

Chapter 1

Introduction, Summary, and Conclusions

Introduction 3

Organization of the Report 8

Preparation of the Report 9

Definitions and Terminology 9

Evidence Evaluation 10

Major Conclusions 11

Chapter Conclusions 12

Chapter 2. Toxicology of Secondhand Smoke 12

Evidence of Carcinogenic Effects from Secondhand Smoke Exposure 12

Mechanisms of Respiratory Tract Injury and Disease Caused by Secondhand Smoke Exposure 12

Mechanisms of Secondhand Smoke Exposure and Heart Disease 12

Chapter 3. Assessment of Exposure to Secondhand Smoke 12

Building Designs and Operations 12

Exposure Models 12

Biomarkers of Exposure to Secondhand Smoke 12

Chapter 4. Prevalence of Exposure to Secondhand Smoke 13

Chapter 5. Reproductive and Developmental Effects from Exposure to Secondhand Smoke 13

Fertility 13

Pregnancy (Spontaneous Abortion and Perinatal Death) 13

Infant Deaths 13

Sudden Infant Death Syndrome 13

Preterm Delivery 13

Low Birth Weight 13

Congenital Malformations 13

Cognitive Development 13

Behavioral Development 13

Height/Growth 13

Childhood Cancer 13

Chapter 6. Respiratory Effects in Children from Exposure to Secondhand Smoke 14

Lower Respiratory Illnesses in Infancy and Early Childhood 14

Middle Ear Disease and Adenotonsillectomy 14

Respiratory Symptoms and Prevalent Asthma in School-Age Children 14

Childhood Asthma Onset 14

Atopy 14

Lung Growth and Pulmonary Function 14

Chapter 7. Cancer Among Adults from Exposure to Secondhand Smoke 14

Lung Cancer 14

Breast Cancer 15

Nasal Sinus Cavity and Nasopharyngeal Carcinoma 15

Cervical Cancer 15

Chapter 8. Cardiovascular Diseases from Exposure to Secondhand Smoke	15
Chapter 9. Respiratory Effects in Adults from Exposure to Secondhand Smoke	15
Odor and Irritation	15
Respiratory Symptoms	15
Lung Function	15
Asthma	16
Chronic Obstructive Pulmonary Disease	16
Chapter 10. Control of Secondhand Smoke Exposure	16
Methodologic Issues	17
Classification of Secondhand Smoke Exposure	17
Misclassification of Secondhand Smoke Exposure	19
Use of Meta-Analysis	21
Confounding	22
Tobacco Industry Activities	23
References	24

Introduction

The topic of passive or involuntary smoking was first addressed in the 1972 U.S. Surgeon General's report (*The Health Consequences of Smoking*, U.S. Department of Health, Education, and Welfare [USDHEW] 1972), only eight years after the first Surgeon General's report on the health consequences of active smoking (USDHEW 1964). Surgeon General Dr. Jesse Steinfeld had raised concerns about this topic, leading to its inclusion in that report. According to the 1972 report, nonsmokers inhale the mixture of sidestream smoke given off by a smoldering cigarette and mainstream smoke exhaled by a smoker, a mixture now referred to as "secondhand smoke" or "environmental tobacco smoke." Cited experimental studies showed that smoking in enclosed spaces could lead to high levels of cigarette smoke components in the air. For carbon monoxide (CO) specifically, levels in enclosed spaces could exceed levels then permitted in outdoor air. The studies supported a conclusion that "an atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals" (USDHEW 1972, p. 7). The possibility that CO emitted from cigarettes could harm persons with chronic heart or lung disease was also mentioned.

Secondhand tobacco smoke was then addressed in greater depth in Chapter 4 (Involuntary Smoking) of the 1975 Surgeon General's report, *The Health Consequences of Smoking* (USDHEW 1975). The chapter noted that involuntary smoking takes place when nonsmokers inhale both sidestream and exhaled mainstream smoke and that this "smoking" is "involuntary" when "the exposure occurs as an unavoidable consequence of breathing in a smoke-filled environment" (p. 87). The report covered exposures and potential health consequences of involuntary smoking, and the researchers concluded that smoking on buses and airplanes was annoying to nonsmokers and that involuntary smoking had potentially adverse consequences for persons with heart and lung diseases. Two studies on nicotine concentrations in nonsmokers raised concerns about nicotine as a contributing factor to atherosclerotic cardiovascular disease in nonsmokers.

The 1979 Surgeon General's report, *Smoking and Health: A Report of the Surgeon General* (USDHEW 1979), also contained a chapter entitled "Involuntary Smoking." The chapter stressed that "attention to involuntary smoking is of recent vintage, and only

limited information regarding the health effects of such exposure upon the nonsmoker is available" (p. 11–35). The chapter concluded with recommendations for research including epidemiologic and clinical studies. The 1982 Surgeon General's report specifically addressed smoking and cancer (U.S. Department of Health and Human Services [USDHHS] 1982). By 1982, there were three published epidemiologic studies on involuntary smoking and lung cancer, and the 1982 Surgeon General's report included a brief chapter on this topic. That chapter commented on the methodologic difficulties inherent in such studies, including exposure assessment, the lengthy interval during which exposures are likely to be relevant, and accounting for exposures to other carcinogens. Nonetheless, the report concluded that "Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem" (p. 251).

Involuntary smoking was also reviewed in the 1984 report, which focused on chronic obstructive pulmonary disease and smoking (USDHHS 1984). Chapter 7 (Passive Smoking) of that report included a comprehensive review of the mounting information on smoking by parents and the effects on respiratory health of their children, data on irritation of the eye, and the more limited evidence on pulmonary effects of involuntary smoking on adults. The chapter began with a compilation of measurements of tobacco smoke components in various indoor environments. The extent of the data had increased substantially since 1972. By 1984, the data included measurements of more specific indicators such as acrolein and nicotine, and less specific indicators such as particulate matter (PM), nitrogen oxides, and CO. The report reviewed new evidence on exposures of nonsmokers using biomarkers, with substantial information on levels of cotinine, a major nicotine metabolite. The report anticipated future conclusions with regard to respiratory effects of parental smoking on child respiratory health (Table 1.1).

Involuntary smoking was the topic for the entire 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking* (USDHHS 1986). In its 359 pages, the report covered the full breadth of the

Table 1.1 Conclusions from previous Surgeon General's reports on the health effects of secondhand smoke exposure

Disease and statement	Surgeon General's report
Coronary heart disease: "The presence of such levels" as found in cigarettes "indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from. . .coronary heart disease." (p. 7)	1972
Chronic respiratory symptoms (adults): "The presence of such levels" as found in cigarettes "indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease. . . ." (p. 7)	1972
Pulmonary function: "Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to affect adversely animal pulmonary. . .function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known." (pp. 7–8)	1972
Asthma: "The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma." (p. 13)	1984
Bronchitis and pneumonia: "The children of smoking parents have an increased prevalence of reported respiratory symptoms, and have an increased frequency of bronchitis and pneumonia early in life." (p. 13)	1984
Pulmonary function (children): "The children of smoking parents appear to have measurable but small differences in tests of pulmonary function when compared with children of nonsmoking parents. The significance of this finding to the future development of lung disease is unknown." (p. 13)	1984
Pulmonary function (adults): ". . .some studies suggest that high levels of involuntary [tobacco] smoke exposure might produce small changes in pulmonary function in normal subjects. . . . Two studies have reported differences in measures of lung function in older populations between subjects chronically exposed to involuntary smoking and those who were not. This difference was not found in a younger and possibly less exposed population." (p. 13)	1984
Acute respiratory infections: "The children of parents who smoke have an increased frequency of a variety of acute respiratory illnesses and infections, including chest illnesses before 2 years of age and physician-diagnosed bronchitis, tracheitis, and laryngitis, when compared with the children of nonsmokers." (p. 13)	1986
Bronchitis and pneumonia: "The children of parents who smoke have an increased frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared with the children of nonsmokers." (p. 13)	1986
Cancers other than lung: "The associations between cancers, other than cancer of the lung, and involuntary smoking require further investigation before a determination can be made about the relationship of involuntary smoking to these cancers." (p. 14)	1986
Cardiovascular disease: "Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease." (p. 14)	1986

Table 1.1 Continued

Disease and statement	Surgeon General's report
Chronic cough and phlegm (children): "Chronic cough and phlegm are more frequent in children whose parents smoke compared with children of nonsmokers." (p. 13)	1986
Chronic obstructive pulmonary disease (COPD): "Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone." (pp. 13–14) "The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study." (p. 13)	1986
Lung cancer: "Involuntary smoking can cause lung cancer in nonsmokers." (p. 13)	1986
Middle ear effusions: "A number of studies report that chronic middle ear effusions are more common in young children whose parents smoke than in children of nonsmoking parents." (p. 14)	1986
Pulmonary function (children): "The children of parents who smoke have small differences in tests of pulmonary function when compared with the children of nonsmokers. Although this decrement is insufficient to cause symptoms, the possibility that it may increase susceptibility to chronic obstructive pulmonary disease with exposure to other agents in adult life, e.g., [sic] active smoking or occupational exposures, needs investigation." (p. 13)	1986
Other: "An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals." (p. 7)	1972
"Cigarette smoke can make a significant, measurable contribution to the level of indoor air pollution at levels of smoking and ventilation that are common in the indoor environment." (p. 13)	1984
"Cigarette smoke in the air can produce an increase in both subjective and objective measures of eye irritation." (p. 13)	1984
"Nonsmokers who report exposure to environmental tobacco smoke have higher levels of urinary cotinine, a metabolite of nicotine, than those who do not report such exposure." (p. 13)	1984
"The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke." (p. 13)	1986
"Validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments." (p. 14)	1986

Sources: U.S. Department of Health, Education, and Welfare 1972; U.S. Department of Health and Human Services 1984, 1986.

topic, addressing toxicology and dosimetry of tobacco smoke; the relevant evidence on active smoking; patterns of exposure of nonsmokers to tobacco smoke; the epidemiologic evidence on involuntary smoking and disease risks for infants, children, and adults; and policies to control involuntary exposure to tobacco smoke. That report concluded that involuntary smoking caused lung cancer in lifetime nonsmoking adults and was associated with adverse effects on respiratory health in children. The report also stated that simply separating smokers and nonsmokers within the same airspace reduced but did not eliminate exposure to secondhand smoke. All of these findings are relevant to public health and public policy (Table 1.1). The lung cancer conclusion was based on extensive information already available on the carcinogenicity of active smoking, the qualitative similarities between secondhand and mainstream smoke, the uptake of tobacco smoke components by nonsmokers, and the epidemiologic data on involuntary smoking. The three major conclusions of the report (Table 1.2), led Dr. C. Everett Koop, Surgeon General at the time, to comment in his preface that “the right of smokers to smoke ends where their behavior affects the health and well-being of others; furthermore, it is the smokers’ responsibility to ensure that they do not expose nonsmokers to the potential [sic] harmful effects of tobacco smoke” (USDHHS 1986, p. xii).

Two other reports published in 1986 also reached the conclusion that involuntary smoking increased the risk for lung cancer. The International Agency for Research on Cancer (IARC) of the World Health Organization concluded that “passive smoking gives rise to some risk of cancer” (IARC 1986, p. 314). In its monograph on tobacco smoking, the agency supported this conclusion on the basis of the characteristics of sidestream and mainstream smoke, the

absorption of tobacco smoke materials during an involuntary exposure, and the nature of dose-response relationships for carcinogenesis. In the same year, the National Research Council (NRC) also concluded that involuntary smoking increases the incidence of lung cancer in nonsmokers (NRC 1986). In reaching this conclusion, the NRC report cited the biologic plausibility of the association between exposure to secondhand smoke and lung cancer and the supporting epidemiologic evidence. On the basis of a pooled analysis of the epidemiologic data adjusted for bias, the report concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25 percent, compared with nonsmokers married to nonsmokers. With regard to the effects of involuntary smoking on children, the NRC report commented on the literature linking secondhand smoke exposures from parental smoking to increased risks for respiratory symptoms and infections and to a slightly diminished rate of lung growth.

Since 1986, the conclusions with regard to both the carcinogenicity of secondhand smoke and the adverse effects of parental smoking on the health of children have been echoed and expanded (Table 1.3). In 1992, the U.S. Environmental Protection Agency (EPA) published its risk assessment of secondhand smoke as a carcinogen (USEPA 1992). The agency’s evaluation drew on toxicologic information on secondhand smoke and the extensive literature on active smoking. A comprehensive meta-analysis of the 31 epidemiologic studies of secondhand smoke and lung cancer published up to that time was central to the decision to classify secondhand smoke as a group A carcinogen—namely, a known human carcinogen. Estimates of approximately 3,000 U.S. lung cancer deaths per year in nonsmokers were attributed to secondhand smoke. The report also covered other respiratory health effects in

Table 1.2 **Major conclusions of the 1986 Surgeon General’s report, *The Health Consequences of Involuntary Smoking***

1. Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers.
2. The children of parents who smoke compared with the children of nonsmoking parents have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures.
3. The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke.

Source: U.S. Department of Health and Human Services 1986, p. 7.

Table 1.3 Selected major reports, other than those of the U.S. Surgeon General, addressing adverse effects from exposure to tobacco smoke

Agency	Publication	Place and date of publication
National Research Council	<i>Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects</i>	Washington, D.C. United States 1986
International Agency for Research on Cancer (IARC)	<i>Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking</i> (IARC Monograph 38)	Lyon, France 1986
U.S. Environmental Protection Agency (EPA)	<i>Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders</i>	Washington, D.C. United States 1992
National Health and Medical Research Council	<i>The Health Effects of Passive Smoking</i>	Canberra, Australia 1997
California EPA (Cal/EPA), Office of Environmental Health Hazard Assessment	<i>Health Effects of Exposure to Environmental Tobacco Smoke</i>	Sacramento, California United States 1997
Scientific Committee on Tobacco and Health	<i>Report of the Scientific Committee on Tobacco and Health</i>	London, United Kingdom 1998
World Health Organization	<i>International Consultation on Environmental Tobacco Smoke (ETS) and Child Health. Consultation Report</i>	Geneva, Switzerland 1999
IARC	<i>Tobacco Smoke and Involuntary Smoking</i> (IARC Monograph 83)	Lyon, France 2004
Cal/EPA, Office of Environmental Health Hazard Assessment	<i>Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant</i>	Sacramento, California United States 2005

children and adults and concluded that involuntary smoking is causally associated with several adverse respiratory effects in children. There was also a quantitative risk assessment for the impact of involuntary smoking on childhood asthma and lower respiratory tract infections in young children.

In the decade since the 1992 EPA report, scientific panels continued to evaluate the mounting evidence linking involuntary smoking to adverse health effects (Table 1.3). The most recent was the 2005 report of the California EPA (Cal/EPA 2005). Over time, research has repeatedly affirmed the conclusions of the 1986 Surgeon General's reports and studies have further identified causal associations of involuntary smoking with diseases and other health disorders. The epidemiologic evidence on involuntary smoking has

markedly expanded since 1986, as have the data on exposure to tobacco smoke in the many environments where people spend time. An understanding of the mechanisms by which involuntary smoking causes disease has also deepened.

As part of the environmental health hazard assessment, Cal/EPA identified specific health effects causally associated with exposure to secondhand smoke. The agency estimated the annual excess deaths in the United States that are attributable to secondhand smoke exposure for specific disorders: sudden infant death syndrome (SIDS), cardiac-related illnesses (ischemic heart disease), and lung cancer (Cal/EPA 2005). For the excess incidence of other health outcomes, either new estimates were provided or estimates from the 1997 health hazard assessment were

used without any revisions (Cal/EPA 1997). Overall, Cal/EPA estimated that about 50,000 excess deaths result annually from exposure to secondhand smoke (Cal/EPA 2005). Estimated annual excess deaths for the total U.S. population are about 3,400 (a range of 3,423 to 8,866) from lung cancer, 46,000 (a range of 22,700 to 69,600) from cardiac-related illnesses, and 430 from SIDS. The agency also estimated that between 24,300 and 71,900 low birth weight or pre-term deliveries, about 202,300 episodes of childhood asthma (new cases and exacerbations), between 150,000 and 300,000 cases of lower respiratory illness in children, and about 789,700 cases of middle ear infections in children occur each year in the United States as a result of exposure to secondhand smoke.

This new 2006 Surgeon General's report returns to the topic of involuntary smoking. The health effects of involuntary smoking have not received comprehensive coverage in this series of reports since 1986. Reports since then have touched on selected aspects of the topic: the 1994 report on tobacco use among young people (USDHHS 1994), the 1998 report on tobacco use among U.S. racial and ethnic minorities (USDHHS 1998), and the 2001 report on women and smoking (USDHHS 2001). As involuntary smoking remains widespread in the United States and elsewhere, the preparation of this report was motivated by the persistence of involuntary smoking as a public health problem and the need to evaluate the substantial new evidence reported since 1986. This report substantially expands the list of topics that were included in the 1986 report. Additional topics include SIDS, developmental effects, and other reproductive effects; heart disease in adults; and cancer sites beyond the lung. For some associations of involuntary smoking with adverse health effects, only a few studies were reviewed in 1986 (e.g., ear disease in children); now, the relevant literature is substantial. Consequently, this report uses meta-analysis to quantitatively summarize evidence as appropriate. Following the approach used in the 2004 report (*The Health Consequences of Smoking*, USDHHS 2004), this 2006 report also systematically evaluates the evidence for causality, judging the extent of the evidence available and then making an inference as to the nature of the association.

Organization of the Report

This twenty-ninth report of the Surgeon General examines the topics of toxicology of secondhand smoke, assessment and prevalence of exposure to

secondhand smoke, reproductive and developmental health effects, respiratory effects of exposure to secondhand smoke in children and adults, cancer among adults, cardiovascular diseases, and the control of secondhand smoke exposure.

This introductory chapter (Chapter 1) includes a discussion of the concept of causation and introduces concepts of causality that are used throughout this report; this chapter also summarizes the major conclusions of the report. Chapter 2 (Toxicology of Secondhand Smoke) sets out a foundation for interpreting the observational evidence that is the focus of most of the following chapters. The discussion details the mechanisms that enable tobacco smoke components to injure the respiratory tract and cause nonmalignant and malignant diseases and other adverse effects. Chapter 3 (Assessment of Exposure to Secondhand Smoke) provides a perspective on key factors that determine exposures of people to secondhand smoke in indoor environments, including building designs and operations, atmospheric markers of secondhand smoke, exposure models, and biomarkers of exposure to secondhand smoke. Chapter 4 (Prevalence of Exposure to Secondhand Smoke) summarizes findings that focus on nicotine measurements in the air and cotinine measurements in biologic materials. The chapter includes exposures in the home, workplace, public places, and special populations. Chapter 5 (Reproductive and Developmental Effects from Exposure to Secondhand Smoke) reviews the health effects on reproduction, on infants, and on child development. Chapter 6 (Respiratory Effects in Children from Exposure to Secondhand Smoke) examines the effects of parental smoking on the respiratory health of children. Chapter 7 (Cancer Among Adults from Exposure to Secondhand Smoke) summarizes the evidence on cancer of the lung, breast, nasal sinuses, and the cervix. Chapter 8 (Cardiovascular Diseases from Exposure to Secondhand Smoke) discusses coronary heart disease (CHD), stroke, and subclinical vascular disease. Chapter 9 (Respiratory Effects in Adults from Exposure to Secondhand Smoke) examines odor and irritation, respiratory symptoms, lung function, and respiratory diseases such as asthma and chronic obstructive pulmonary disease. Chapter 10 (Control of Secondhand Smoke Exposure) considers measures used to control exposure to secondhand smoke in public places, including legislation, education, and approaches based on building designs and operations. The report concludes with "A Vision for the Future." Major conclusions of the report were distilled from the chapter conclusions and appear later in this chapter.

Preparation of the Report

This report of the Surgeon General was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Coordinating Center for Health Promotion, Centers for Disease Control and Prevention (CDC), and U.S. DHHS. Initial chapters were written by 22 experts who were selected because of their knowledge of a particular topic. The contributions of the initial experts were consolidated into 10 major chapters that were then reviewed by more than 40 peer reviewers. The entire manuscript was then sent to more than 30 scientists and experts who reviewed it for its scientific integrity. After each review cycle, the drafts were revised by the scientific editors on the basis of the experts' comments. Subsequently, the report was reviewed by various institutes and agencies

within U.S. DHHS. Publication lags, even short ones, prevent an up-to-the-minute inclusion of all recently published articles and data. Therefore, by the time the public reads this report, there may be additional published studies or data. To provide published information as current as possible, this report includes an Appendix of more recent studies that represent major additions to the literature.

This report is also accompanied by a companion database of key evidence that is accessible through the Internet (<http://www.cdc.gov/tobacco>). The database includes a uniform description of the studies and results on the health effects of exposure to secondhand smoke that were presented in a format compatible with abstraction into standardized tables. Readers of the report may access these data for additional analyses, tables, or figures.

Definitions and Terminology

The inhalation of tobacco smoke by nonsmokers has been variably referred to as "passive smoking" or "involuntary smoking." Smokers, of course, also inhale secondhand smoke. Cigarette smoke contains both particles and gases generated by the combustion at high temperatures of tobacco, paper, and additives. The smoke inhaled by nonsmokers that contaminates indoor spaces and outdoor environments has often been referred to as "secondhand smoke" or "environmental tobacco smoke." This inhaled smoke is the mixture of sidestream smoke released by the smoldering cigarette and the mainstream smoke that is exhaled by a smoker. Sidestream smoke, generated at lower temperatures and under somewhat different combustion conditions than mainstream smoke, tends to have higher concentrations of many of the toxins found in cigarette smoke (USDHHS 1986). However, it is rapidly diluted as it travels away from the burning cigarette.

Secondhand smoke is an inherently dynamic mixture that changes in characteristics and concentration with the time since it was formed and the

distance it has traveled. The smoke particles change in size and composition as gaseous components are volatilized and moisture content changes; gaseous elements of secondhand smoke may be adsorbed onto materials, and particle concentrations drop with both dilution in the air or environment and impaction on surfaces, including the lungs or on the body. Because of its dynamic nature, a specific quantitative definition of secondhand smoke cannot be offered.

This report uses the term secondhand smoke in preference to environmental tobacco smoke, even though the latter may have been used more frequently in previous reports. The descriptor "secondhand" captures the involuntary nature of the exposure, while "environmental" does not. This report also refers to the inhalation of secondhand smoke as involuntary smoking, acknowledging that most nonsmokers do not want to inhale tobacco smoke. The exposure of the fetus to tobacco smoke, whether from active smoking by the mother or from her exposure to secondhand smoke, also constitutes involuntary smoking.

Evidence Evaluation

Following the model of the 1964 report, the Surgeon General’s reports on smoking have included comprehensive compilations of the evidence on the health effects of smoking. The evidence is analyzed to identify causal associations between smoking and disease according to enunciated principles, sometimes referred to as the “Surgeon General’s criteria” or the “Hill” criteria (after Sir Austin Bradford Hill) for causality (USDHEW 1964; USDHHS 2004). Application of these criteria involves covering all relevant observational and experimental evidence. The criteria, offered in a brief chapter of the 1964 report entitled “Criteria for Judgment,” included (1) the consistency of the association, (2) the strength of the association, (3) the specificity of the association, (4) the temporal relationship of the association, and (5) the coherence of the association. Although these criteria have been criticized (e.g., Rothman and Greenland 1998), they have proved useful as a framework for interpreting evidence on smoking and other postulated causes of disease, and for judging whether causality can be inferred.

In the 2004 report of the Surgeon General, *The Health Consequences of Smoking*, the framework for interpreting evidence on smoking and health was revisited in depth for the first time since the 1964 report (USDHHS 2004). The 2004 report provided a four-level hierarchy for interpreting evidence (Table 1.4). The categories acknowledge that evidence can be “suggestive” but not adequate to infer a causal relationship, and also allows for evidence that is “suggestive of no causal relationship.” Since the 2004 report, the individual chapter conclusions have consistently used this four-level hierarchy (Table 1.4), but

evidence syntheses and other summary statements may use either the term “increased risk” or “cause” to describe instances in which there is sufficient evidence to conclude that active or involuntary smoking causes a disease or condition. This four-level framework also sharply and completely separates conclusions regarding causality from the implications of such conclusions.

That same framework was used in this report on involuntary smoking and health. The criteria dating back to the 1964 Surgeon General’s report remain useful as guidelines for evaluating evidence (USDHEW 1964), but they were not intended to be applied strictly or as a “checklist” that needed to be met before the designation of “causal” could be applied to an association. In fact, for involuntary smoking and health, several of the criteria will not be met for some associations. Specificity, referring to a unique exposure-disease relationship (e.g., the association between thalidomide use during pregnancy and unusual birth defects), can be set aside as not relevant, as all of the health effects considered in this report have causes other than involuntary smoking. Associations are considered more likely to be causal as the strength of an association increases because competing explanations become less plausible alternatives. However, based on knowledge of dosimetry and mechanisms of injury and disease causation, the risk is anticipated to be only slightly or modestly increased for some associations of involuntary smoking with disease, such as lung cancer, particularly when the very strong relative risks found for active smokers are compared with those for lifetime nonsmokers. The finding of only a small elevation in risk, as in the

Table 1.4 Four-level hierarchy for classifying the strength of causal inferences based on available evidence

Level 1	Evidence is sufficient to infer a causal relationship.
Level 2	Evidence is suggestive but not sufficient to infer a causal relationship.
Level 3	Evidence is inadequate to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).
Level 4	Evidence is suggestive of no causal relationship .

Source: U.S. Department of Health and Human Services 2004.

example of spousal smoking and lung cancer risk in lifetime nonsmokers, does not weigh against a causal association; however, alternative explanations for a risk of a small magnitude need full exploration and cannot be so easily set aside as alternative explanations for a stronger association. Consistency, coherence, and the temporal relationship of involuntary smoking with disease are central to the interpretations in this report. To address coherence, the report draws not only on the evidence for involuntary smoking, but on the even more extensive literature on active smoking and disease.

Although the evidence reviewed in this report comes largely from investigations of secondhand smoke specifically, the larger body of evidence on active smoking is also relevant to many of the associations that were evaluated. The 1986 report found secondhand smoke to be qualitatively similar to mainstream smoke inhaled by the smoker and concluded that secondhand smoke would be expected to have “a toxic and carcinogenic potential that would

not be expected to be qualitatively different from that of MS [mainstream smoke]” (USDHHS 1986, p. 23). The 2004 report of the Surgeon General revisited the health consequences of active smoking (USDHHS 2004), and the conclusions substantially expanded the list of diseases and conditions caused by smoking. Chapters in the present report consider the evidence on active smoking that is relevant to biologic plausibility for causal associations between involuntary smoking and disease. The reviews included in this report cover evidence identified through search strategies set out in each chapter. Of necessity, the evidence on mechanisms was selectively reviewed. However, an attempt was made to cover all health studies through specified target dates. Because of the substantial amount of time involved in preparing this report, lists of new key references published after these cut-off dates are included in an Appendix. Literature reviews were extended when new evidence was sufficient to possibly change the level of a causal conclusion.

Major Conclusions

This report returns to involuntary smoking, the topic of the 1986 Surgeon General’s report. Since then, there have been many advances in the research on secondhand smoke, and substantial evidence has been reported over the ensuing 20 years. This report uses the revised language for causal conclusions that was implemented in the 2004 Surgeon General’s report (USDHHS 2004). Each chapter provides a comprehensive review of the evidence, a quantitative synthesis of the evidence if appropriate, and a rigorous assessment of sources of bias that may affect interpretations of the findings. The reviews in this report reaffirm and strengthen the findings of the 1986 report. With regard to the involuntary exposure of nonsmokers to tobacco smoke, the scientific evidence now supports the following major conclusions:

1. Secondhand smoke causes premature death and disease in children and in adults who do not smoke.
2. Children exposed to secondhand smoke are at an increased risk for sudden infant death syndrome (SIDS), acute respiratory infections, ear problems,

and more severe asthma. Smoking by parents causes respiratory symptoms and slows lung growth in their children.

3. Exposure of adults to secondhand smoke has immediate adverse effects on the cardiovascular system and causes coronary heart disease and lung cancer.
4. The scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke.
5. Many millions of Americans, both children and adults, are still exposed to secondhand smoke in their homes and workplaces despite substantial progress in tobacco control.
6. Eliminating smoking in indoor spaces fully protects nonsmokers from exposure to secondhand smoke. Separating smokers from nonsmokers, cleaning the air, and ventilating buildings cannot eliminate exposures of nonsmokers to secondhand smoke.

Chapter Conclusions

Chapter 2. Toxicology of Secondhand Smoke

Evidence of Carcinogenic Effects from Secondhand Smoke Exposure

1. More than 50 carcinogens have been identified in sidestream and secondhand smoke.
2. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and its condensates and tumors in laboratory animals.
3. The evidence is sufficient to infer that exposure of nonsmokers to secondhand smoke causes a significant increase in urinary levels of metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The presence of these metabolites links exposure to secondhand smoke with an increased risk for lung cancer.
4. The mechanisms by which secondhand smoke causes lung cancer are probably similar to those observed in smokers. The overall risk of secondhand smoke exposure, compared with active smoking, is diminished by a substantially lower carcinogenic dose.

Mechanisms of Respiratory Tract Injury and Disease Caused by Secondhand Smoke Exposure

5. The evidence indicates multiple mechanisms by which secondhand smoke exposure causes injury to the respiratory tract.
6. The evidence indicates mechanisms by which secondhand smoke exposure could increase the risk for sudden infant death syndrome.

Mechanisms of Secondhand Smoke Exposure and Heart Disease

7. The evidence is sufficient to infer that exposure to secondhand smoke has a prothrombotic effect.

8. The evidence is sufficient to infer that exposure to secondhand smoke causes endothelial cell dysfunctions.
9. The evidence is sufficient to infer that exposure to secondhand smoke causes atherosclerosis in animal models.

Chapter 3. Assessment of Exposure to Secondhand Smoke

Building Designs and Operations

1. Current heating, ventilating, and air conditioning systems alone cannot control exposure to secondhand smoke.
2. The operation of a heating, ventilating, and air conditioning system can distribute secondhand smoke throughout a building.

Exposure Models

3. Atmospheric concentration of nicotine is a sensitive and specific indicator for secondhand smoke.
4. Smoking increases indoor particle concentrations.
5. Models can be used to estimate concentrations of secondhand smoke.

Biomarkers of Exposure to Secondhand Smoke

6. Biomarkers suitable for assessing recent exposures to secondhand smoke are available.
7. At this time, cotinine, the primary proximate metabolite of nicotine, remains the biomarker of choice for assessing secondhand smoke exposure.
8. Individual biomarkers of exposure to secondhand smoke represent only one component of a complex mixture, and measurements of one marker may not wholly reflect an exposure to other components of concern as a result of involuntary smoking.

Chapter 4. Prevalence of Exposure to Secondhand Smoke

1. The evidence is sufficient to infer that large numbers of nonsmokers are still exposed to secondhand smoke.
2. Exposure of nonsmokers to secondhand smoke has declined in the United States since the 1986 Surgeon General's report, *The Health Consequences of Involuntary Smoking*.
3. The evidence indicates that the extent of secondhand smoke exposure varies across the country.
4. Homes and workplaces are the predominant locations for exposure to secondhand smoke.
5. Exposure to secondhand smoke tends to be greater for persons with lower incomes.
6. Exposure to secondhand smoke continues in restaurants, bars, casinos, gaming halls, and vehicles.

Chapter 5. Reproductive and Developmental Effects from Exposure to Secondhand Smoke

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability.

Pregnancy (Spontaneous Abortion and Perinatal Death)

2. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion.

Infant Deaths

3. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality.

Sudden Infant Death Syndrome

4. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome.

Preterm Delivery

5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery.

Low Birth Weight

6. The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight.

Congenital Malformations

7. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations.

Cognitive Development

8. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children.

Behavioral Development

9. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children.

Height/Growth

10. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth.

Childhood Cancer

11. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood cancer.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and childhood cancer.
13. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke during infancy and childhood cancer.
14. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood leukemias.
15. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood lymphomas.
16. The evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to secondhand smoke and childhood brain tumors.
17. The evidence is inadequate to infer the presence or absence of a causal relationship between prenatal and postnatal exposure to secondhand smoke and other childhood cancer types.

Chapter 6. Respiratory Effects in Children from Exposure to Secondhand Smoke

Lower Respiratory Illnesses in Infancy and Early Childhood

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and lower respiratory illnesses in infants and children.
2. The increased risk for lower respiratory illnesses is greatest from smoking by the mother.

Middle Ear Disease and Adenotonsillectomy

3. The evidence is sufficient to infer a causal relationship between parental smoking and middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion.

4. The evidence is suggestive but not sufficient to infer a causal relationship between parental smoking and the natural history of middle ear effusion.
5. The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and an increase in the risk of adenoidectomy or tonsillectomy among children.

Respiratory Symptoms and Prevalent Asthma in School-Age Children

6. The evidence is sufficient to infer a causal relationship between parental smoking and cough, phlegm, wheeze, and breathlessness among children of school age.
7. The evidence is sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age.

Childhood Asthma Onset

8. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of wheeze illnesses in early childhood.
9. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma.

Atopy

10. The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and the risk of immunoglobulin E-mediated allergy in their children.

Lung Growth and Pulmonary Function

11. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and persistent adverse effects on lung function across childhood.
12. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke after birth and a lower level of lung function during childhood.

Chapter 7. Cancer Among Adults from Exposure to Secondhand Smoke

Lung Cancer

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and lung cancer among lifetime nonsmokers. This conclusion extends to all secondhand smoke exposure, regardless of location.
2. The pooled evidence indicates a 20 to 30 percent increase in the risk of lung cancer from secondhand smoke exposure associated with living with a smoker.

Breast Cancer

3. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer.

Nasal Sinus Cavity and Nasopharyngeal Carcinoma

4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a risk of nasal sinus cancer among nonsmokers.
5. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and a risk of nasopharyngeal carcinoma among nonsmokers.

Cervical Cancer

6. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and the risk of cervical cancer among lifetime nonsmokers.

Chapter 8. Cardiovascular Diseases from Exposure to Secondhand Smoke

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risks of coronary heart disease morbidity and mortality among both men and women.
2. Pooled relative risks from meta-analyses indicate a 25 to 30 percent increase in the risk of coronary

heart disease from exposure to secondhand smoke.

3. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and an increased risk of stroke.
4. Studies of secondhand smoke and subclinical vascular disease, particularly carotid arterial wall thickening, are suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and atherosclerosis.

Chapter 9. Respiratory Effects in Adults from Exposure to Secondhand Smoke

Odor and Irritation

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and odor annoyance.
2. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and nasal irritation.
3. The evidence is suggestive but not sufficient to conclude that persons with nasal allergies or a history of respiratory illnesses are more susceptible to developing nasal irritation from secondhand smoke exposure.

Respiratory Symptoms

4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms including cough, wheeze, chest tightness, and difficulty breathing among persons with asthma.
5. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms including cough, wheeze, chest tightness, and difficulty breathing among healthy persons.
6. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and chronic respiratory symptoms.

Lung Function

7. The evidence is suggestive but not sufficient to infer a causal relationship between short-term secondhand smoke exposure and an acute decline in lung function in persons with asthma.
8. The evidence is inadequate to infer the presence or absence of a causal relationship between short-term secondhand smoke exposure and an acute decline in lung function in healthy persons.
9. The evidence is suggestive but not sufficient to infer a causal relationship between chronic secondhand smoke exposure and a small decrement in lung function in the general population.
10. The evidence is inadequate to infer the presence or absence of a causal relationship between chronic secondhand smoke exposure and an accelerated decline in lung function.

Asthma

11. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and adult-onset asthma.
12. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a worsening of asthma control.

Chronic Obstructive Pulmonary Disease

13. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and risk for chronic obstructive pulmonary disease.
14. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and morbidity in persons with chronic obstructive pulmonary disease.

Chapter 10. Control of Secondhand Smoke Exposure

1. Workplace smoking restrictions are effective in reducing secondhand smoke exposure.
2. Workplace smoking restrictions lead to less smoking among covered workers.
3. Establishing smoke-free workplaces is the only effective way to ensure that secondhand smoke exposure does not occur in the workplace.
4. The majority of workers in the United States are now covered by smoke-free policies.
5. The extent to which workplaces are covered by smoke-free policies varies among worker groups, across states, and by sociodemographic factors. Workplaces related to the entertainment and hospitality industries have notably high potential for secondhand smoke exposure.
6. Evidence from peer-reviewed studies shows that smoke-free policies and regulations do not have an adverse economic impact on the hospitality industry.
7. Evidence suggests that exposure to secondhand smoke varies by ethnicity and gender.
8. In the United States, the home is now becoming the predominant location for exposure of children and adults to secondhand smoke.
9. Total bans on indoor smoking in hospitals, restaurants, bars, and offices substantially reduce secondhand smoke exposure, up to several orders of magnitude with incomplete compliance, and with full compliance, exposures are eliminated.
10. Exposures of nonsmokers to secondhand smoke cannot be controlled by air cleaning or mechanical air exchange.

Methodologic Issues

Much of the evidence on the health effects of involuntary smoking comes from observational epidemiologic studies that were carried out to test hypotheses related to secondhand smoke and risk for diseases and other adverse health effects. The challenges faced in carrying out these studies reflect those of observational research generally: assessment of the relevant exposures and outcomes with sufficient validity and precision, selection of an appropriate study design, identification of an appropriate and sufficiently large study population, and collection of information on other relevant factors that may confound or modify the association being studied. The challenge of accurately classifying secondhand smoke exposures confronts all studies of such exposures, and consequently the literature on approaches to and limitations of exposure classification is substantial. Sources of bias that can affect the findings of epidemiologic studies have been widely discussed (Rothman and Greenland 1998), both in general and in relation to studies of involuntary smoking. Concerns about bias apply to any study of an environmental agent and disease risk: misclassification of exposures or outcomes, confounding effect modification, and proper selection of study participants. In addition, the generalizability of findings from one population to another (external validity) further determines the value of evidence from a study. Another methodologic concern affecting secondhand smoke literature comes from the use of meta-analysis to combine the findings of epidemiologic studies; general concerns related to the use of meta-analysis for observational data and more specific concerns related to involuntary smoking have also been raised. This chapter considers these methodologic issues in anticipation of more specific treatment in the following chapters.

Classification of Secondhand Smoke Exposure

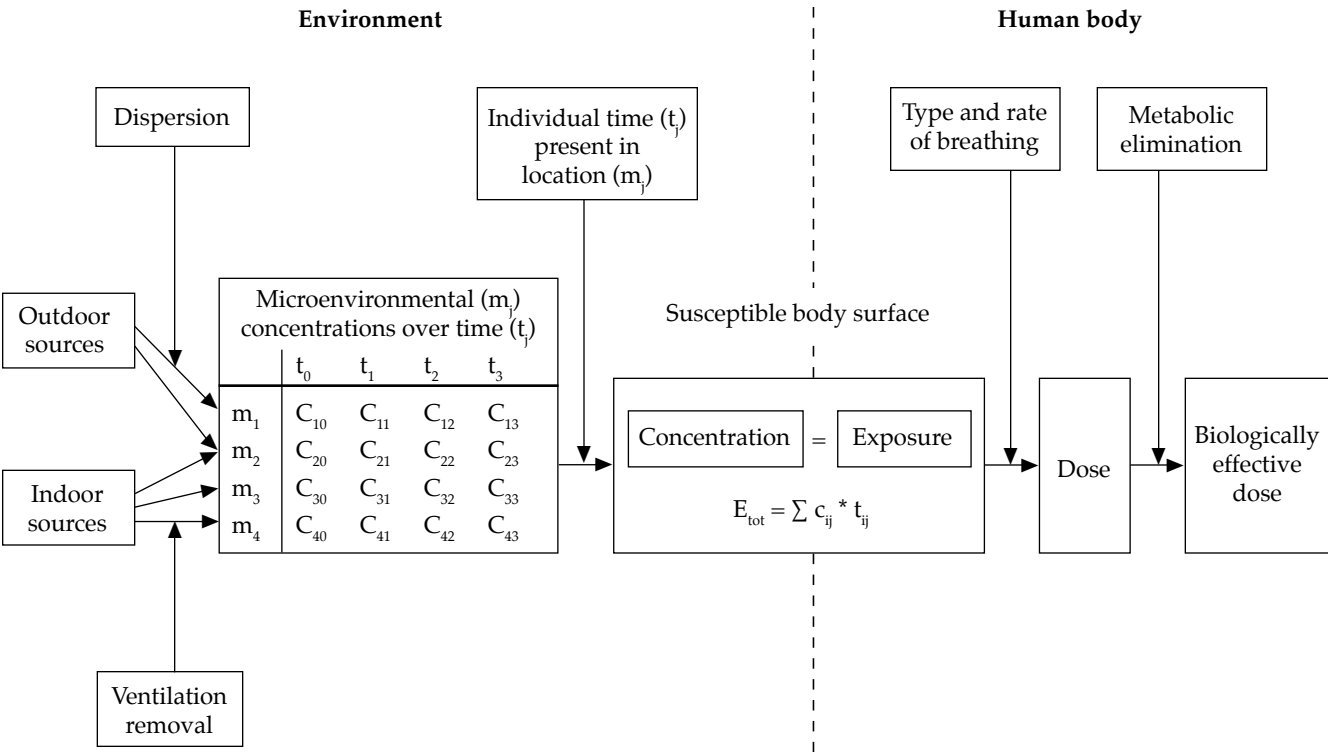
For secondhand smoke, as for any environmental factor that may be a cause of disease, the exposure assessment might encompass the time and place of the exposure, cumulative exposures, exposure during a particular time, or a recent exposure (Jaakkola and Jaakkola 1997; Jaakkola and Samet 1999). For example, exposures to secondhand smoke across the full life

span may be of interest for lung cancer, while only more recent exposures may be relevant to the exacerbation of asthma. For CHD, both temporally remote and current exposures may affect risk. Assessments of exposures are further complicated by the multiplicity of environments where exposures take place and the difficulty of characterizing the exposure in some locations, such as public places or workplaces. Additionally, exposures probably vary qualitatively and quantitatively over time and across locations because of temporal changes and geographic differences in smoking patterns.

Nonetheless, researchers have used a variety of approaches for exposure assessments in epidemiologic studies of adverse health effects from involuntary smoking. Several core concepts that are fundamental to these approaches are illustrated in Figure 1.1 (Samet and Jaakkola 1999). Cigarette smoking is, of course, the source of most secondhand smoke in the United States, followed by pipes, cigars, and other products. Epidemiologic studies generally focus on assessing the exposure, which is the contact with secondhand smoke. The concentrations of secondhand smoke components in a space depend on the number of smokers and the rate at which they are smoking, the volume into which the smoke is distributed, the rate at which the air in the space exchanges with uncontaminated air, and the rate at which the secondhand smoke is removed from the air. Concentration, exposure, and dose differ in their definitions, although the terms are sometimes used without sharp distinctions. However, surrogate indicators that generally describe a source of exposure may also be used to assess the exposure, such as marriage to a smoker or the number of cigarettes smoked in the home. Biomarkers can provide an indication of an exposure or possibly the dose, but for secondhand smoke they are used for recent exposure only.

People are exposed to secondhand smoke in a number of different places, often referred to as “microenvironments” (NRC 1991). A microenvironment is a definable location that has a constant concentration of the contaminant of interest, such as secondhand smoke, during the time that a person is there. Some key microenvironments for secondhand smoke include the home, the workplace, public places, and transportation environments (Klepeis 1999). Based

Figure 1.1 The determinants of exposure, dose, and biologically effective dose that underlie the development of health effects from smoking



Source: Samet and Jaakkola 1999. Reprinted with permission.

on the microenvironmental model, total exposure can be estimated as the weighted average of the concentrations of secondhand smoke or indicator compounds, such as nicotine, in the microenvironments where time is spent; the weights are the time spent in each microenvironment. Klepeis (1999) illustrates the application of the microenvironmental model with national data from the National Human Activity Pattern Survey conducted by the EPA. His calculations yield an overall estimate of exposure to airborne particles from smoking and of the contributions to this exposure from various microenvironments.

Much of the epidemiologic evidence addresses the consequences of an exposure in a particular microenvironment, such as the home (spousal smoking and lung cancer risk or maternal smoking and risk for asthma exacerbation), or the workplace (exacerbation of asthma by the presence of smokers). Some studies have attempted to cover multiple microenvironments

and to characterize exposures over time. For example, in the multicenter study of secondhand smoke exposure and lung cancer carried out in the United States, Fontham and colleagues (1994) assessed exposures during childhood, in workplaces, and at home during adulthood. Questionnaires that assess exposures have been the primary tool used in epidemiologic studies of secondhand smoke and disease. Measurement of biomarkers has been added in some studies, either as an additional and complementary exposure assessment approach or for validating questionnaire responses. Some studies have also measured components of secondhand smoke in the air.

Questionnaires generally address sources of exposure in microenvironments and can be tailored to address the time period of interest. Questionnaires represent the only approach that can be used to assess exposures retrospectively over a life span, because available biomarkers only reflect exposures

over recent days or, at most, weeks. Questionnaires on secondhand smoke exposure have been assessed for their reliability and validity, generally based on comparisons with either biomarker or air monitoring data as the “gold” standard (Jaakkola and Jaakkola 1997). Two studies evaluated the reliability of questionnaires on lifetime exposures (Pron et al. 1988; Coultas et al. 1989). Both showed a high degree of repeatability for questions concerning whether a spouse had smoked, but a lower reliability for responses concerning the quantitative aspects of an exposure. Emerson and colleagues (1995) evaluated the repeatability of information from parents of children with asthma. They found a high reliability for parent-reported tobacco use and for the number of cigarettes to which the child was exposed in the home during the past week.

To assess validity, questionnaire reports of current or recent exposures have been compared with levels of cotinine and other biomarkers. These studies tend to show a moderate correlation between levels of cotinine and questionnaire indicators of exposures (Kawachi and Colditz 1996; Cal/EPA 1997; Jaakkola and Jaakkola 1997). However, cotinine levels reflect not only exposure but metabolism and excretion (Benowitz 1999). Consequently, exposure is only one determinant of variation in cotinine levels among persons; there also are individual variations in metabolism and excretion rates. In spite of these sources of variability, mean levels of cotinine vary as anticipated across categories of self-reported exposures (Cal/EPA 1997; Jaakkola and Jaakkola 1997), and self-reported exposures are moderately associated with measured levels of markers (Cal/EPA 1997; Jaakkola and Jaakkola 1997).

Biomarkers are also used for assessing exposures to secondhand smoke. A number of biomarkers are available, but they vary in their specificity and in the dynamics of the temporal relationship between the exposure and the marker level (Cal/EPA 1997; Benowitz 1999). These markers include specific tobacco smoke components (nicotine) or metabolites (cotinine and tobacco-specific nitrosamines), nonspecific biomarkers (thiocyanate and CO), adducts with tobacco smoke components or metabolites (4-aminobiphenyl-hemoglobin adducts, benzo[*a*]pyrene-DNA adducts, and polycyclic aromatic hydrocarbon-albumin adducts), and nonspecific assays (urinary mutagenicity). Cotinine has been the most widely used biomarker, primarily because of its specificity, half-life, and ease of measurement in body fluids (e.g., urine, blood, and saliva). Biomarkers are discussed

in detail in Chapter 3 (Assessment of Exposure to Secondhand Smoke).

Some epidemiologic studies have also incorporated air monitoring, either direct personal sampling or the indirect approach based on the microenvironmental model. Nicotine, present in the gas phase of secondhand smoke, can be monitored passively with a special filter or actively using a pump and a sorbent. Hammond and Leaderer (1987) first described a diffusion monitor for the passive sampling of nicotine in 1987; this device has now been widely used to assess concentrations in different environments and to study health effects. Airborne particles have also been measured using active monitoring devices.

Each of these approaches for assessing exposures has strengths and limitations, and preference for one over another will depend on the research question and its context (Jaakkola and Jaakkola 1997; Jaakkola and Samet 1999). Questionnaires can be used to characterize sources of exposures, such as smoking by parents. With air concentrations of markers and time-activity information, estimates of secondhand smoke exposures can be made with the microenvironmental model. Biomarkers provide exposure measures that reflect the patterns of exposure and the kinetics of the marker; the cotinine level in body fluids, for example, reflects an exposure during several days. Air monitoring may be useful for validating measurements of exposure. Exposure assessment strategies are matched to the research question and often employ a mixture of approaches determined by feasibility and cost constraints.

Misclassification of Secondhand Smoke Exposure

Misclassification may occur when classifying exposures, outcomes, confounding factors, or modifying factors. Misclassification may be differential on either exposure or outcome, or it may be random (Armstrong et al. 1992). Differential or nonrandom misclassification may either increase or decrease estimates of effect, while random misclassification tends to reduce the apparent effect and weaken the relationship of exposure with disease risk. In studies of secondhand smoke and disease risk, exposure misclassification has been a major consideration in the interpretation of the evidence, although misclassification of health outcome measures has not been a substantial issue in this research. The consequences for epidemiologic studies of misclassification in general are well established (Rothman and Greenland 1998).

An extensive body of literature on the classification of exposures to secondhand smoke is reviewed in this and other chapters, as well as in some publications on the consequences of misclassification (Wu 1999). Two general patterns of exposure misclassification are of concern to secondhand smoke: (1) random misclassification that is not differential by the presence or absence of the health outcome and (2) systematic misclassification that is differential by the health outcome. In studying the health effects of secondhand smoke in adults, there is a further concern as to the classification of the active smoking status (never, current, or former smoking); in studies of children, the accuracy of secondhand smoke exposure classification is the primary methodologic issue around exposure assessment, but unreported active smoking by adolescents is also a concern.

With regard to random misclassification of secondhand smoke exposures, there is an inherent degree of unavoidable measurement error in the exposure measures used in epidemiologic studies. Questionnaires generally assess contact with sources of an exposure (e.g., smoking in the home or workplace) and cannot capture all exposures nor the intensity of exposures; biomarkers provide an exposure index for a particular time window and have intrinsic variability. Some building-related factors that determine an exposure cannot be assessed accurately by a questionnaire, such as the rate of air exchange and the size of the microenvironment where time is spent, nor can concentrations be assessed accurately by subjective reports of the perceived level of tobacco smoke. In general, random misclassification of exposures tends to reduce the likelihood that studies of secondhand smoke exposure will find an effect. This type of misclassification lessens the contrast between exposure groups, because some truly exposed persons are placed in the unexposed group and some truly unexposed persons are placed in the exposed group. Differential misclassification, also a concern, may increase or decrease associations, depending on the pattern of misreporting.

One particular form of misclassification has been raised with regard to secondhand smoke exposure and lung cancer: the classification of some current or former smokers as lifetime nonsmokers (USEPA 1992; Lee and Forey 1995; Hackshaw et al. 1997; Wu 1999). The resulting bias would tend to increase the apparent association of secondhand smoke with lung cancer, if the misclassified active smokers are also more likely to be classified as involuntary smokers. Most studies of lung cancer and secondhand smoke have used spousal smoking as a main exposure variable. As

smoking tends to aggregate between spouses (smokers are more likely to marry smokers), misclassification of active smoking would tend to be differential on the basis of spousal smoking (the exposure under investigation). Because active smoking is strongly associated with increased disease risk, greater misclassification of an actively smoking spouse as a nonsmoker among spouses of smokers compared with spouses of nonsmokers would lead to risk estimates for spousal smoking that are biased upward by the effect of active smoking. This type of misclassification is also relevant to studies of spousal exposure and CHD risk or other diseases also caused by active smoking, although the potential for bias is less because the association of active smoking with CHD is not as strong as with lung cancer.

There have been a number of publications on this form of misclassification. Wu (1999) provides a review, and Lee and colleagues (2001) offer an assessment of potential consequences. A number of models have been developed to assess the extent of bias resulting from the misclassification of active smokers as lifetime nonsmokers (USEPA 1992; Hackshaw et al. 1997). These models incorporate estimates of the rate of misclassification, the degree of aggregation of smokers by marriage, the prevalence of smoking in the population, and the risk of lung cancer in misclassified smokers (Wu 1999). Although debate about this issue continues, analyses show that estimates of upward bias from misclassifying active smokers as lifetime nonsmokers cannot fully explain the observed increase in risk for lung cancer among lifetime nonsmokers married to smokers (Hackshaw et al. 1997; Wu 1999).

There is one additional issue related to exposure misclassification. During the time the epidemiologic studies of secondhand smoke have been carried out, exposure has been widespread and almost unavoidable. Therefore, the risk estimates may be biased downward because there are no truly unexposed persons. The 1986 Surgeon General's report recognized this methodologic issue and noted the need for further data on population exposures to secondhand smoke (USDHHS 1986). This bias was also recognized in the 1986 report of the NRC, and an adjustment for this misclassification was made to the lung cancer estimate (NRC 1986). Similarly, the 1992 report of the EPA commented on background exposure and made an adjustment (USEPA 1992). Some later studies have attempted to address this issue; for example, in a case-control study of active and involuntary smoking and breast cancer in Switzerland, Morabia and colleagues (2000) used a questionnaire to assess exposure and

identified a small group of lifetime nonsmokers who also reported no exposure to secondhand smoke. With this subgroup of controls as the reference population, the risks of secondhand smoke exposure were substantially greater for active smoking than when the full control population was used.

This Surgeon General's report further addresses specific issues of exposure misclassification when they are relevant to the health outcome under consideration.

Use of Meta-Analysis

Meta-analysis refers to the process of evaluating and combining a body of research literature that addresses a common question. Meta-analysis is composed of qualitative and quantitative components. The qualitative component involves the systematic identification of all relevant investigations, a systematic assessment of their characteristics and quality, and the decision to include or exclude studies based on predetermined criteria. Consideration can be directed toward sources of bias that might affect the findings. The quantitative component involves the calculation and display of study results on common scales and, if appropriate, the statistical combination of these results across studies and an exploration of the reasons for any heterogeneity of findings. Viewing the findings of all studies as a single plot provides insights into the consistency of results and the precision of the studies considered. Most meta-analyses are based on published summary results, although they are most powerful when applied to data at the level of individual participants. Meta-analysis is most widely used to synthesize evidence from randomized clinical trials, sometimes yielding findings that were not evident from the results of individual studies. Meta-analysis also has been used extensively to examine bodies of observational evidence.

Beginning with the 1986 NRC report, meta-analysis has been used to summarize the evidence on involuntary smoking and health. Meta-analysis was central to the 1992 EPA risk assessment of secondhand smoke, and a series of meta-analyses supported the conclusions of the 1998 report of the Scientific Committee on Tobacco and Health in the United Kingdom. The central role of meta-analysis in interpreting and applying the evidence related to involuntary smoking and disease has led to focused criticisms of the use of meta-analysis in this context. Several papers that acknowledged support from the tobacco industry have addressed the epidemiologic findings for lung cancer, including the selection and quality of the

studies, the methods for meta-analysis, and dose-response associations (Fleiss and Gross 1991; Tweedie and Mengersen 1995; Lee 1998, 1999). In a lawsuit brought by the tobacco industry against the EPA, the 1998 decision handed down by Judge William L. Osteen, Sr., in the North Carolina Federal District Court criticized the approach EPA had used to select studies for its meta-analysis and criticized the use of 90 percent rather than 95 percent confidence intervals for the summary estimates (*Flue-Cured Tobacco Cooperative Stabilization Corp. v. United States Environmental Protection Agency*, 857 F. Supp. 1137 [M.D.N.C. 1993]). In December 2002, the 4th U.S. Circuit Court of Appeals threw out the lawsuit on the basis that tobacco companies cannot sue the EPA over its secondhand smoke report because the report was not a final agency action and therefore not subject to court review (*Flue-Cured Tobacco Cooperative Stabilization Corp. v. The United States Environmental Protection Agency*, No. 98-2407 [4th Cir., December 11, 2002], cited in 17.7 TPLR 2.472 [2003]).

Recognizing that there is still an active discussion around the use of meta-analysis to pool data from observational studies (versus clinical trials), the authors of this Surgeon General's report used this methodology to summarize the available data when deemed appropriate and useful, even while recognizing that the uncertainty around the meta-analytic estimates may exceed the uncertainty indicated by conventional statistical indices, because of biases either within the observational studies or produced by the manner of their selection. However, a decision to not combine estimates might have produced conclusions that are far more uncertain than the data warrant because the review would have focused on individual study results without considering their overall pattern, and without allowing for a full accounting of different sample sizes and effect estimates.

The possibility of publication bias has been raised as a potential limitation to the interpretation of evidence on involuntary smoking and disease in general, and on lung cancer and secondhand smoke exposure specifically. A 1988 paper by Vandenbroucke used a descriptive approach, called a "funnel plot," to assess the possibility that publication bias affected the 13 studies considered in a review by Wald and colleagues (1986). This type of plot characterizes the relationship between the magnitude of estimates and their precision. Vandenbroucke suggested the possibility of publication bias only in reference to the studies of men. Bero and colleagues (1994) concluded that there

had not been a publication bias against studies with statistically significant findings, nor against the publication of studies with nonsignificant or mixed findings in the research literature. The researchers were able to identify only five unpublished “negative” studies, of which two were dissertations that tend to be delayed in publication. A subsequent study by Misakian and Bero (1998) did find a delay in the publication of studies with nonsignificant results in comparison with studies having significant results; whether this pattern has varied over the several decades of research on secondhand smoke was not addressed. More recently, Copas and Shi (2000) assessed the 37 studies considered in the meta-analysis by Hackshaw and colleagues (1997) for publication bias. Copas and Shi (2000) found a significant correlation between the estimated risk of exposure and sample size, such that smaller studies tended to have higher values. This pattern suggests the possibility of publication bias. However, using a funnel plot of the same studies, Lubin (1999) found little evidence for publication bias.

On this issue of publication bias, it is critical to distinguish between indirect statistical arguments and arguments based on actual identification of previously unidentified research. The strongest case against substantive publication bias has been made by researchers who mounted intensive efforts to find the possibly missing studies; these efforts have yielded little—nothing that would alter published conclusions (Bero et al. 1994; Glantz 2000). Presumably because this exposure is a great public health concern, the findings of studies that do not have statistically significant outcomes continue to be published (Kawachi and Colditz 1996).

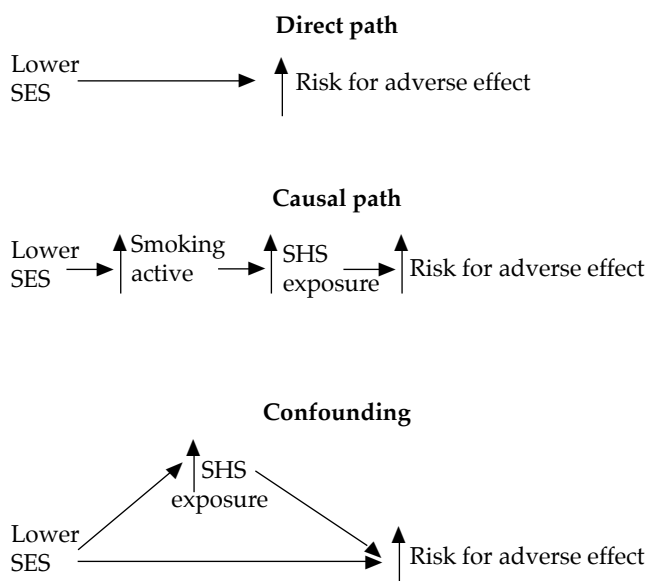
The quantitative results of the meta-analyses, however, were not determinate in making causal inferences in this Surgeon General's report. In particular, the level of statistical significance of estimates from the meta-analyses was not a predominant factor in making a causal conclusion. For that purpose, this report relied on the approach and criteria set out in the 1964 and 2004 reports of the Surgeon General, which involved judgments based on an array of quantitative and qualitative considerations that included the degree of heterogeneity in the designs of the studies that were examined. Sometimes this heterogeneity limits the inference from meta-analysis by weakening the rationale for pooling the study results. However, the availability of consistent evidence from heterogeneous designs can strengthen the meta-analytic findings by making it unlikely that a common bias could persist across different study designs and populations.

Confounding

Confounding, which refers in this context to the mixing of the effect of another factor with that of secondhand smoke, has been proposed as an explanation for associations of secondhand smoke with adverse health consequences. Confounding occurs when the factor of interest (secondhand smoke) is associated in the data under consideration with another factor (the confounder) that, by itself, increases the risk for the disease (Rothman and Greenland 1998). Correlates of secondhand smoke exposures are not confounding factors unless an exposure to them increases the risk of disease. A factor proposed as a potential confounder is not necessarily an actual confounder unless it fulfills the two elements of the definition. Although lengthy lists of potential confounding factors have been offered as alternatives to direct associations of secondhand smoke exposures with the risk for disease, the factors on these lists generally have not been shown to be confounding in the particular data of interest.

The term confounding also conveys an implicit conceptualization as to the causal pathways that link secondhand smoke and the confounding factor to

Figure 1.2 Model for socioeconomic status (SES) and secondhand smoke (SHS) exposure



Arrows indicate directionality of association.

disease risk. Confounding implies that the confounding factor has an effect on risk that is independent of secondhand smoke exposure. Some factors considered as potential confounders may, however, be in the same causal pathway as a secondhand smoke exposure. Although socioeconomic status (SES) is often cited as a potential confounding factor, it may not have an independent effect but can affect disease risk through its association with secondhand smoke exposure (Figure 1.2). This figure shows general alternative relationships among SES, secondhand smoke exposure, and risk for an adverse effect. SES may have a direct effect, or it may indirectly exert its effect through an association with secondhand smoke exposure, or it may confound the relationship between secondhand smoke exposure and disease risk. To control for SES as a potential confounding factor without considering underlying relationships may lead to incorrect risk estimates. For example, controlling for SES would not be appropriate if it is a determinant of secondhand smoke exposure but has no direct effect.

Nonetheless, because the health effects of involuntary smoking have other causes, the possibility of confounding needs careful exploration when assessing associations of secondhand smoke exposure with adverse health effects. In addition, survey data from

the last several decades show that secondhand smoke exposure is associated with correlates of lifestyle that may influence the risk for some health effects, thus increasing concerns for the possibility of confounding (Kawachi and Colditz 1996). Survey data from the United States (Matanoski et al. 1995) and the United Kingdom (Thornton et al. 1994) show that adults with secondhand smoke exposures generally tend to have less healthful lifestyles. However, the extent to which these patterns of association can be generalized, either to other countries or to the past, is uncertain.

The potential bias from confounding varies with the association of the confounder to secondhand smoke exposures in a particular study and to the strength of the confounder as a risk factor. The importance of confounding to the interpretation of evidence depends further on the magnitude of the effect of secondhand smoke on disease. As the strength of an association lessens, confounding as an alternative explanation for an association becomes an increasing concern. In prior reviews, confounding has been addressed either quantitatively (Hackshaw et al. 1997) or qualitatively (Cal/EPA 1997; Thun et al. 1999). In the chapters in this report that focus on specific diseases, confounding is specifically addressed in the context of potential confounding factors for the particular diseases.

Tobacco Industry Activities

The evidence on secondhand smoke and disease risk, given the public health and public policy implications, has been reviewed extensively in the published peer-reviewed literature and in evaluations by a number of expert panels. In addition, the evidence has been criticized repeatedly by the tobacco industry and its consultants in venues that have included the peer-reviewed literature, public meetings and hearings, and scientific symposia that included symposia sponsored by the industry. Open criticism in the peer-reviewed literature can strengthen the credibility of scientific evidence by challenging researchers to consider the arguments proposed by critics and to rebut them.

Industry documents indicate that the tobacco industry has engaged in widespread activities, however, that have gone beyond the bounds of accepted scientific practice (Glantz 1996; Ong and Glantz 2000, 2001; Rampton and Stauber 2000; Yach and Bialous

2001; Hong and Bero 2002; Diethelm et al. 2004). Through a variety of organized tactics, the industry has attempted to undermine the credibility of the scientific evidence on secondhand smoke. The industry has funded or carried out research that has been judged to be biased, supported scientists to generate letters to editors that criticized research publications, attempted to undermine the findings of key studies, assisted in establishing a scientific society with a journal, and attempted to sustain controversy even as the scientific community reached consensus (Garne et al. 2005). These tactics are not a topic of this report, but to the extent that the scientific literature has been distorted, they are addressed as the evidence is reviewed. This report does not specifically identify tobacco industry sponsorship of publications unless that information is relevant to the interpretation of the findings and conclusions.

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