

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.

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.* Liliensfeld and Liliensfeld, 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

	Conclusion OEHHA 1997	Conclusion OEHHA 1997	Conclusion Update	Conclusion Update
Outcome	Annual Excess # in CA	Annual Excess # in US	Annual Excess # in CA	Annual Excess # in US
Pregnancy: Low Birth Weight Pre-Term Delivery	1,200-2,200	9,700-18,600	1,600 ¹ 4,700 ¹	24,500 ² 71,900 ²
Asthma (in children): # Episodes ³ # New cases #Exacerbations			31,000 ⁴	202,300 ⁵
	960-3120	8,000-26,000	N/A	N/A
	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 (Pirke *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 7.4.11.

N/A = data not available.

1.7. References

- Anderson RN, Arias E (2003). The effect of revised populations on mortality statistics for the United States, 2000. Table 2. Comparison of deaths, crude death rates, and age-related death rates for 113 selected causes of death: United States, 2000. *National Vital Statistics Report* 51 (9).
- Bero LA, Glantz SA, Rennie D (1994). Publication bias and public health policy on environmental tobacco smoke. *JAMA* 272(2):133-6.
- Breslow NE, Day NE (1980). *Statistical Methods in Cancer Research. Volume I: The Analysis of Case-Control Data.* International Agency for Research on Cancer Scientific Publication Series No. 32, IARC, Lyon. Pp. 73-78
- 2001 California Health Interview Survey (2002). Asthma symptom prevalence in California in 2001. www.healthpolicy.ucla.edu/pubs/files/Asthma_Rpt_FINAL_R.pdf.
- California Department of Health Services (CDHS, 2001). The California tobacco control program: a decade of progress, results from the California Tobacco Survey, 1990-1999. Sacramento, CA: California Department of Health Services, Tobacco Control Section.
- California Department of Health Services (CDHS, 2000a). Vital Statistics of California 2000. Table 2-6. Number and percent of live births with selected medical characteristics by race/ethnic group of mother, California 2000. www.dhs.ca.gov/hisp/chs/ohir/reports/vitalstatisticsofcalifornia/vsofca2000.pdf
- California Department of Health Services (CDHS, 2000b). Vital Statistics of California 2000. Table 4-8. Leading causes of infant death by race/ethnic group of child, California, 2000. www.dhs.ca.gov/hisp/chs/ohir/reports/vitalstatisticsofcalifornia/vsofca2000.pdf
- California Department of Health Services (CDHS, 2000c). Vital Statistics of California 2000. Table 5-9. Deaths, death rates, and age-adjusted death rates for leading causes by sex, California, 1999-2000. www.dhs.ca.gov/hisp/chs/ohir/reports/vitalstatisticsofcalifornia/vsofca2000.pdf
- California Environmental Protection Agency (Cal EPA, 1997). Health effects of exposure to environmental tobacco smoke. Final Report, September, 1997. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Sacramento, CA.
- Centers for Disease Control (CDC, 2002a). National Center for Health Statistics. Table E. Number of infant deaths, percent of total infant deaths, and infant mortality rates for 2000, and percent change in infant mortality rates from 1999 to 2000 for the 10 leading causes of infant death in 2000: United States. *National Vital Statistics Report* 50 (15): 13.
- Centers for Disease Control (CDC, 2002b) *Vital Statistics Report. Vol 51(2) 2002. Births: Final data for 2001.*
- Coultas DB, Peake GT, Samet JM (1989). Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. *Am J Epidemiol.* 130(2):338-47.
- Emmons KM, Abrams DB, Marshall RJ, Etzel RA, Novotny TE, Marcus BH, Kane ME (1992). Exposure to environmental tobacco smoke in naturalistic settings. *Am J Publ Health* 82:24-27.
- Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, *et al.* (1994). Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *JAMA* 271(22):1752-9.
- Freid VM, Makuc DM, Rooks RN (1998). Ambulatory health care visits by children. Principal diagnosis and place of visit for years 1993-1995. *National Vital Statistics* 13 (137). Table 2.

- Friedman GD, Petiti DB, Bawol RD (1983). Prevalence and Correlates of Passive Smoking. *Am J Public Health* 73:401-405.
- Gilpin EA, Emery SL, Farkas AJ, Distefan JM, White MM, Pierce JP (2001). The California tobacco control program: a decade of progress, results from the California Tobacco Surveys, 1990-1999. University of California, San Diego: La Jolla, CA.
- Greenberg RA, Bauman KE, Glover LH, Strecher VJ, Kleinbaum DG, Haley NJ, Stedman HC, Fowler MG, Loda FA (1989). Ecology of passive smoking by young infants. *J Pediatr* 114:774-780.
- Greenland S (1987). Quantitative methods in the review of epidemiologic literature. *Epidemiol Reviews* 9:1-30
- Greenland S, Longnecker MP (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 135:1301-9.
- Hertz-Picciotto (1998). Environmental epidemiology. In: Modern Epidemiology. Rothman K and Greenland S, eds. Lippincott-Raven Publishers, Philadelphia, PA. Pp 557-561.
- Hill AB (1971). Principles of Medical Statistics. Chapter XXIV: Statistical Evidence and Inference. pp. 309-323. Oxford University Press, Oxford, UK .
- Institute of Medicine (2004). Gulf War and Health: Updated Literature Review of Sarin. The National Academy of Sciences, National Academies Press, Washington, D.C. www.nap.edu.. Pp. 20-22.
- International Agency for Research on Cancer (IARC, 2004). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoke and Involuntary Smoking. Volume 83. Lyon, France: World Health Organization.
- Johnson KC, Hu J, Mao Y (2001). Lifetime residential and workplace exposure to environmental tobacco smoke and lung cancer in never-smoking women, Canada 1994-97. *Intl J Cancer* 93(6):902-6.
- Kelsey JL, Whittemore, AS, Evans, AS (1996). Methods in observational epidemiology / 2nd ed. (432 p.) Oxford University Press, New York: 1996. Pp.37-40.
- Lilienfeld AM and Lilienfeld DE (1980a). Foundations of Epidemiology, 2nd Edition. Oxford University Press, 1980. Pp. 289-321.
- Lilienfeld AM and Lilienfeld DE (1980b). Foundations of Epidemiology, 2nd Edition. Oxford University Press, 1980. Pp.217-218.
- Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC (2002b). Surveillance for Asthma – United States, 1980-1999. *MMWR* 51 (ss-1) Pp 1-13.
- National Cancer Institute (NCI, 1999). *Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency. Smoking and Tobacco Control Monograph no. 10*. Bethesda, MD. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Pub. No. 99-4645, 1999.
- National Research Council (NRC, 1986g). *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, NRC, National Academy Press, Washington, DC.Pp.10-12.
- Nyberg F, Isaksson I, Harris JR, Pershagen G (1997). Misclassification of smoking status and lung cancer risk from environmental tobacco smoke in never-smokers. *Epidemiology* 8:304-309.

Nyberg F, Agudo A, Boffetta P, Fortes C, Gonzalez CA, Pershagen G (1998b). A European validation study of smoking and environmental tobacco smoke exposure in nonsmoking lung cancer cases and controls. *Cancer Causes Cont* 9(2):173-82.

Office of Environmental Health Hazard Assessment (OEHHA, 1998) Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant. Part B. Health Risk Assessment for Diesel Exhaust. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. April 22, 1998. Pp6-30; C-25.

Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR (1996). Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *JAMA* 275(16):1233-40.

Rothman KJ and Greenland S., eds. (1998). *Modern Epidemiology*. Lippincott-Raven Publishers, Philadelphia, PA. Pp.24-28; 643-673.

U.S. Department of Health and Human Services (U.S. DHHS, 1982). *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General*. U.S. DHHS, Public Health Service, Office on Smoking and Health, U.S. Government Printing Office, Washington, DC. Pp. 1-25.

U.S. Department of Health and Human Services (U.S. DHHS, 1986a). *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General*. U.S. DHHS, Public Health Service, Office on Smoking and Health, U.S. Government Printing Office, Washington, DC. Pp. 66-102.

U.S. Department of Health and Human Services (U.S. DHHS, 2004a). *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General*. U.S. DHHS, Public Health Service, Office on Smoking and Health, U.S. Government Printing Office, Washington, DC. Pp. 17-24

U.S. Department of Health, Education and Welfare (U.S. DHEW, 1979). *Smoking and Health: A Report of the Surgeon General*. U.S. DHEW, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79-50066. pp.1-24 to 1-25.

U.S. Environmental Protection Agency (U.S. EPA, 1992a). *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA/600/6-90/006F. Pp 5-66--5-68.

U.S. Environmental Protection Agency (U.S. EPA, 1992b). *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA/600/6-90/006F Pp 7-20--7-21.

U.S. Environmental Protection Agency (U.S. EPA, 1992c). *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA/600/6-90/006F Pp 6-1--6-31.

U.S. Environmental Protection Agency (U.S. EPA, 1992d). *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA/600/6-90/006F Pp B-11.

Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, Walker M, Cook DG (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ* 329(7459):200-205.