In California in 1999, an estimated 81.7% of the adult population (or 19,530,547 persons ≥ 18 years of age) were nonsmokers according to the 1999 California Tobacco Survey (Gilpin *et al.*, 2001). Of this group, 12.75% (2,490,145) were exposed to ETS at work and/or at home during the two weeks preceding the survey. In the following calculations, it is assumed that the general population is exposed at the same rate, and that the effects of exposure to ETS at home and at work are similar.

The 1997 Cal/EPA document suggested that ETS exposure increased the risk of CHD 20-50%. For CHD risk associated with ETS exposure at home, Ciruzzi *et al*. (1998) found an adjusted OR of 1.68 (95% CI 1.20-2.51) for exposure to one or more relatives. We expect the risk of CHD to fall in the range of 1.2-1.68. During 2000 in California there were 68,533 cardiac deaths (CDHS, 2000c). As stated above, the data suggest that the risk (OR) for cardiovascular disease associated with ETS is in the range of 1.2-1.68. The population attributable risk (PAR) may be calculated from the formula: PAR = p(OR-1)/p(OR-1)+1, where p is the portion of the nonsmoking population exposed to ETS. For nonsmoking indoor workers, the lower OR of 1.2 gives an attributable risk of 0.025 [0.1275*(1.2-1)]/[0.1275*(1.2-1)+1 = 0.025], and the upper OR of 1.68 gives 0.080 [0.1275*(1.68-1)]/ [0.1275*(1.68-1)+1 = 0.080]. Thus the PAR is in the range of 2.5-8.0%. For cardiac death in California in 2000, this translates into 1,700 – 5,483 excess deaths attributable to ETS exposure. For the U.S., there were 515,204 cases of death due to ischemic heart disease in 2000 (Anderson and Arias, 2003). According to Pirkle *et al*. (1996), the rate of ETS exposure among non-smoking adults in NHANES-III was approximately 23%. For the lower end of the range, a = 0.23(1.2-1)/(0.23(1.2-1)+1) = 0.044, and 515,204 x 0.044 = 22,669. For the high end, a = 0.23(1.68-1)/(0.23(1.68-1)+1) = 0.135, and 0.135 x 515,204 = 69,553. Thus the range of excess deaths from heart disease attributable to ETS exposure in the U.S. in 2000 was 22,669 – 69,553.

These estimates may be high as they are based on any ETS exposure and exposure intensities were not determined. On the other hand they exclude other ETS exposures outside of work or home, such as in vehicles and in other environments, and they exclude outdoor workers. Thus the actual number of exposed persons and ETS exposure levels may be higher. The upper risk estimate used in this calculation of the PAR is higher than that used in the 1997 Cal/EPA document, reflecting the growing body of evidence more strongly linking ETS exposure to CHD. As a result, the general decline in ETS exposure, reflected in the lower end of this estimate, is partially offset by the stronger causal association.

Thus recent research continues to indicate that ETS exposure increases the risk of cardiovascular disease and stroke. It is also evident that these effects exacerbate or are exacerbated by under-lying conditions, and individuals with other chronic conditions such as diabetes, vascular disease or hypertension comprise a susceptible population at even greater risk from ETS exposure.

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