United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Office of Atmospheric and
Indoor Air Programs
Washington DC 20460

EPA/600/6-90/006A
May 1990
External Review Draft

Research and Development/Air and Radiation

EPA

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

Review Draft
(Do Not Cite or Quote)

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

TO: OTS LIBRARY STAFF
FROM: TIM
NOTE THIS F.Y.I.:

JUN 25 1990

EPA AND PASSIVE SMOKING

ACTION

On June 25, 1990, EPA transmitted to its Science Advisory Board (SAB) for review and comment two draft documents on Environmental Tobacco Smoke (ETS) entitled *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children (EPA/600/6-90/006A)* and *Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies (EPA/400/6-90/004.)* Companion notices in the June 25, 1990 **Federal Register** also announce a simultaneous public review process, commencing June 25, 1990 and ending August 31, 1990, in which the public is invited to comment on the draft documents.

STATUS

Both documents are public review drafts. They have been released by the Environmental Protection Agency only to solicit scientific and public input on their contents and, therefore, do not represent Agency policy. Consequently, it is inappropriate to quote or cite information from these documents until they are released in final form by the Agency.

DESCRIPTION OF DOCUMENTS

The first document -- *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children* ---proposes to classify ETS according to EPA's carcinogen risk assessment guidelines, to estimate the excess lung cancer deaths attributable to ETS exposure, and to assess the association between passive smoking and respiratory effects. The draft risk assessment was prepared by the Human Health Assessment Group of the Office of Health and Environmental Assessment of the Office of Research and Development at the request of the Indoor Air Division of the Office of Atmospheric and Indoor Air Programs in the Office of Air and Radiation.

The second document -- *Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies* -- is intended to provide government and private sector decision-makers with information on the technical basis for controlling involuntary exposure to environmental tobacco smoke and to describe a variety of technical and policy options for instituting effective smoking restrictions. The guide to workplace smoking policies is based on the overall body of literature on passive smoking, including the 1986 reports of the Surgeon General and the National Research Council. Its review has been timed to coincide with the review of the risk assessment in order to ensure that up-to-date information from the risk assessment would be incorporated into the guide to workplace smoking policies. The draft workplace policy guide was prepared by the Indoor Air Division.

A third document under development -- but not yet available for public review -- is a *Technical Compendium of Information on Environmental Tobacco Smoke.* This document was jointly conceived and funded by several agencies of the Department of Health and Human Services in addition to EPA, including the Office on Smoking and Health (Centers for Disease Control), the Office of Disease Prevention and Health Promotion (Public Health Service) the Heart, Lung and Blood Institute, and the National Cancer Institute (National Institutes of Health). The compendium consists of individual

chapters by several authors summarizing existing information in a number of areas relevant to ETS, including exposure, health effects, risks, public attitudes, and smoking policies. The technical compendium has already been subjected to a limited external peer review and its chapters are now being revised to incorporate changes. When those revisions are completed, EPA's Science Advisory Board will also be given an opportunity to review this document before it is finalized as a multi-agency publication.

All of these documents are being devloped under the authority of Title IV of the Superfund Amendments and Reauthorization Act of 1986, which provides EPA with broad authority to conduct research and disseminate information on all aspects of indoor air quality.

SCIENCE ADVISORY BOARD REVIEW

The *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children* and *The Guide to Workplace Smoking Policies* will be the subject of an SAB review meeting. A separate Federal Register notice announcing the dates of the SAB review meeting will be published shortly.

HOW TO OBTAIN COPIES OF THE PUBLIC REVIEW DRAFTS

A limited number of copies are available and may be obtained by contacting:

ORD Publications Office, CERI-FRN
U.S. Environmental Protection Agency
26 West Martin Luther King Drive
Cincinnati, Ohio 45268
(513) 569-7562; FTS 684-7562

COMMENT PERIOD

Comments on both documents must be submitted separately, in writing, and must be postmarked NO LATER THAN AUGUST 31, 1990. Addresses for submission of comments are provided with the public review drafts.

PLEASE NOTE THAT EPA IS UNABLE TO PROVIDE POLICY OR TECHNICAL COMMENT ON THE CONTENT OF EITHER DOCUMENT AT THIS TIME SINCE THEY ARE UNDERGOING SCIENTIFIC AND PUBLIC REVIEWS AND ARE SUBJECT TO CHANGE

U.S. ENVIRONMENTAL PROTECTION AGENCY

(FRL)

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children; External Review Draft

AGENCY: U.S. Environmental Protection Agency

ACTION: Notice of availability of external review draft and request for public comments.

SUMMARY: This notice announces the availability of the external review draft of the **Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children**, EPA/600/6-90/006A. This document will be the subject of a Science Advisory Board (SAB) meeting. Notice of the date and place of the SAB meeting will be published in a subsequent **Federal Register** notice.

DATES: The Agency will make the draft document available for public review and comment on or about Monday, June 25, 1990. Comments must be postmarked by Friday, August 31, 1990.

ADDRESSES: To obtain a single copy of the draft document, interested parties should contact the ORD Publications Office, CERI-FRN, U.S. Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268, (513)569-7562 or FTS/684-7562. Please provide your name and mailing address and

request the external review draft by title and EPA number.

The draft document also will be available for public inspection and copying in the Public Information Reference Unit of the EPA Library, U.S. Environmental Protection Agency Headquarters, Waterside Mall, 401 M Street, SW, Washington, DC 20460.

Commenters are requested to submit their comments in writing to: Project Officer for Environmental Tobacco Smoke, Technical Information Staff, Office of Health and Environmental Assessment (RD-689), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Steven Bayard, (202)382-5722 or FTS/382-5722.

SUPPLEMENTARY INFORMATION: Because Environmental Tobacco Smoke (ETS) is a widespread pollutant of indoor air and because it has been previously found to be associated with several respiratory tract diseases and disorders, EPA's Office of Indoor Air and Atmospheric Programs requested that the Human Health Assessment Group, Office of Health and Environmental Assessment, prepare a health assessment document for ETS. This project is carried out under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1988).

The health assessment document addresses the scientific, mostly epidemiologic, evidence on the possible respiratory effects, including lung cancer, of passive smoking or ETS. This issue was examined previously in two 1986 reports, one by the

U.S. Surgeon General, titled **The Health Consequences of Involuntary Smoking**; the other by the National Research Council, titled **Environmental Tobacco Smoke, Measuring Exposures and Assessing Health Effects.** The EPA draft report extends the analyses of those reports to include subsequent epidemiologic evidence on the potential association between ETS and 1) lung cancer in nonsmoking adults, and 2) respiratory disorders in children. With respect to lung cancer in adults the draft report concludes that 1) ETS is causally associated with lung cancer in nonsmoking adults and that, according to EPA guidelines for carcinogen risk assessment, ETS is a Group A (known human) carcinogen; and 2) that approximately 3800 lung cancer deaths per year among nonsmokers (never-smoker and former smokers) of both sexes in the United States are attributable to ETS. This figure is for total ETS exposure, with no separate breakdown for domestic vs. occupational or social exposures.

With respect to respiratory effects in children, the draft report concludes that ETS from parental smoking, especially during infancy, is associated with increased prevalence of acute lower-respiratory tract infections (bronchitis and pneumonia), respiratory symptoms of irritation (cough, sputum, wheeze), and middle ear effusions (a sign of chronic middle ear disease). It also concludes that ETS is associated with reduced lung function and with a small reduction in the rate of pulmonary growth and development in children of mothers who smoke during their early childhood. No conclusions are drawn regarding a potential

association of parental smoking with increased acute upper-respiratory tract illnesses (colds and sore throats), an increased prevalence of asthma, or exacerbation of symptoms in asthmatic children.

JUN 19 1990

(Date)

Carl R. Gerber, Acting
Assistant Administrator for
Research and Development

United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Office of Atmospheric and
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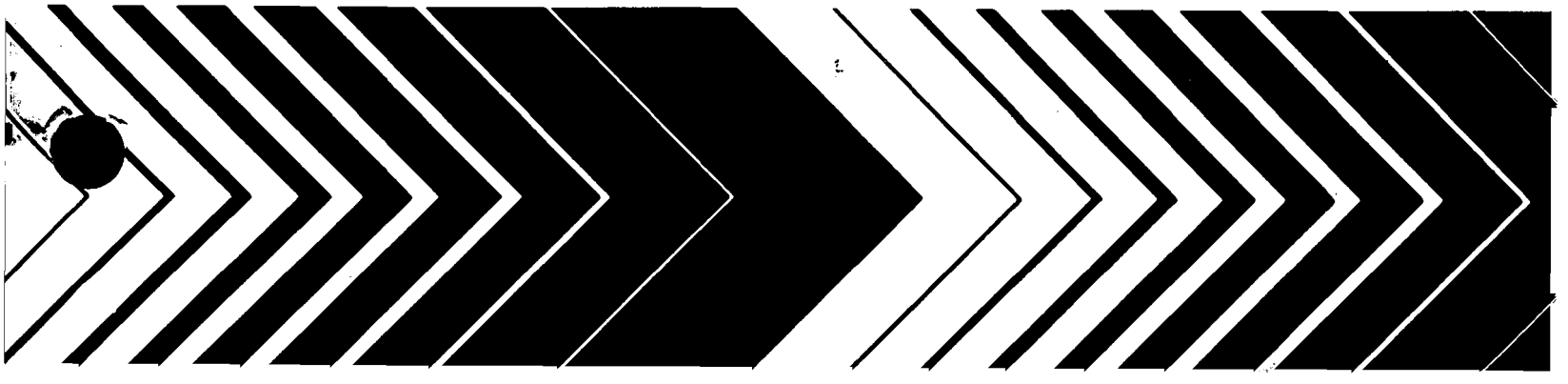

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EPA/600/6-90/006A
May 1990
External Review Draft

HEALTH EFFECTS OF PASSIVE SMOKING:

ASSESSMENT OF LUNG CANCER IN ADULTS

AND RESPIRATORY DISORDERS IN CHILDREN

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Office of Health and Environmental Assessment
Office of Research and Development
and
Indoor Air Division
Office of Atmospheric and Indoor Air Programs
Office of Air and Radiation

U.S. Environmental Protection Agency
Washington, D.C.

DISCLAIMER

This document is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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PREFACE

This assessment of the health effects associated with passive smoking has been prepared by the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for its scientific accuracy and conclusions. The assessment was prepared at the request of the Indoor Air Division, Office of Indoor Air and Atmospheric Programs, Office of Air and Radiation, which defined its scope and provided funding.

The document has been developed under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

A comprehensive search of the scientific literature for this document is complete through September 1989. In addition, a few studies published since September of 1989 have been included in response to recommendations made by reviewers.

Due to both resource and time constraints, the scope of this review has been limited to an analysis of respiratory effects, with emphasis on the epidemiologic data. Further, because two thorough reviews on passive smoking were completed in 1986 (by the U.S. Surgeon General and the National Research Council), this document provides a summary of those reports with a more comprehensive analysis of the literature appearing subsequent to those reports and an integration of all the results.

With respect to quantitation of lung cancer risk, the document has used the actual epidemiologic data and vital statistics to estimate the number of nonsmokers affected. It does not use high- to low-dose extrapolation models since exposures in the epidemiology studies were at true environmental levels. However, measures of exposure-response and modeling are examined in two appendices. One appendix analyzes the two main, currently-used proxies for environmental tobacco smoke (ETS) exposure, respirable suspended particulates and body cotinine levels. The other appendix examines methodologies and models treating ETS as a complex mixture of carcinogens with both initiating and promoting properties. It also outlines several possible approaches for exposure-response assessment.

Two other issues that have not been addressed in this draft but which have drawn comments from reviewers of earlier drafts are (1) the possible synergistic lung cancer effect of ETS and radon, and (2) the relative lung cancer hazards and risks of home and the workplace. These issues will be more fully covered in a revised version of this document.

It is the Agency's intent to revise and update this document following the public comment period and review by the Agency's Science Advisory Board.

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
ADC	adenocarcinoma
AMW	American war veterans
B[a]P	benzo[a]pyrene
BR	bronchial responsiveness
CEA	cigarette-equivalents approach
C.I.	confidence interval
Coh	cohort study
COPD	chronic obstructive pulmonary disease
CS[1]	current smoker
CSC	cigarette smoke condensate
DA	Direct Approach
ES[1]	ever-smoker
ETS	environmental tobacco smoke
FEF_{25-75}	forced expiratory flow rate, mid-expiratory phase
FEV_1	forced expiratory volume at one second
FS[1]	former smoker
FVC	forced vital capacity
GI	gastro-intestinal
GSD	geometric standard deviation
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
LCD	lung cancer deaths

[1] used for both singular and plural forms

ABBREVIATIONS (continued)

MAF	marriage aggregation factor
MMAD	mass median aerodynamic diameter
MS	mainstream smoke
NCI	National Cancer Institute
NHIS	National Health Interview Survey
NP	nasopharyngeal
NRC	National Research Council
NS[1]	never-smoker
OR	observed risk
P	pulmonary
PAH	polycyclic aromatic hydrocarbons
PAR	population-attributable risk
RPA	Relative Potency Approach
RR	relative risk
RSP	respirable suspended particulates
RSV	respiratory syncytial virus
SCC	small cell carcinoma
SDA	Seventh-Day Adventists
SS	sidestream smoke
TB	tracheobronchial
U.S. DHHS	U.S. Department of Health and Human Services
U.S. DOT	U.S. Department of Transportation
U.S. SG	U.S. Surgeon General
WHO	World Health Organization

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used for both singular and plural forms

AUTHORS, CONTRIBUTORS, AND REVIEWERS

This document was prepared as a joint collaboration between the Office of Research and Development, Office of Health and Environmental Assessment and the Office of Air and Radiation, Office of Atmospheric and Indoor Air Programs, Indoor Air Staff. The project manager with overall responsibility for this report and its conclusions is

Steven Bayard, Ph.D.
Human Health Assessment Group
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC 20460

The primary author of this report is

Kenneth G. Brown, Ph.D.
Kenneth G. Brown, Inc.
P. O. Box 16608
Chapel Hill, NC 27516-6608

who wrote all chapters and Appendix B.

Three other authors are

Appendix A:
Charles G. Humble
Department of Epidemiology
School of Public Health
University of North Carolina
Chapel Hill, NC 27514

Appendix C:
Douglas Crawford-Brown, Ph.D.
Associate Professor
Department of Environmental Sciences and Engineering
School of Public Health
University of North Carolina
Chapel Hill, NC 27514

Appendix D:
Todd W. Thorslund, Sc.D.
Vice President
Clement Associates, Inc.
9300 Lee Highway
Fairfax, VA 22031

A contributor to Chapter 5 was

Sandra A. Peters, Ph.D.
800 Powell Street
Chapel Hill, NC 27514

Technical Assistance to Chapters 2 and 3 was provided by

Chu-Chih Chen
Department of Biostatistics
School of Public Health
University of North Carolina
Chapel Hill, NC 27514

Earlier drafts, in whole or in part, were reviewed by

Michael Berry, Ph.D.
David Burns, M.D.
Rebecca Calderon, Ph.D.
Chao Chen, Ph.D.
Thomas Evans
Lawrence Glass, Ph.D.
Richard Hertzberg, Ph.D.
Aparna Koppikar, Ph.D.
Karen Milne
James Repace
Charles Ris, P.E.
Sherry Selevan, Ph.D.
Marvin Schneiderman, Ph.D.
Richard Walentowicz
A. Judson Wells, Ph.D.
Jeannette Wiltse, Ph.D., J.D.

In addition, the following people have provided helpful discussions or supplied copies of recent manuscripts on other material relevant to this report: R.C. Brownson, A. Charlton, A. Collies, K.M. Cummings, M.P. Ericksen, D. Fennell, J.E. Garfinkel, R. Greenberg, F.W. Henderson, D. Hoffman, W. Hoffman, M.J. Jarvis, L.C. Koo, M. Layard, W.K. Lam, M.D. Lebowitz, J. Lewtas, T. Martonen, A.B. Murray, B.D. Ostro, J. Repace, E. Riboli, M.A. Richardson, J.M. Samet, D. Sandler, and S.R. Tannenbaum. Overall document preparation and typing was done by Stacy Henkle.

1. EXECUTIVE SUMMARY

In 1986, the National Research Council (NRC) and the U.S. Surgeon General (U.S. SG) assessed the health effects of exposure to environmental tobacco smoke (ETS). Both of the 1986 reports conclude that ETS exposure is causally associated with lung cancer and that children of parents who smoke have increased frequency of respiratory symptoms and acute respiratory illnesses and evidence of reduced lung function. The two reports were developed and edited by different processes, which strengthens the validity of the conclusions common to both reports. The NRC report is the product of a committee of experts; the U.S. SG report is a composite of contributions from individual experts that were edited, based on the review of other knowledgeable individuals, and then cleared through the U.S. Public Health Service.

This document extends the analyses of those reports to include subsequent epidemiologic evidence on the potential association between ETS and (1) lung cancer in nonsmoking adults, and (2) respiratory disease and pulmonary effects in children. It concludes that passive smoking is causally associated with lung cancer in adults and that exposure of young children to ETS from parental smoking, particularly during infancy, is associated with increased prevalence of acute lower-respiratory-tract infections (bronchitis and pneumonia), respiratory symptoms of irritation (cough, sputum, wheeze), and middle ear effusions (a sign of chronic middle ear disease). Passive smoking in early childhood is also associated with reduced lung function in children of mothers who smoke and with a small reduction in the child's rate of pulmonary growth and development. No conclusions are drawn regarding a potential association of parental smoking with the child's increased acute upper-respiratory-tract illnesses (colds and sore throats), an increased prevalence of asthma, or exacerbation of symptoms in asthmatic children.

This report also estimates that approximately 3800 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. This figure is an extension of the estimate of 1750 (95% C.I. 910, 2660) for female never-smokers alone, an overall value calculated from all the epidemiologic studies on lung cancer and ETS. The 1750 value and its confidence interval includes reasonable estimates of exposure and risk for single female never-smokers. Projection of the 1750 estimate to 3800 for all nonsmokers of both sexes is based on reasonable estimates of exposure and risk for all never-smoking men and for former smokers of both sexes. No further quantitative estimates of ETS-related health effects in adults or children are made.

1.1. ETS AND LUNG CANCER

The U.S. SG (1989) estimates that smoking is responsible for more than one of every six deaths in the United States and that it accounted for 87% of the lung cancer deaths in males and 75% in females in 1985. Smokers, however, are not the only ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain many of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers. Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is still biologically plausible. (U.S. EPA guidelines [Fed. Reg., 1986] assume that unless there is evidence to the contrary, any level of exposure to a carcinogen carries a potential risk of cancer.)

Based on the firmly established causal relationship of lung cancer with active smoking, the lung is considered to be the site most likely affected by passive smoking. The ubiquity of ETS and its absorption by members of the general population have been well documented by air

sampling and by bioassays for nicotine and cotinine. This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This document addresses that question by reviewing and analyzing the cumulative evidence from epidemiologic studies. These studies compare individuals with higher ETS exposures to those with lower exposures. Typically the study subjects are married women who have never smoked but are married to a smoker (higher exposure) and those married to a nonsmoker (lower exposure). Following the nomenclature of the literature, the higher and lower exposed persons are referred to as "exposed" and "unexposed." Of course there is exposure to ETS from sources other than spousal smoking, collectively designated as "background" exposure, which applies to the so-called unexposed as well as the exposed. Background exposure is taken into account in characterization of population risk (Chapter 4), but it is not required for the statistical assessment of the evidence of excess lung cancer risk from spousal smoking (Chapter 3).

The epidemiologic evidence of a lung cancer hazard is statistically assessed by methods of meta-analysis to obtain overall results. The data and study results included apply to female married never-smokers. Several studies include male subjects, but the percentage of male never-smokers is relatively small and the data are scant by comparison. In some instances former smokers are included with never-smokers. All the ETS exposures are considered to be at true environmental levels.

Based on these analyses and following the U.S. EPA guidelines for carcinogen risk assessment (Fed. Reg., 1986), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight of evidence, principally:

- Biological plausibility. ETS is taken up by the lungs and distributed throughout the body. The similarity of carcinogens identified in SS and MS along with the established causal relationship between lung cancer and smoking make it reasonable to suspect that ETS is also a lung carcinogen.

- Consistency of response. The two completed cohort studies and sixteen of the 21 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.

- Upward trend in dose-response. Of the two major cohort studies, the Japanese study (Hirayama) demonstrates a strong association between passive smoking and lung cancer, including an upward trend in dose-response. The upward trend is well supported by the preponderance of evidence in the 13 case-control studies that classified data by exposure level. The Hirayama study has undergone extensive critical review that led to some corrections and revisions but failed to discredit the findings. Differences in life-style and culture may be a factor in the Japanese study reporting a stronger association between ETS and lung cancer than the American study (American Cancer Society).

- Detectable association at environmental exposure levels. Within the population of women who are lifelong nonsmokers, the excess lung cancer risk of those married to a smoker is large enough to be observed. Carcinogenic responses are usually detectable only in high exposure circumstances, such as occupational settings or in highly dosed experimental animals.

- Broad-based evidence. The 21 case-control and three prospective studies provide data from eight different countries and from a wide variety of study designs and protocols conducted by many different research teams. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk from ETS exposure. The evidence remains statistically conclusive, however, after adjustments for smoker misclassification. The summary estimate of relative risk from raw data of both the case-control and cohort studies is 1.41 (95% C.I. 1.26, 1.57) before adjustment for misclassification and 1.28 (95% C.I. 1.12, 1.45) afterward ($p < 0.01$).

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the ubiquity of ETS. Current smokers comprise approximately 30% of the adult U.S. population and consume over one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to ETS. Cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported

nonsmokers tested (50% equates to 62 million U.S. nonsmokers of age 18 or above). The estimate of 3800 lung cancer deaths per year in nonsmokers attributable to ETS is based on data from epidemiologic studies at actual environmental exposure levels. Some mathematical modeling is required to adjust for expected bias from self-reported misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. The approach, however, does not rely on a mathematical model of dose-response or low dose extrapolation of observations obtained at extraordinarily high exposure levels.

The components of the 3800 figure include approximately 1750 female never-smokers, 800 male never-smokers, and 1250 former smokers. The 800 value for males is probably low based on information in the limited epidemiologic data for male never-smokers. Little is known about the lung cancer risk of ETS to former smokers. The estimate of 1250 former smokers is based on the assumption that the risk to former smokers is the same as the risk to never-smokers, which may be conservative from a biological perspective. If the estimate of 3800 total lung cancer deaths per year is recalculated using the lower (upper) confidence limit from study data on female never-smokers and the lower (upper) plausible value regarding population exposure to ETS, then a value of 1800 (6100) is obtained. It is unlikely that the number of lung cancer deaths per year attributable to passive smoking by nonsmokers is below 1800 or above 6100.

Other quantitative approaches to characterize population risk could have been used. Dose-response assessments based on the cigarette-equivalents approach to relate the risk of passive smoking to active smoking are reviewed. Published variations of this general approach have typically used either cotinine concentrations or respirable suspended particulates as a surrogate measure of exposure to ETS. They typically ignore the epidemiologic data on ETS and lung cancer and follow the paradigm of low-dose extrapolation from a dose-response curve (a dose-response curve for the lung cancer risk of active smokers in this case). Examples of the cigarette-equivalents approach provide additional estimates of lung cancer risk that, with the

exception of one low value, range from a few hundred to over 4000 lung cancer deaths per year. Although this report prefers the more direct approach based on epidemiologic data to characterize the lung cancer risk, there are also potential benefits from a dose-response assessment. For example, a dose-response model would be useful for evaluating the effectiveness of abatement procedures and the risk from varied environmental conditions. Methods based on the cigarette-equivalents approach could benefit from improved understanding of the biokinetic similarities and differences between passive and active smoking that may affect extrapolation of risk from active smoking to risk of passive smoking. A mathematical model relevant to that objective is developed as a basis for future study (Appendix C). Three additional quantitative methods for dose-response assessment of passive smoking, along the lines of the general cigarette-equivalents approach, are outlined with solicitation for comments and advice (Appendix D).

1.2 ETS AND RESPIRATORY DISORDERS IN CHILDREN

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. A recent study of 433 healthy neonates in central North Carolina found that 64% of them lived in households with a smoker and that 75% of smoking mothers smoked near their infants. Cotinine concentrations were correlated with smoking (especially by the mother) in the infant's presence. Nine to twelve million American children under five years of age may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986).

With regard to the respiratory effects of passive smoking in children, this report focuses on the epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. SG) that bears on the potential association of parental smoking with detrimental health effects

in their children. These include symptoms of respiratory irritation (cough, sputum, or wheeze); acute diseases of the lower respiratory tract (pneumonia and bronchitis); indications of chronic middle ear infections (predominantly middle ear effusions); reduced lung function (from forced expiratory volume and flow-rate measurements); prevalence of asthma; exacerbation of symptoms in asthmatics; and acute upper-respiratory-tract infections (colds and sore throats). The thirty or so recently published studies essentially corroborate the previous conclusions of the NRC and U.S. SG regarding respiratory symptoms, respiratory illnesses, and pulmonary function; strengthen support for those conclusions by the additional weight of evidence; and extend research in some directions. In particular, recent studies on middle ear effusion strengthens previous evidence to warrant the conclusion in this report of an association with parental smoking. Additional research also supports the hypothesis that early respiratory illness is associated with long-term pulmonary effects (reduced lung function and possibly increased risk of chronic obstructive lung disease).

The NRC and U.S. SG reports conclude that both the prevalence of respiratory symptoms and the incidence of respiratory infections are higher in the children of smoking parents. Estimates of the increased risk of wheezing vary from zero to over sixfold. In the seven studies of respiratory symptoms subsequent to the two reports, increased cough was observed in a range of ages from birth to mid-teens. Recent studies also supplement the evidence for increased wheeze. Overall, the cumulative evidence supports the previous conclusion of the NRC and U.S. SG. Six of the studies subsequent to those reports have addressed the topic of parental smoking and respiratory illness in children, and all have reported statistically significant results. The cumulative evidence indicates strongly that parental, especially the mother's, smoking is associated with increased incidence of respiratory illnesses in the first one-to-two years of life, particularly for bronchitis and pneumonia. Recent studies also solidify the evidence of a link between parental smoking and increased middle ear disease in young children.

The U.S. SG and NRC reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. This conclusion is statistically supported, but the topic itself is difficult to study and to evaluate quantitatively because of the relatively large inter-individual variability in temporal patterns of lung growth and development. Family history may be an important factor as well. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Study results on ETS and lung function in children that have appeared since those reports add some additional evidence supporting an association of ETS exposure with decreased lung function. Furthermore, this evidence adds support to the supposition that acute respiratory illness during childhood has a long-term effect on lung growth and development (suggesting an indirect association with ETS exposure, by virtue of its association with increased pneumonia and bronchitis in infants). Overall, the weight of evidence indicates that ETS exposure is associated with decreased lung function in childhood and with a small reduction in their rate of pulmonary growth and development.

This report concludes that the detrimental respiratory effects described in children are associated with exposure to ETS, but a causal association has not been established. Causation is biologically plausible, but other factors that cannot be fully assessed may be influencing the observed study data. One confounding variable, for example, is direct transmission of respiratory infections from smoking parents, who tend to have more infections than nonsmokers. Also, parental recall and the increased incidence of respiratory symptoms in smoking parents may be contributing an upward bias to the response attributable to ETS exposure. Studies have generally not controlled for in utero exposure to agents in tobacco smoke (Chen et al., 1988, is a

notable exception). Some studies that include children above the age of seven may also be upwardly biased by subjects' unreported experimentation with cigarette smoking.

It is improbable, however, that sources of bias or confounding factors account for the totality of study findings on increased occurrence of detrimental respiratory effects in children of parents who smoke. The overall evidence of a health risk is based on numerous investigations that vary broadly in design and location, source of data, objective, protocol, and methods of analysis. Most studies have controlled for bias and potential confounding factors to the extent possible. The upward dose-response trends exhibited in several studies suggest that an alternative explanatory factor would have to be highly correlated with the level of ETS exposure, e.g., the number of cigarettes smoked per day by the mother. In view of these considerations, the substantial epidemiologic evidence, the serious health consequences of some of the observed effects, and the large number of children potentially at risk, it is prudent and reasonable to treat passive smoking as a risk factor for acute respiratory diseases and chronic obstructive pulmonary disorders in infants and young children.

2. INTRODUCTION

Over 300,000 deaths per year from all causes of disease in the United States are attributable to cigarette smoking. Some 100,000 of these smoking-related deaths are from lung cancer, which is almost 90% of lung cancer cases from all causes (figures for 1985, U.S. SG, 1989). Forty-three known or suspected carcinogens have been identified in tobacco smoke, most of which are in both mainstream smoke (MS, produced during "puffs") and sidestream smoke (SS, from the cigarette tip between puffs). The relative distribution of carcinogens and other toxins differs between SS and MS, however, often with much larger total amounts (by weight) in the SS from a cigarette. More of the cigarette tobacco is burned in the generation of SS than MS, on average, but a more significant factor is the less complete combustion of tobacco at the lower temperatures producing SS. Environmental tobacco smoke (ETS) to which a passive smoker is exposed principally consists of SS, usually in greatly diluted concentrations depending on the proximity to the source and related environmental conditions, e.g., ventilation. Aging also affects the composition of chemicals in ETS and their relative distribution between the vapor and particulate phases.

Passive and active smokers are exposed to many of the same carcinogens, however, and active smoking has been firmly established as causally related to lung cancer. It is biologically plausible that passive smoking is also causally related to lung cancer. Consequently, the epidemiologic studies available on lung cancer and ETS exposure are examined for detectable evidence of increased lung cancer risk from passive smoking. It should be noted that it is extremely unusual when considering a low dose exposure to an agent known to be carcinogenic at higher doses to have as complete or as extensive a set of measures of exposure to the population at environmental levels; it is almost unprecedented to have epidemiologic evidence in as many different populations as is present for ETS. Nevertheless, statistical analysis of the

combined study results could be inconclusive. Statistical significance is evidence that an effect is at a sufficiently high level to be detected with the data available; lack of significance only supports the conclusion that it is below a level that the data have adequately high power to detect with assurance.

A first step is to gain some idea of the magnitude of exposure to ETS in the general population. Surrogate measures of ambient concentrations of ETS, such as respirable suspended particulates (RSP), have confirmed passive smokers' exposure in real and simulated environments. Concentrations of cotinine, a tobacco-specific metabolite of nicotine measurable in blood, saliva, and urine, confirm the uptake and systemic distribution of nicotine from ETS in passive smokers. Positive cotinine concentrations in 50% to 75% of self-reported nonsmokers, including persons reporting no exposure to tobacco smoke in the detectable period (up to a few days, depending on the body fluid tested), demonstrate the ubiquity of ETS. Conservatively, over 100 million U.S. adult nonsmokers are exposed to ETS at levels detectable in urinary cotinine assays.

The first epidemiologic results associating passive smoking with lung cancer appeared in the early 1980s. The epidemiologic studies amassed quickly, along with interest in the results and controversy over issues and conclusions. At the request of two Federal Agencies, the U.S. Environmental Protection Agency (Office of Air and Radiation) and the Department of Health and Human Services (Office of Smoking and Health), the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences of exposure. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail, including summary analyses of the evidence from ten case-control and three cohort (prospective) studies. It concludes that "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

The NRC committee was particularly concerned with potential bias in study results from current and former smokers incorrectly self-reported as lifelong nonsmokers (never-smokers). Under plausible assumptions for misreported smoking habits, it concludes that the true relative risk lies between 1.15 and 1.35, with 1.25 the most likely value. When these relative risks are also corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a "plausible" range of 1.24 to 1.61. (Technical Note: "Relative risk," RR, is used somewhat generically throughout this report for technical ease and because the name is descriptive of the intended measure. For 2-by-2 contingency tables of raw data from classifying exposed/unexposed against cancer/non-cancer, as analyzed in the NRC report, the sample odds ratio is estimated in place of RR. These terms are discussed in standard texts of statistical methods for epidemiology. A good technical discussion with examples may be found in Agresti, 1990, Section 2.2.)

Two other major reports on passive smoking have appeared: the U.S. Surgeon General's report on the health consequences of passive smoking (U.S. SG, 1986), and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987). The U.S. SG's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. The report quotes the summary statement on passive smoking of a previous IARC working group that found the epidemiologic evidence available at that time (1985) compatible with either the presence or absence of lung cancer risk. Based on other considerations related

to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer.

The summary analysis across epidemiologic studies conducted by the NRC is extended in this report to include nine additional case-control studies for which the raw data are available (for 19 from a total of 21 case-control studies). The committee's approach to hazard identification is further complemented by other statistical analysis across studies (meta-analysis) of results adjusted for potential confounding variables. The two major cohort studies (from Japan and the U.S.) are reviewed and compared. Their results are combined with those from the case-control studies to give an overall estimate of relative risk (Chapter 3). The population risk is then characterized by estimation of the annual number of lung cancer deaths among nonsmokers attributable to passive smoking (Chapter 4).

Results from dose-response risk assessments of lung cancer and ETS are examined in this report. The methods tend to be variations on the "cigarette-equivalents" approach, the basis of which is extrapolation of lung cancer risk for passive smoking from a dose-response curve of active smoking. Although this approach makes use of the dose-response information previously obtained for active smoking, the information contained in the epidemiologic studies is not fully utilized. The cigarette-equivalents approach is limited by incomplete knowledge regarding the biological basis for comparing the carcinogenic potential of passive and active smoking. A mathematical model has been developed to aid the study of the biokinetic similarities and differences between passive and active smoking. The model also serves to identify parameters where information is currently lacking.

The conclusions of this report do not require a dose-response risk assessment, but such a construct could be useful for evaluation of the effectiveness of abatement procedures and for confirmation of population risk estimates from another perspective. Three alternative approaches are described in this report (Appendix D), with solicitation of comments and advice. The three alternatives include: (1) a relative potency approach in which the dose-equivalent potency of ETS relative to a positive control, such as benzo[a]pyrene (B[a]P), is established from animal lung implant studies. That relationship is then included with the relative cancer potency of various polycyclic aromatic hydrocarbons (PAHs) and an existing inhalation dose-response model for B(a)P to establish a dose-response model for ETS; (2) a mixture approach based on a modification of the method in (1) and the relative concentrations of the known lung carcinogens in ETS; and (3) a direct approach using epidemiologic cohort studies on ETS.

Acute health effects in children from household exposure to ETS is a second health-related concern examined in this report (Chapter 5). Epidemiologic evidence subsequent to the major NRC and U.S. SG reports of 1986 is summarized and compared with the conclusions of the two previous reports for respiratory symptoms, respiratory illness, and pulmonary function. Recent studies on related health concerns in children are also reviewed. These studies investigate the effects of parental smoking on prevalence of asthma, chronic middle ear diseases, and upper-respiratory-tract infection, and on the severity of conditions in asthmatics. Potential confounding factors and sources of bias that limit quantitative estimation of health hazards attributable to ETS are addressed.

3. EPIDEMIOLOGIC EVIDENCE OF LUNG CANCER FROM ENVIRONMENTAL TOBACCO SMOKE

3.1. INTRODUCTION

The 21 case-control studies currently available are listed in Table 3-1. The studies are denoted by the first few letters of the first author's name for easy reference. The NRC report (1986) reviews and analyzes ten of the studies shown in Table 3-1: AKIB, BUFF, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC. The study designated as WU in the table is excluded because the raw data were not available. (Raw data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excludes an earlier version of the KOO study and the studies by Knoth et al. (1983), Miller (1984), and Sandler et al. (1985) for various reasons (NRC, 1986). Aside from WU, these studies are also omitted from this report.

The U.S. SG's report (1986) contains particularly good summary reviews of the studies available at that time. The studies are selectively described or compared in several sources as well (NRC, 1986; IARC, 1987; Balter et al., 1986; Blot and Fraumeni, 1986; Correa, 1986; Eriksen et al., 1988; Kuller et al., 1986; Repace and Lowrey, 1985; Riboli, 1987; Samet, 1988a,b; Saracci and Riboli, 1989; Weiss, 1986; Wells, 1988b; Überla, 1987; and Varela, 1987). Appendix A contains summaries of the studies subsequent to the NRC report, two of which are unpublished dissertations (LAMW and VARE). The other studies described in Appendix A include BROW, GAO, GENG, HUMB, INOU, LAMT, SHIM, SVEN, and WU. Tables 3-2, 3-3, and 3-4 display descriptive characteristics of all 21 case-control studies.

TABLE 3-1. CASE-CONTROL STUDIES OF ETS: CHARACTERISTICS

Study	Location	Matched variables	Final sample matched for ETS	Includes an adjusted statistical analysis[7]
AKIB (Akiba et al., 1986)	Japan (Hiroshima, Nagasaki)	Age, sex, residence, RERF participant	Yes	No
BROW[1] (Brownson et al., 1987)	USA (Colorado)	Age, sex	No[2]	Yes
BUFF (Buffler et al., 1984)	USA (Texas)	Age, sex	No[2]	No
CHAN (Chan and Fung, 1982)	Hong Kong	Matched but variables unspecified	No[2]	No
CORR[3] (Correa et al., 1983)	USA (Louisiana)	Age (± 5), sex, race	No[2]	No
GAO (Gao et al., 1987)	China (Shanghai)	Age (± 5)	No[2]	Yes
GARF (Garfinkel et al., 1985)	USA	Age (± 5)	Yes	Yes
GENG (Geng et al., 1986)	China (Tianjin)	Age (± 2), sex, race, marital status	No[2]	No
HUMB (Humble et al., 1987)	USA (New Mexico)	Age (± 10), sex, ethnicity	No[2]	Yes

(continued on following page)

TABLE 3-1. (continued)

Study	Location	Matched variables	Final sample matched for ETS	Includes an adjusted statistical analysis[7]
INOU (Inoue and Hirayama, 1988)	Japan (Kanagawa, Miura)	Age, year of death (± 2.5), district	No[2]	Yes
KABA (Kabat and Wynder, (1984)	USA (New York)	Age (±5), sex, race, hospital	Yes	No
KOO (Koo et al., 1987)	Hong Kong	Age (± 5), residence, housing	No[2]	No
LAMT (Lam et al., 1987)	Hong Kong	Age (±5), residence	No[2]	No
LAMW[8] (Lam, 1985)	Hong Kong	Age, socio-economic status, residence[5]	No[2]	Yes
LEE (Lee et al., 1986)	England	Age, sex, hospital location, time of interview	No[2,4]	Yes
PERS (Pershagen et al., 1987)	Sweden	Age (± 1), sex	Yes	Yes
SHIM (Shimizu et al., 1988)	Japan (Nagoya)	Age (±1), hospital, admission date	Yes	Yes

(continued on following page)

TABLE 3-1. (continued)

Study	Location	Matched variables	Final sample matched for ETS	Includes an adjusted statistical analysis[7]
SVEN (Svensson et al., 1988)	Sweden (Stockholm)	Age	No[2]	Yes
TRIC (Trichopoulos et al., 1981)	Greece (Athens)	Age, socio-economic status[6]	No[2]	No
VARE (Varela, 1987)	USA (New York)	Age, sex, county, smoking history	Yes	Yes
WU (Wu et al., 1985)	USA (Los Angeles)	Age (±5), sex, race	No[2]	Yes

[1] Adenocarcinoma only.
[2] Not matched on smoking status (smoker/nonsmoker).
[3] Bronchoalveolar cancer excluded.
[4] Ongoing study modified for passive smoking with follow-up.
[5] "Similar" in age, SES, and residence.
[6] "Similar" in age and SES.
[7] Generally refers to (conditional) logistic regression and to stratification or standardization of variables in analysis.
[8] W.K. Lam is the author of LAMW and co-author of LAMT, a separate study.

TABLE 3-2. CASE-CONTROL STUDIES OF ETS: CHARACTERISTICS

Study	Percent proxy response[1] Ca	Co	Female[2] age Ca	Co	Source of controls	Number female controls	Percent female controls "exposed"[3]
AKIB	90	88	70.2 35-95	* *	Atomic bomb survivors	270	70
BROW	69	39	66.3	68.2	Cancer cases[4]	47	15[5]
BUFF	82	76	30-79	30-79	Cancer cases[6]	196	84
CHAN	*	*	39-70	39-70	Orthopaedic patients	139	47
CORR	*	*	*	*	Hospital patients[8]	133	46
GAO	0	*	35-69	35-69	General population	375	74
GARF	*	*	≥40	≥40	Cancer cases[9]	402	61
GENG	*	*	≤65	≤65	*	93	44
HUMB	*	*	≤85	≤85	General population	162	56
INOU	100	100	*	*	Cerebro-vascular disease (deaths)	64	*
KABA	*	*	61.6	53.9	Patients[10]	25	60
KOO	*	*	*	*	"Healthy"[11]	136	49

(continued on following page)

TABLE 3-2. (continued)

Study	Percent proxy response[1] Ca	Co	Female[2] age Ca	Co	Source of controls	Number female controls	Percent female controls "exposed"[3]
LAMT	*	*	*	*	"Healthy"[12]	335	45
LAMW	*	*	67.5	66	Hospitalized orthopedic patients	144	44
LEE	38[13]	38	35-74	35-74	Patients[14]	66	68
PERS	*[15]	*	*[16]	*	*[17]	347	43
SHIM	*	*	59 35-81	58 35-81	Patients[18]	*	*
SVEN	0	0	66.3		General population	174	66
TRIC	*	*	62.8	62.3	Hospitalized orthopedic patients	190	43
VARE	33[19]	33[19]	67.1[19]	68.1[19]	New York State Dept. of Motor Vehicles	218[20]	*
WU	*	*	<76	<76	Neighbor-hood[12]	52	63

[1] "Ca" and "Co" stand for "cases" and "controls", respectively.
[2] Single values are the average or median. Paired values are the range.
[3] Definition of "exposed" differs between studies. See Table 3-4 and 3-5.
[4] Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
[5] "Exposed" to ETS 4 or more hours/day.
[6] Population-based and decedent comparison subjects selected from state and federal records.
[8] Assorted ailments.
[9] Colo-rectal cancer

[10] Diseases not related to smoking.
[11] Selected from a healthy population.
[12] Living in neighborhood of matched case.
[13] Applies only to the 143 patients in the follow-up study.
[14] Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[15] No overall percentages given.
[16] Two control groups: 15-65 and 35-85 for both cases and controls in groups 1 and 2 respectively.
[17] Two control groups were randomly chosen from the cohort under study
[18] Patients in the same or adjacent wards with other diseases.
[19] Includes males and females and long-term ex-smokers.
[20] Includes 69 ex-smokers.
* Data not available.

TABLE 3-3. CASE-CONTROL STUDIES OF ETS: SOURCES

Study	Adulthood: Spouse(s) 1	Adulthood: Spouse(s) >1	Adulthood: Others at home	Adulthood: Away from home	Childhood exposure from mother/father
AKIB	X				X
BROW	X		X	X	
BUFF			X		
CHAN[1]					
CORR		X			X
GAO		X	X	X	X
GARF		X	X	X	X
GENG	X		X[2]	X	
HUMB		X			
INOU	X				
KABA	X		X	X	
KOO	X		X		
LAMT	X				
LAMW	X		X	X	
LEE		X		X[3]	
PERS	X				X
SHIM	X		X	X	
SVEN	X		X	X	X
TRIC		X			

(continued on following page)

TABLE 3-3. (continued)

Study	Adulthood: Spouse(s) 1	Adulthood: Spouse(s) >1	Adulthood: Others at home	Adulthood: Away from home	Childhood exposure from mother/father
VARE		X	X	X[4]	
WU		X	X	X	X

[1] Not stated. See footnote 1 of Table 3-4.
[2] Exposure to mother's or father's smoking is presumed to mean in adulthood.
[3] Separate for workplace, travel, leisure.
[4] Separate for workplace and social circumstances.

TABLE 3-4. CASE-CONTROL STUDIES OF ETS: MEASURE OF EXPOSURE TO ETS AND OTHER SUBSTANCES

Study	ETS exposure measures				Related exposures	
	Cig./ day	Total years	Total cigs.	Other	Cooking/ heating	Work/ environ.
AKIB	X					
BROW				hrs./day		X
BUFF		X				X
CHAN				X[1]	X	
CORR				pack-yrs.		
GAO		X			X	X
GARF	X[2]			hrs./day		
GENG	X	X				
HUMB	X	X				
INOU	X[3]					
KABA				no units		X
KOO	X	X		X[4]		
LAMT	X[5]					
LAMW				no units		
LEE				X[6]		X
PERS				no units		X
SHIM	X				X	X
SVEN				X[7]		

(continued of following page)

TABLE 3-4. (continued)

Study	ETS exposure measures: Cig./day	Total years	Total cigs.	Other	Related exposures: Cooking/heating	Work/environ.
TRIC	X[8]		X			
VARE	X	X	X	person-yrs.		
WU				X[9]	X	X

1 Exposed/unexposed determined from a single question, "Are you exposed to the tobacco smoke of others at home or at work?" (Lam T.H. et al., 1987; Chan and Fung, 1979).
2 Cig./day smoked by husband at home.
3 Smoker at home defined as $\geq$5 cig./day.
4 Others include total hours of exposure and mean hrs./day.
5 A woman was considered exposed to her husband's smoke if they had lived together continuously for at least one year.
6 Exposure designated as 0 (unexposed), 1,2,3.
7 Exposure is "yes" or "no" for each source.
8 Exposed within the last 5 years.
9 Exposed if husband smoked.

These studies compare individuals with higher ETS exposures to those with lower exposures. All of them have made observations on never-smoking married women. Those married to a smoker are assumed to be at higher exposures than those not married to a smoker. These two groups are referred to as "exposed" and "unexposed", respectively, following the established terminology. Those terms refer to spousal smoking only, however, and obscure the presence of other sources of ETS, collectively referred to as "background" sources. Background exposure is taken into account in the next chapter under characterization of the population risk, where it becomes necessary to think of the unexposed classification as referring to exposure from background sources only and the exposed classification as including both background and spousal smoking. For the purpose of hazard identification in this chapter, background exposure does not explicitly enter into the discussion. The relative risk comparison of exposed to unexposed individuals, however, is implicitly a comparison of "exposed to both background and spousal smoke" to "exposed to background only".

Several differences in the case-control studies may be noted. The unit of measure of ETS exposure (e.g., cig./day or total years of exposure) varies between studies. A few studies include former smokers as nonsmokers if they have abstained from tobacco usage for some minimum period, while others do not. Classification of a subject as ETS-exposed depends on the questions asked, which differ across studies. The proportion of controls classified as exposed is shown by study in Figure 3-1. Exposure percentages cover a range from 43% to 84%, a two-fold difference, with the BROW study is an outlier at 15%. The referent populations are defined by a number of parameters, such as whether the subjects were alive or dead and, if alive, whether or not they were hospitalized. Other general study characteristics that vary relate to study design, protocol, interpretation, and analysis of data, potential confounding factors included in the matching and/or data analysis, and confirmation of primary lung cancers. Study differences do not invalidate statistically testing the hypothesis that exposure to ETS is unrelated to lung cancer occurrence. (Technical Note: The Breslow-Day test for homogeneity of the odds ratio is not significant, $p = 0.48$. [Breslow and Day, 1980].) ETS studies have primarily

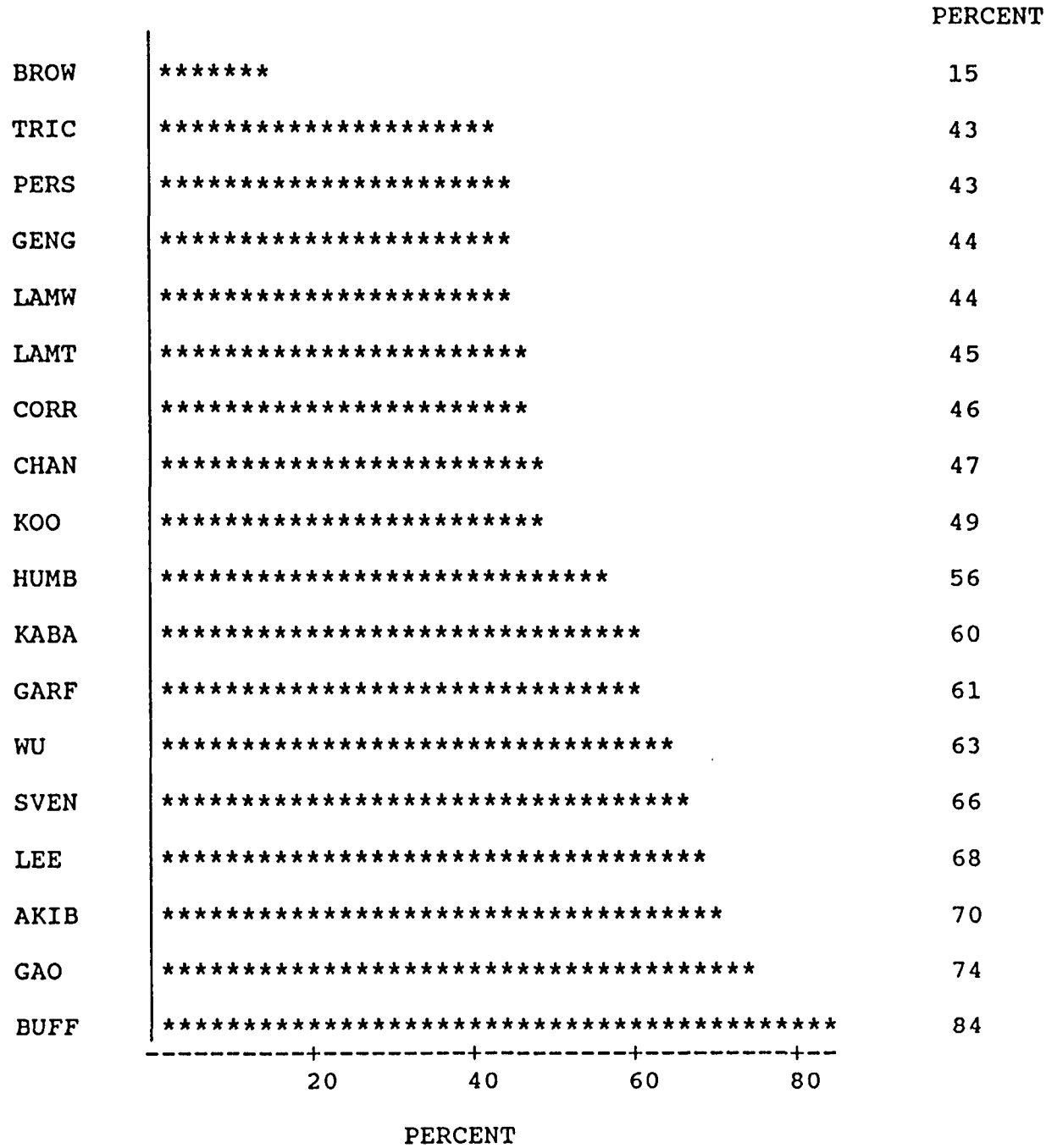


FIGURE 3-1. PERCENTAGE OF CONTROLS EXPOSED TO ETS BY STUDY

considered exposure to married never-smoking women, generally classified as exposed or unexposed to ETS based on their spouse's smoking status. Consequently, analysis in this report primarily focuses on the data for females. Data on males is sparse by comparison, and there may be sex-related exposure differences to ETS (Cummings et al., 1986; Friedman et al., 1983).

The case-control studies are tested for an association between ETS exposure and lung cancer from three perspectives.

1) Raw data are available for 19 of the 21 studies in Table 3-5. Three statistical tests are applied to these data to test for an association between ETS exposure and lung cancer occurrence.

2) Eleven studies provide results of statistical analyses that adjust for covariables, e.g., age, duration of spousal smoking, etc. Statistical modeling, such as logistic regression, or stratification on variables are two general approaches. The estimated relative risks and confidence intervals from these methods are used in two statistical tests of the combined evidence from the eleven studies.

3) Fourteen case-control studies contain crude classifications of exposure to ETS suitable for evaluating whether there is an upward trend in lung cancer occurrence as ETS exposure increases. These "dose-response" data from the studies are plotted for comparison.

This statistical testing is in the next three sections (Sections 3.2-3.4). It is followed by a discussion of potential sources of bias in the case-control studies (Section 3.5). The two major cohort studies are then described and compared (Sections 3.6 and 3.7), followed by the summary and conclusions of this chapter.

3.2. META-ANALYSIS OF CASE-CONTROL STUDIES FROM RAW DATA

The statistical power to detect a small but meaningful increase in lung cancer risk from a single case-control study is often small, but it can be improved by analyzing the total evidence from all studies simultaneously (meta-analysis). The NRC (1986) followed the lead of a committee member (Wald, 1986) who estimated an overall relative risk across all studies by the statistical method in Yusuf et al. (1985). Blot and Fraumeni (1986) and Wells (1988b) achieved the same objective using the

TABLE 3-5. CASE-CONTROL STUDIES: "UNEXPOSED" VS. "EXPOSED" FROM RAW DATA

Study	Exposure	No. cases	No. controls	RR[1]	C.I.[1]	S[1]	P^1_S
AKIB							
Female (cig./day)	0	21	82	**1.52**	**(0.88,2.63)**	**1.48**	**0.07**
	≥1	73	188	1.5	(1.0,2.5)[2]		
Male (cig./day)	0	16	101				
	≥1	3	19	1.8	(0.5,5.6)		
BROW[3]							
Female	unexposed	15	40	**1.52**	**(0.39,5.99)**	**0.61**	**0.27**
	exposed[4]	4	7	1.5			
Male (hrs./day)	0-3	2	11				
	≥4	2	8	1.38			
BUFF							
Female (tot. yrs.)	unexposed	8	32	**0.81**	**(0.34,1.90)**	**-0.49**	**0.69**
	exposed[18]	33	164	0.8	(0.3,1.8)		
Male (tot. yrs.)	unexposed	6	34				
	exposed[18]	5	56	0.5	(0.2,1.7)		
CHAN							
Female	unexposed	50	73	**0.75**	**(0.43,1.30)**	**-1.02**	**0.85**
	exposed[5]	34	66	0.8	(0.4,1.3)		
CORR							
Female[6]	0	8	72	**2.07**	**(0.82,5.25)**	**1.52**	**0.06**
	≥1	14	61	2.07	(0.8,5.0)		
Male (pack-yrs.)	0	6	154				
	≥1	2	26	2.0			

(continued on following page)

TABLE 3-5. (continued)

Study	Exposure	No. cases	No. controls	RR[1]	C.I.[1]	S[1]	P^1_s
GAO							
Female (tot. yrs.)	0-19	57	99	**1.19**	**(0.82,1.73)**	**0.91**	**0.18**
	≥20	189	276				
GARF							
Female (cig./day)	0	44	157	**1.31**	**(0.87,1.98)**	**1.29**	**0.10**
	≥1[7]	90	245	1.31	(0.99,1.73)		
GENG							
Female (cig./day)	0	20	52	**2.16**	**(1.08,4.29)**	**2.19**	**0.01**
	≥1	34	41	2.16	(1.05,4.53)		
HUMB[8]							
Female (cig./day)	0	5	71	**2.34**	**(0.81,6.75)[2]**	**1.57**	**0.06**
	≥1	15	91	1.8	(0.6,5.4)		
INOU[9]							
Female (cig./day)	<4	4	17	**2.55**	**(0.74,8.78)**	**1.50**	**0.07**
	≥4	18	30				
KABA							
Female	unexposed	11	10	**0.79**	**(0.25,2.45)**	**-0.41**	**0.66**
	exposed[10]	13	15				
Male	unexposed	7	7				
	exposed[10]	5	5	1.00	(0.20,4.90)		
KOO							
Female (cig./day)	0	35	70	**1.55**	**(0.90,2.67)**	**1.56**	**0.06**
	exposed[11]	51	66	1.55	(0.94,3.08)		

(continued on following page)

TABLE 3-5. (continued)

Study	Exposure	No. cases	No. controls	RR[1]	C.I.[1]	S[1]	P^1_S
LAMT							
Female	0	84	183	**1.65**	**(1.16,2.35)**	**2.77**	**0.003**
(cig./day)	≥1	115	152	1.65	(1.16,2.35)		
LAMW							
Female	unexposed	23	80	**2.01**	**(1.09,3.71)**	**2.24**	**0.01**
	exposed[11]	37	64	2.01			
LEE							
Female	unexposed[12]	10	21	**1.03**	**(0.41,2.55)**	**0.05**	**0.48**
	exposed[13]	22	45	1.00[14]	(0.37,2.71)[14]		
Male	unexposed[12]	7	16				
	exposed[13]	8	14	1.30	(0.38,4.42)		
PERS							
Female	unexposed[15]	34	197	**1.28[14]**	**(0.76,2.15)**	**0.91**	**0.18**
	exposed[16]	33	150	1.28[14]	(0.75,2.15)		
SVEN							
Female	unexposed	10	60	**1.26**	**(0.57,2.82)**	**0.57**	**0.28**
	exposed[16]	24	114				
TRIC							
Female	0	24	109	**2.13**	**(1.19,3.83)**	**2.55**	**0.005**
(cig./day)	≥1	38	81				
WU[17]							
Female	unexposed	9	22	**1.41**	**(0.54,3.67)**	**0.70**	**0.24**
	exposed[4]	19	33	1.2			

Footnotes for Table 3-5.

[1] Values of RR, C.I., S, and P_s on the first row of an entry (boldface) are our calculations for Mantel-Haenszel odds ratio. Values in the second row are from the study. S is the square root of the Mantel-Haenszel statistic with sign of (-) if $R<1$ and (+) if $R>1$. P_s is one-tailed significance value from normal tables, and equals one-half the corresponding two-sided p-value for the M-H chi- squared statistic. Confidence intervals are 95% unless noted otherwise.

[2] 90% C.I.

[3] Data communicated from R.C. Brownson.

[4] Exposed if husband smoked.

[5] Exposure based on single question, "Are you exposed to the tobacco smoke of others at home or at work?" (Lam et al., 1987; Chan et al., 1979).

[6] Data partially from Table 12-4, NRC (1986).

[7] Cigar or pipe smoking by husband while at home is included in category of $\geq$1 cig./day.

[8] Data communicated from C.G. Humble. Eight (total) cases were observed in males, so a separate odds ratio for males alone was not reported in the study.

[9] Raw data were calculated from information given in the reference to INOU by A. Judson Wells.

[10] Based on spouse's current or past smoking habits.

[11] Exposed if husband ever smoked in presence of spouse.

[12] Only the controls in the follow-up study.

[13] Exposed if husband ever smoked during marriage.

[14] Standardized for age.

[15] Data for controls from Saracci and Riboli (1989).

[16] No measure of exposure given.

[17] Raw data were calculated from information in Table 11 of the Surgeon General's report (U.S. SG, 1986, p. 99) by A. Judson Wells.

[18] Any current household member who smokes regularly.

Mantel-Haenszel (M-H) method (Mantel and Haenszel, 1959; Mantel, 1963), a standard approach for the combination of information from 2-by-2 contingency tables. (Wells included adjusted analyses when available, using the raw data to calculate weights.) The two methods are basically equivalent. In this report, the M-H method is applied to the raw data for females in the case-control studies shown in Table 3-5.

The M-H estimate of relative risk (odds ratio) and its associated confidence interval are shown in boldface type in Table 3-5 for females of each case-control study where the raw data are available (SHIM and VARE are excluded). Each study's own relative risk estimate and confidence interval are also displayed when available. The M-H estimate of the overall RR for females is 1.42 (95% C.I. 1.24, 1.63) for 19 case-control studies. (All confidence intervals hereafter are 95% if not indicated otherwise.) The corresponding value in the NRC report for females of 10 case-control studies and 3 cohort studies is 1.32 (1.16, 1.51). The NRC reports 1.62 (0.99, 2.64) for males. Wells (1988b) obtained an overall relative risk estimate of 1.44 (1.26, 1.66) for females from 14 case-control studies and three cohort studies. Wells' higher estimate may be due in part to his exclusion of the CHAN study, the first and probably least sophisticated of the four Hong Kong studies (CHAN, LAMW, KOO, and LAMT). It also produced the lowest relative risk estimate in Table 3-5, namely 0.75 (0.43, 1.33).

A statistic referred to as "S" is included in Table 3-5. (Technical Note: S is the square-root of the M-H chi-squared statistic with the sign "+" if the odds ratio exceeds 1 and the sign "-" if otherwise. Equivalently, it is the estimated log-odds ratio [ln(RR)] divided by its estimated standard error. The estimator S is approximately normally distributed with mean zero under the null hypothesis that the true relative risk equals one [Woolf, 1955].) The values of P_s in Table 3-5 are the one-tailed significance levels of S for testing the null hypothesis that ETS exposure is unrelated to lung cancer occurrence. The rank ordered values of S are displayed in Figure 3-2.

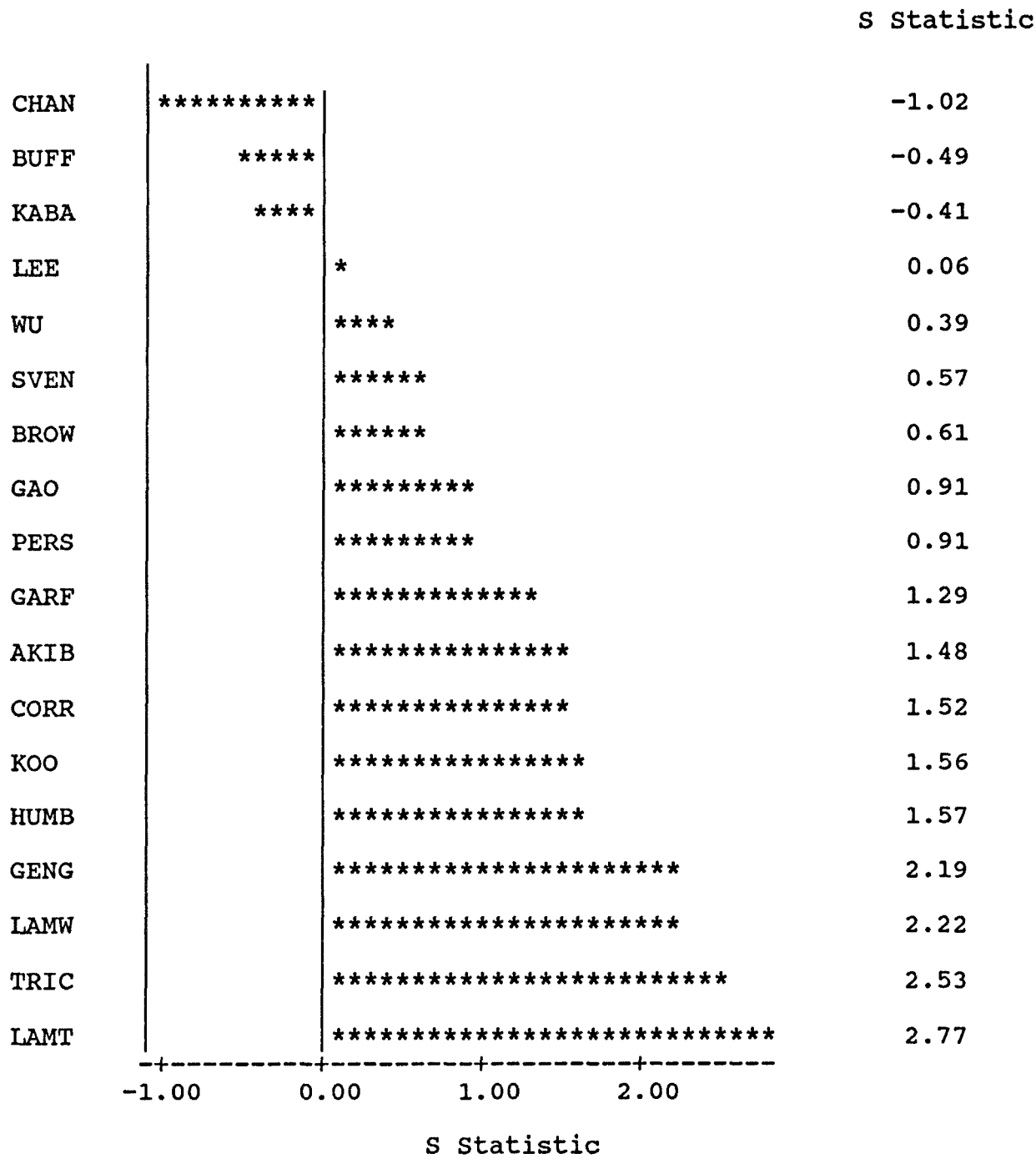


FIGURE 3-2. ORDERED VALUES OF THE S STATISTIC FROM RAW DATA OF STUDIES IN TABLE 3-5

Three statistical tests are conducted of the null hypothesis. The extended M-H chi-squared test statistic is significant at $p < 0.001$ based on the combined evidence from the raw data shown in Table 3-5. The Wilcoxon sign-ranked test (Hollander and Wolfe, 1973) applied to the values of S in Table 3-5 also is significant at $p < 0.001$. (Technical Note: The signed-rank test requires the test statistic for each study to be symmetrically distributed about zero under the null hypothesis. Since S is approximately normally distributed with mean zero, that assumption is appropriate here.) If the null hypothesis is true, then the four studies with $p_s \leq 0.05$ are making a Type I error (false positive). The chance of that many Type I errors in 19 independent studies is 0.013. The predominance of small values of p_s, in general, is informative. Over half of the 19 p_s values are 0.1 or less, an outcome that would occur with probability less than 0.001 if the null hypothesis is true. All of the tests based on the raw data are statistically significant.

3.3. META-ANALYSIS OF CASE-CONTROL STUDIES THAT INCLUDE AN ADJUSTED STATISTICAL ANALYSIS

An adjusted analysis is generally preferable to an analysis of the raw data, even when the data are matched (Schlesselman, 1982). The two studies for which the raw data are unavailable do include results of an adjusted analysis (SHIM, VARE). Table 3-1 identifies the studies with results adjusted for other variables. Some authors have not included complete details, so the choice of studies for inclusion in this section may be subjective. In eleven reports, the relative risk and confidence interval are given for two or more levels of exposure, e.g., 1 to 20, 21 to 40, or 41+ cig./day smoked by the spouse. The RR and confidence interval at a high exposure in these studies were generally selected for inclusion in Table 3-6, but with some exceptions. For example, the highest exposure category in VARE is so extreme (80+ cig./day) that it contains very little data. In this instance, the response for smoking 20 cig./day as predicted from the

logistic regression model fitted to all the data is given in Table 3-6. The table entry for GARF is also from an adjusted analysis for a spouse smoking 20 cig./day. Two studies that provide a relative risk without an associated confidence interval (LAMW and SHIM) are displayed in Table 3-6 for completeness, although they cannot be included in the summary analysis.

The RR and confidence intervals in Table 3-6 are the study authors' conclusions that depend on their methods of analysis. To combine the results across studies, the statistic S was calculated from the RR and confidence interval for each study. (Technical Note: It is assumed that ln(RR) is approximately normally distributed. S equals ln(RR) divided by its estimated standard error, as calculated from the confidence interval reported.) The values of S are displayed in Table 3-6 and plotted in Figure 3-3. Five of the studies had significant values of S ($p < 0.05$). The probability of observing five or more Type I errors in 11 independent studies is less than 0.001. Thus, it is highly unlikely that so many significant test results would be observed if there were, in fact, no association between ETS exposure and lung cancer incidence. (Technical Note: No multiple comparison adjustment is necessary because the choice of a single exposure level is made without regard to statistical significance. Test results reported at exposure levels other than the one used are not relevant and no adjustment for multiple comparisons is needed.)

The Wilcoxon signed-rank test was also applied to the S statistics of Table 3-6, as conducted previously with the raw data, to provide another statistical test of the null hypothesis. The outcome is significant ($p = 0.014$). In this test the magnitude of the evidence from each study is a factor. Both statistical tests indicate that the cumulative evidence that lung cancer is related to ETS exposure would be very unlikely to occur by chance alone.

TABLE 3-6. CASE-CONTROL STUDIES: "UNEXPOSED" VS. "EXPOSED" FEMALES FROM ADJUSTED STATISTICAL ANALYSES

Study	Exposure	RR	95% C.I.	S	P_s
BROW	$\leq$3 vs. $\geq$4 (hrs./day)	1.68	(0.39,2.97)	1.78	0.04
GAO	0-19 vs. $\geq$40 (yrs. with smoking husband)	1.7	(1.0,2.9)	1.95	0.03
GARF	0 vs. 20 (cig./day)	1.70	(0.98,2.94)	1.90	0.03
HUMB[6]	0 vs. $\geq$21 (cig./day)	1.2	(0.26, 5.5)	0.23	0.41
INOU[7]	$\leq$4 vs. $\geq$ 20(cig./day)	3.09	(1.04,11.81)	1.65	0.05
KOO	0 vs. $\geq$ 21(cig./day)	1.19	(0.46,3.03)	0.36	0.36
LAMW[2,3]	Exposed by husband	2.64	*	*	*
LEE[5]	Exposed by husband	1.00	(0.37,2.71)	0.00	0.50
PERS[1]	0 vs. $\geq$ 16(cig./day)	2.40	(0.6,8.7)	1.33	0.09
SHIM[2]	Exposed by husband	1.1	*	*	*
SVEN	Exposed in both childhood and adulthood vs. exposed in neither	1.9	(0.2,3.7)	1.89	0.03
VARE[4]	0 vs. 20 (cig./day)	0.94	(0.76, 1.17)	-0.54	0.70
WU	Exposed by husband	1.2	(0.6,2.5)	0.49	0.31

[1] See footnotes 15-17 of Table 3-2.
[2] Higher RR values associated with adult exposure to smoking by mother or by father's husband. Insufficient information to calculate the S statistic.
[3] No units of exposure. RR=2.64 with p=0.02, and RR=1.61 with p=0.19, for peripheral and central lung adenocarcinoma, respectively.
[4] From Table 4 of Varela, 1987.
[5] See footnotes 12-14 of Table 3-5.
[6] Discussed in Humble et al. (1987) following Table 4, with 90% confidence interval of (0.3,4.4).
[7] The authors assume that husbands who smoke less than five cig./day do not smoke at home.

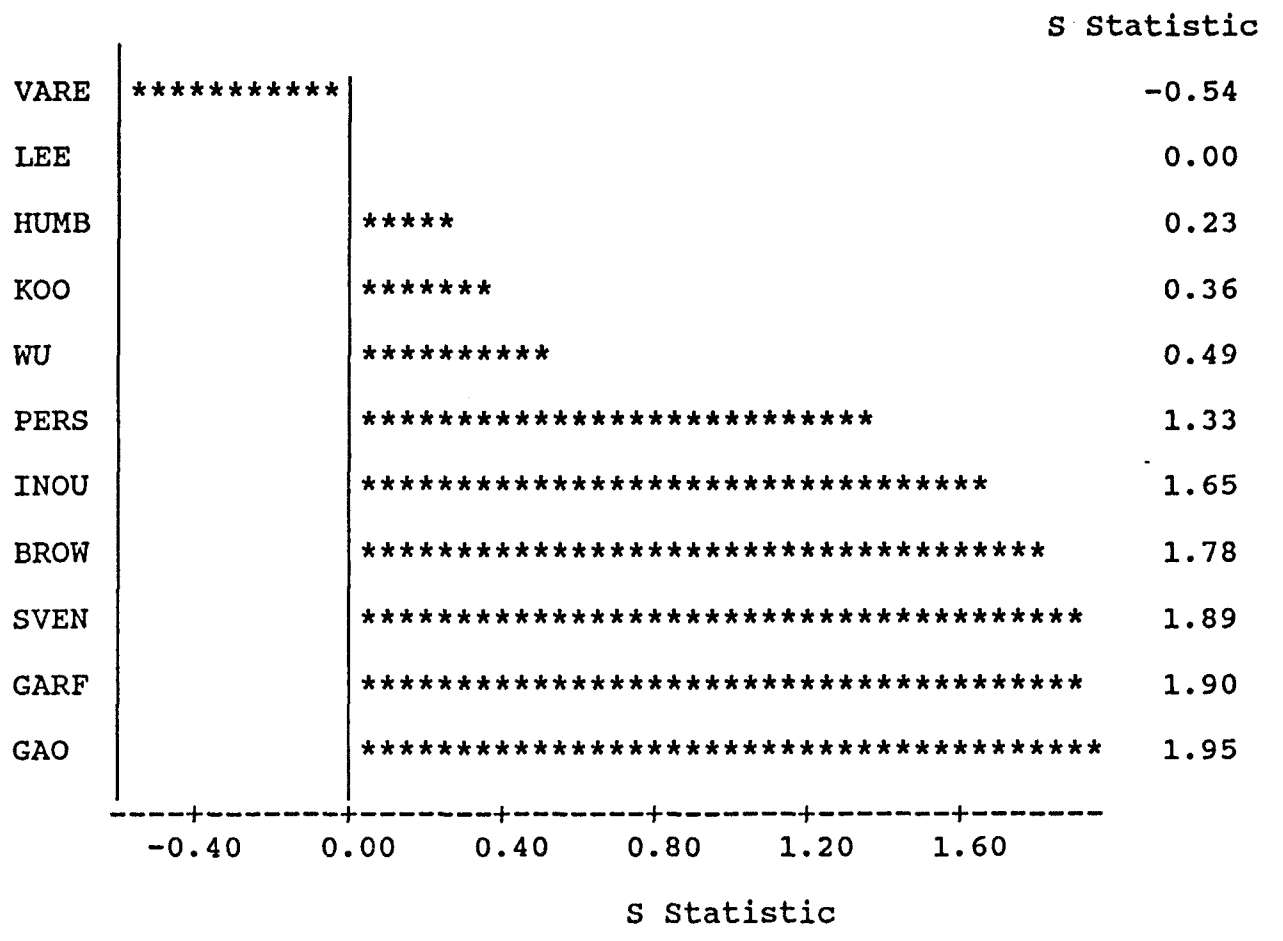


FIGURE 3-3. ORDERED VALUES OF THE S STATISTIC FROM ADJUSTED ANALYSES OF STUDIES IN TABLE 3-6

3.4. EVIDENCE OF DOSE-RESPONSE IN CASE-CONTROL STUDIES WITH MORE THAN ONE EXPOSURE LEVEL

Data for studies that report relative risk (RR) by levels of exposure are given in Table 3-7, along with the results of statistical tests for trends when available. The RRs are plotted against exposure and shown in Figure 3-4. Both adjusted and unadjusted estimates of RR are presented, as data permit. Some observations are apparent from the plots. For example, the estimated RRs increase in seven studies: AKIB, CORR, GAO, GENG, INOU, PERS, and TRIC; decrease slightly in one case: LEE; and are variable in the remaining five plots: GARF, HUMB, KOO, LAMT, and VARE.

If RR is independent of ETS, then the predicted RR at the highest exposure level is less than one with probability at least one-half. (Technical Note: If the distribution of the observed RR under the null hypothesis is symmetric, then the value is one-half. The distribution depends on the statistical method used in a study. All appear to be skewed to the right, judging from the confidence intervals. For a right-skewed distribution, the median is less than the mean. Thus, the probability of values greater than one exceeds one-half.) The observed RR at the highest exposure level is less than one in only two of the 13 studies above. The probability of two or fewer such occurrences by chance alone is approximately 0.012. It can be concluded, therefore, that the plots for trend are consistent with conclusions of the previous statistical tests conducted on the case-control studies, i.e., that the observed association between exposure to ETS and increased occurrence of lung cancer deaths is statistically significant.

TABLE 3-7. CASE-CONTROL STUDIES: EXPOSURE RESPONSE TRENDS FOR FEMALES

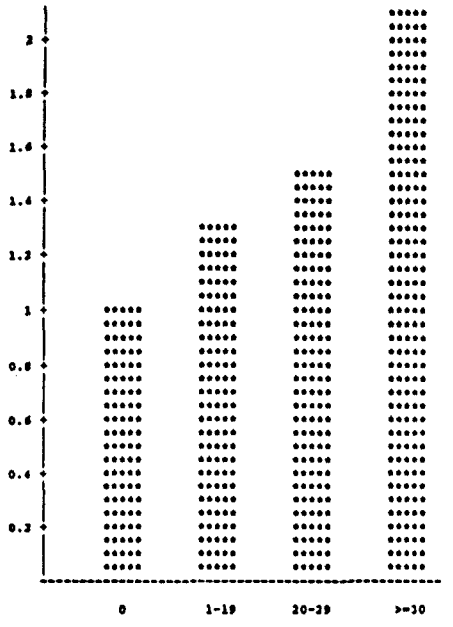
Study	Exposure	RR	C.I.[1]	P-Trend	Analysis: Unadjusted	Analysis: Adjusted
AKIB		1.0		0.06	X	
(cig./day)	1-19	1.3	(0.7,2.3)[2]			
	20-29	1.5	(0.8,2.8)[2]			
	≥30	2.1	(0.7,2.5)[2]			
CORR	0	1.0		*	X	
(pack-yrs.)	1-40	1.18	*			
	≥41	3.52	*			
GAO	0-19	1.0		*		X
(tot.yrs.)[3]	20-29	1.1	(0.7,1.8)			
	30-39	1.3	(0.8,2.1)			
	≥40	1.7	(1.0,2.9)			
GARF	0	1.0		<0.025	X	
(cig./day)	1-9	1.15	(0.8,1.6)			
	10-19	1.08	(0.8,1.5)			
	≥20	2.11	(1.1,4.0)			
GENG	0	1.0		*	X	
(cig./day)	1-9	1.40	(1.1,1.8)			
	10-19	1.97	(1.4,2.7)			
	≥20	2.76	(1.9,4.1)			
HUMB	0	1.0		*	X	
	1-20	1.8	(0.6,5.6)[2]			
	≥21	1.2	(0.3,5.2)[2]			
INOU	0-4	1.0		<0.05		X
(cig./day)	5-19	2.58	(0.4,5.7)[2]			
	≥20	3.09	(1.0,11.8)[2]			
KOO	0	1.0		*		X
(cig./day)[4]	1-10	2.33	(0.9,5.9)			
	11-20	1.74	(0.8,3.8)			
	≥21	1.19	(0.5,3.0)			

(continued on following page)

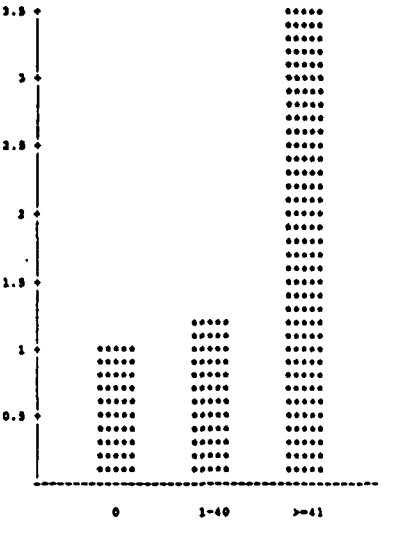
TABLE 3-7. (continued)

Study	Exposure	RR	C.I.[1]	P-Trend	Analysis: Unadjusted	Analysis: Adjusted
LAMT[5]	0	1.0		<0.01	X	
(cig./day)	1-10	2.18	(1.14,4.15)			
	11-20	1.85	(1.19,2.87)			
	≥21	2.07	(1.07,4.03)			
LEE[6]	0	1.0		*		X[6]
	Low	0.92	*			
	High	0.81	*			
PERS[7]	0	1.0		*	X[8]	
(cig./day)	1-15	1.8	(0.6,5.3)			
	≥16	6.4	(1.1,34.7)			
TRIC[9]	0	1.0		*	X	
(cig./day)	1-20	1.95	*			
	≥21	2.55	*			
VARE[10]	0	1.0		*		X
(cig./day)	1-20	0.79	(0.6,1.1)			
	21-40	0.91	(0.6,1.3)			
	41-60	1.23	(0.6,2.4)			
	61-80	0.42	(0.1,2.3)			
	80+	2.86	(0.3, 27.7)			
WU[11]	0	1.0		*		X
(yrs.	1-30	1.2	*			
exposed	≥31	2.0	*			
as adult)						

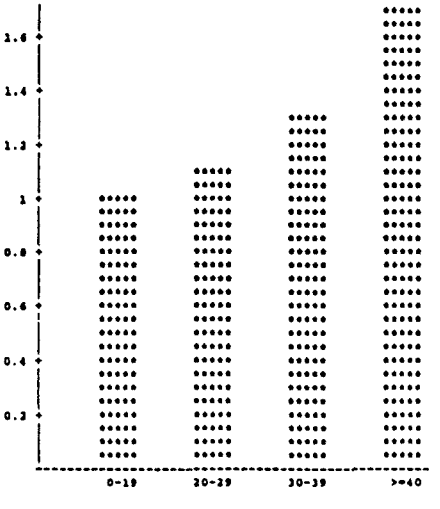
1 Confidence intervals are 95% unless noted otherwise.
2 90% confidence interval.
3 Years lived with a smoking husband.
4 Cig./day smoked by husband.
5 All histologies.
6 Exposure at home only. Standardized for age, spouse smoking, and whether currently married.
7 Small cell carcinoma only. Observed risk was lower for other histologies combined.
8 Stratified analyses and conditional (logistic) regression produced consistent results.
9 Data from Trichopoulos et al. (1983).
10 From Table 2 of Varela (1987) for spouse smoking, presumably including males.
11 Adenocarcinomas only.



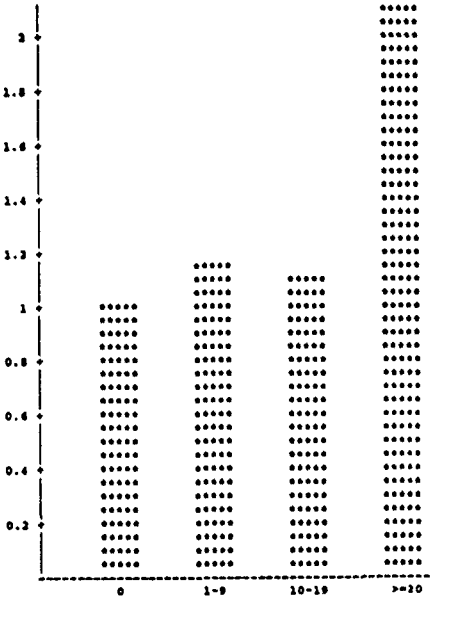
AKIB



CORR

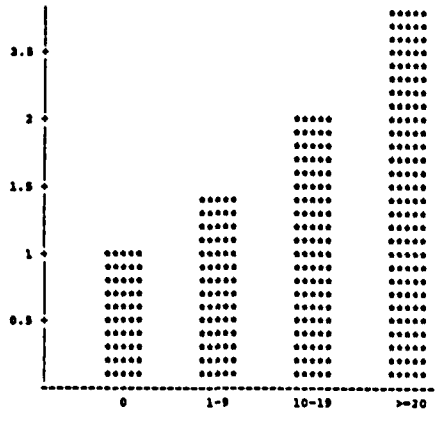


GAO

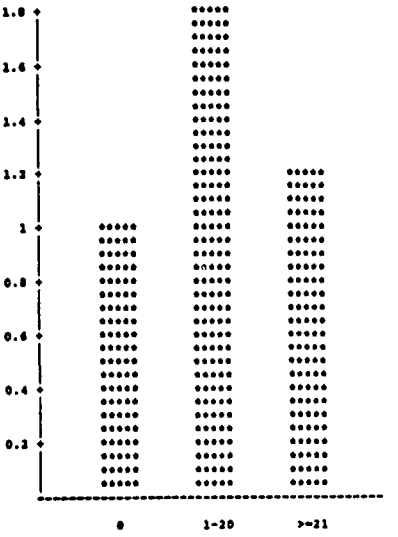


GARF

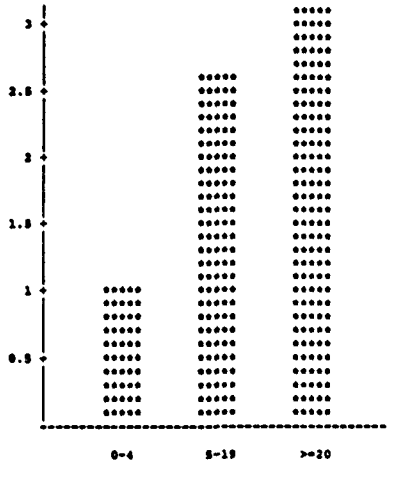
FIGURE 3-4. PLOTS OF RELATIVE RISK AGAINST EXPOSURE FOR STUDIES IN TABLE 3-7



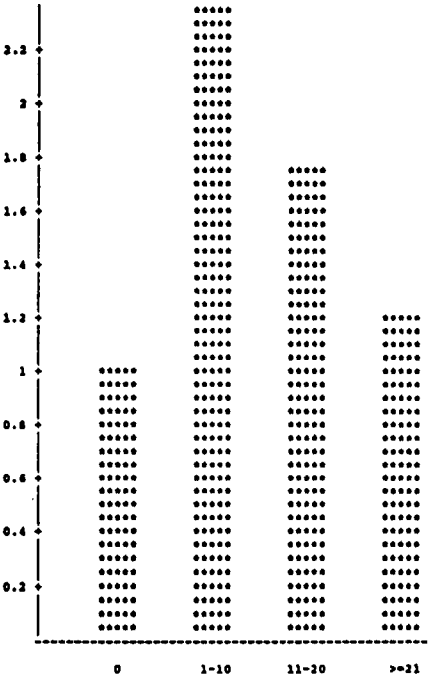
GENG



HUMB

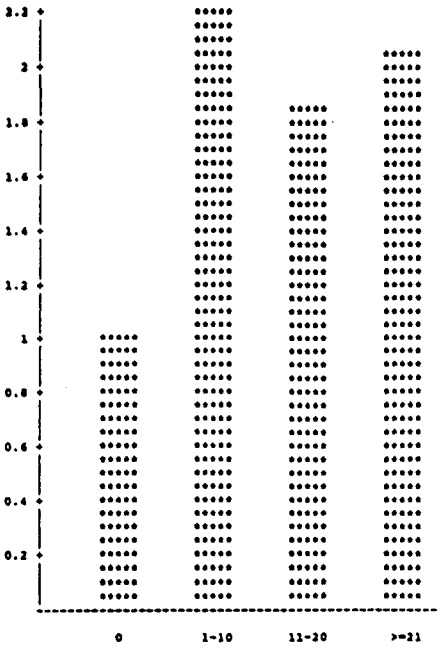


INOU

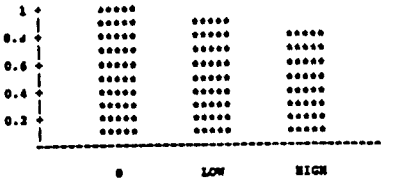


KOO

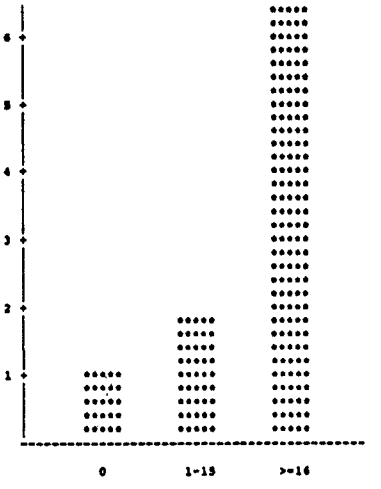
FIGURE 3-4. (continued)



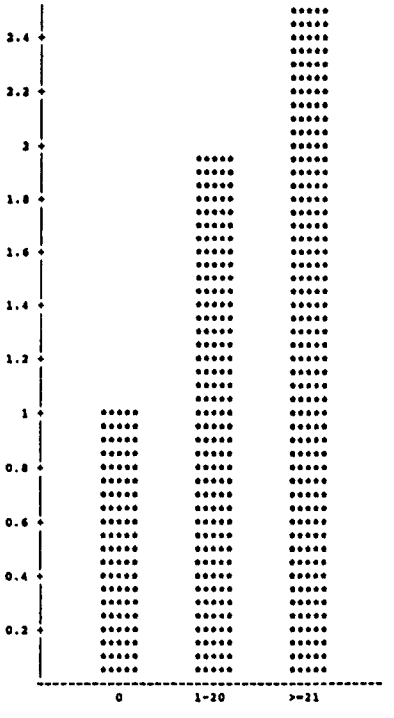
LAMT



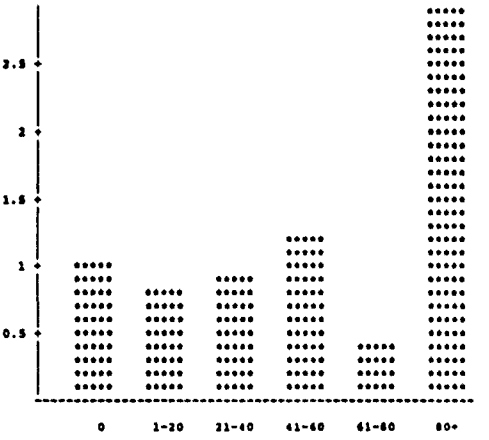
LEE



PERS



TRIC



VARE

FIGURE 3-4. (continued)

3.5. BASIC ISSUES IN POTENTIAL BIAS FROM MISCLASSIFICATION IN CASE-CONTROL STUDIES

Bias, particularly misclassification of subjects by smoking status, is not limited to case-control studies. Quantitative adjustment of the overall observed RR for possible misreporting of smoking habits is addressed in detail in Section 4.4.2.

3.5.1. Background

Estimation bias is due to study design, protocol, or method of analysis that apriori makes the expected outcome too large (positive bias) or too small (negative bias). Although sample size and dispersion contribute to outcome variability, neither repeated sampling nor increasing the sample size will affect bias. In either case, the estimate (on average) simply becomes arbitrarily close to the unknown value of interest, i.e., the true RR plus the bias. In practice, each case-control study has its own bias. If bias is largely random over a set of studies, some averaging effect toward zero would be expected. If there is a consistent source of bias in studies, however, sometimes referred to as "systematic bias," then it cannot be expected to disappear as the number of studies increases.

3.5.2. Sources of Bias

Ever-smokers (former and current smokers) are more likely to incorrectly report themselves as never-smokers (NS) than the reverse. A smoker is more likely than a nonsmoker to marry a smoker, so these misclassified ever-smokers (ES) are more likely to be exposed to ETS than true NS. Among lung cancer cases in a study (all of whom are reported NS), those who are actually former smokers (FS) or current smokers (CS) are disproportionately classified as exposed to ETS (assuming that the smoking habit of the spouse is not misreported as well). These cancer cases classified as exposed to ETS may have been at higher risk for lung cancer

because of a history of smoking, not just because of exposure to ETS. Hence, a lung cancer effect from active smoking may be contaminating the evaluation of the risk of passive smoking. Misreporting among controls tends to overstate the percentage classified as exposed to ETS, due to the concordance of smoking habits in married couples. This artificially elevates the exposed percentage in controls relative to cases, so it contributes to underestimation of risk (or bias in the negative direction).

Subjects classified as unexposed are rarely "truly unexposed"--as supported by data on measurements of cotinine. The NRC report takes this "background" exposure into account in adjusting an overall relative risk for a "net" bias. Recent survey results of Cummings et al. (1989b) provide additional evidence of background exposure in NS. Detectable levels of cotinine were found in 132 of 162 (81%) of the nonsmokers who reported no exposure in the four days preceding the interview. A mean urinary cotinine level of 8.8 ng/mL was found among nonsmokers. Although the study is based on self-selected volunteers, the authors note that the results are consistent with reports from other studies. Cummings and colleagues conclude that exposure to ETS is extremely prevalent, even among those not living with a smoker.

The overall estimate of RR in the NRC report places the excess risk of lung cancer associated with spousal smoking at about 34%. An adjustment for possible misclassification of the never-smoker status reduces the value to 25%. A second adjustment to make the risk relative to a truly unexposed subject, i.e., to take into account a background level of exposure, raises the increased risk to 42%. Consequently, the net adjustment for bias is upwards. The reports of the U.S. SG (1986) and IARC (1987) do not adjust their overall risk estimate for possible bias.

Potential sources of bias have been given considerable attention in the literature, often with an emphasis on the potential for positive bias (over-estimation of relative risk in this case). The following discussion is not complete, but it raises some of the more prominent issues on this

topic. Many of the potential sources of bias that have been raised in the literature could conceivably create negative bias as well. Of greatest concern, of course, has been the potential for bias from misreported classification of smoking status, i.e., CS or FS reported as NS.

The diagnosis of lung cancer in cases may be a source of bias, e.g., a cancer that originated at another primary site and then metastatised in the lung may be incorrectly diagnosed as a primary cancer of the lung (Samet, 1988b). As an example, Garfinkel et al. (1985) report that about 12% of lung cancer patients identified through hospital records were reclassified after histological review. Some studies addressed this issue by including only pathologically confirmed lung cancers or by considering histological cell type in their analyses (e.g., CORR, GARF, PERS, and others).

Bias due to a proxy respondent in place of the subject has also been raised as an issue by Mantel (1987b) and by Kilpatrick (1987), with evidence from two studies. As reported in Eriksen et al. (1988), respondent bias can be a source of bias in either direction (Sackett, 1979). In general the information provided by surrogates has been comparable to that provided by the individuals themselves (Blot et al., 1985). The recent study by Cummings et al. (1989a) of the passive smoking histories of 380 NS further supports that conclusion. They report substantial agreement between subjects and surrogates on most exposure measures.

Vandenbroucke (1988) and Mantel (1987a) have questioned whether there may be a publication bias, i.e., whether studies with non-significant results are less likely to be published. Vandenbroucke constructed a quantitative approach but found publication bias only for the studies on men. Wells (1988a) reviewed the subject and found it unlikely that publication bias has any substantial effect on the RRs that have been calculated from published reports for passive smoking for either men or women.

3.6. COHORT STUDIES: BACKGROUND

The three cohort studies that have been conducted are: Garfinkel (1981); Gillis et al. (1984), which was recently updated by Hole et al., (1989); and Hirayama (1981a, 1984); abbreviated as GARF(Coh), GILL(Coh), and HIRA(Coh), respectively. (The "Coh" in parentheses means a cohort study.) The three studies are included in most of the references cited for summary descriptions and comparisons of case-control studies in Section 3.1. The U.S. SG's report (1986) sketches the basic features of the cohort studies and the salient topics of controversy and discussion that appeared in the literature. The Scottish study, GILL(Coh), which observed only a very small number of lung cancer deaths (6 men and 8 women), is included in the risk assessment in the next chapter but is not discussed further in this section.

Unlike the case-control studies, several of which have appeared since the NRC, IARC, and U.S. SG reports of 1986 and 1987, the two major cohort studies, GARF(Coh) and HIRA(Coh), first appeared in 1981. Consequently, most of the issues regarding these two studies and their somewhat dissimilar results surfaced well before the three major reports were prepared. Critical scrutiny of the Hirayama study had already appeared and had been adequately addressed by Hirayama, as described in the U.S. SG and NRC reports. Judging from the roundtable discussion at the symposium "Medical Perspectives on Passive Smoking" (Lehnert, 1984), previous challenges to Hirayama's work regarding data analysis and other issues appear to have been resolved, aside perhaps from the issue of misreported smoking habits. Even one of the strongest critics of epidemiologic findings (P.N. Lee) offered a qualified acceptance of the strength of the statistical evidence in the Hirayama study: "It is ... clear in Dr. Hirayama's data that if one takes the age of the husband or wife into account and does the analysis correctly, there is a statistically significant association in lung cancer risk, but the significance is not nearly as marked as in the incorrect analysis."

In contrast, the study by Garfinkel and colleagues at the American Cancer Society (ACS) has undergone much less questioning and critical examination, although the problems experienced in conducting the study and the potential for error in the results have not gone unnoticed. The difference in outcomes in HIRA(Coh) and GARF(Coh) has been a source of concern to many, but to our knowledge no one has conducted a statistical review of GARF(Coh) or compared the statistical methodology in the two studies. Those topics are addressed in the following section.

3.7. SOME COMPARATIVE ASPECTS OF THE TWO MAJOR COHORT STUDIES: HIRA(Coh) AND GARF(Coh)

3.7.1. Overview

An increase in risk of lung cancer from ETS was observed in both cohort studies, with statistical significance ($p < 0.05$) achieved in HIRA(Coh) but not in GARF(Coh). In the former study, the observed risk increases as spousal smoking increases (a "dose-response" relationship that would be expected if passive smoking is causally related to lung cancer). Data from the American study, however, estimate a higher risk at the lower of two exposure categories (spouse smokes < 20 cig./day) than at the higher one (spouse smokes 20+ cig./day). Some researchers have interpreted this outcome as evidence that there is not a "dose-response" relationship in the American study, or more strongly, that the results demonstrate that there is no increased risk of lung cancer from ETS exposure. The statistical evidence supporting an association between lung cancer incidence and ETS exposure in GARF(coh) is inconclusive--it is consistent with either the presence or absence of a true dose-response relationship. This conclusion follows from the 95% confidence intervals for the lung cancer mortality ratio at the low (< 20 cig./day) and high (20+ cig./day) exposures, equal to (0.85, 1.89) and (0.77, 1.61), respectively. These confidence intervals are consistent with a wide range of possibilities. For example, 1.0

(corresponding to no increase in lung cancer mortality) is in both confidence intervals, but so are values corresponding to a substantial dose-response relationship, e.g., 1.25 and 1.50 at the low and high exposures, respectively.

In the following section, the Japanese study (HIRA(Coh)) and the American study (GARF(Coh)) are reviewed, with an emphasis on the cultural differences in the populations sampled and the differences in study design, execution, and analysis of data that may help to compare outcomes of the two studies. In the final section, data comparisons are made for the two studies to evaluate if there are widespread differences across all age-exposure group combinations, or just specific ones.

3.7.2. Comparative Review and Discussion of the Cohort Studies

HIRA(Coh) is a census-population based study of adults aged 40 or above, begun in 1965 in 29 Health Center Districts in Japan. A total of 200 cases of lung cancer occurred among the 91,540 nonsmoking married women who were followed. A total of 265,118 subjects were enrolled for the entire study (122,261 males and 142,857 females, including unmarried women) accounting for 94.8% of the total census in the study area. Subjects were tracked by establishing a record linkage system between the data/interview records and death certificates (Hirayama, 1983b, 1984). Interviewers were blind to the smoking status of subjects (NRC, 1986).

In the Japanese study, relative risks of 1.42, 1.58, and 1.91 were observed for nonsmoking wives with husbands who smoked 1 to 14, 15 to 19, and 20+ cigarettes per day, respectively. The corresponding value for women whose husbands were former smokers is 1.36, which falls between the values for nonsmoking and light smoking husbands (Hirayama, 1984). The observed increase in risk across the exposure categories, with former smokers classified between nonsmokers and the 1 to 14 cig./day group, is statistically significant by the Mantel-Haenszel test (one-tailed $p < 0.002$). Also, RR for women married to smokers increased with age and

with duration of exposure to spousal smoking (age and duration of exposure are likely correlated, so these should not be construed to be independent results).

GARF(Coh), the ACS's Cancer Prevention Study (CPS-I), began in 1959 when 68,000 volunteers in 25 states enrolled more than one million men and women for long-term follow-up. Volunteers were instructed to recruit people they knew well. Subject participation was fairly evenly divided across large cities, small cities and suburbs, small towns, and rural areas. Overall, about 3% of the population over the age of 45 in 1121 counties was recruited. Enrollment included all family members of age 30 or above, provided at least one member of the household was at least 45.

Each year, for six years, the volunteers were asked to report the vital status (alive or dead) of the persons contacted. For subjects who had died, death certificates were obtained from state departments of health to determine the cause of death. Additionally, physicians who certified the cancer deaths were contacted and asked to supply information to verify the primary sites of the cancers. In the first six years, information was received confirming the primary sites of cancer in 78% of the cases, and microscopic confirmation was obtained in 69% of the cases. Death certificates overstated the lung cancer rates by 11.8% (Garfinkel, 1981, 1984, 1985). The study was essentially terminated after six years, as originally planned in 1965, until it was decided to conduct a second follow-up beginning in 1971. Follow-up was achieved for 98.4% of the subjects. The follow-up was terminated, however, because tracing became increasingly difficult due to death or movement of the volunteers and their substitutes (Garfinkel, 1985). Apparently death certificates did not continue to be followed up by a medical report after the first six years. For lung cancer cases in all women, married or not, 203 out of a total of 564 (36%) reported by death certificates were accompanied by a medical report.

The American study does not provide conclusive results regarding a possible association of lung cancer with ETS exposure. The ratio of observed to expected lung cancer deaths, referred

to as the mortality ratio (Garfinkel, 1981), is 1.27 and 1.10 for nonsmoking women with husbands who smoked < 20 cig./day and 20+ cig./day, respectively. Neither value is statistically significant. When data from the Hirayama study are grouped according to the same exposure levels (< 20 cig./day and 20+ cig./day), the observed relative risks are 1.45 and 1.91, with one-tailed p-values of 0.03 and 0.001, respectively (Hirayama, 1984).

The American cohort study appears to contain more statistical uncertainty than the Japanese study. Some of the general factors contributing to uncertainty in study data are related to sample size, variability in the population sampled, sample design and protocol, treatment of missing or incomplete data, accuracy and reliability of collecting and reporting data, and methods of statistical analysis. When the data produce a clear pattern, such as HIRA(Coh), with a consistent upward trend across exposure categories and age groups that cannot be ascribed to chance alone, one has some assurance that the sources of variability are not obscuring a dose-response relationship. Apparent differences between outcomes of the two studies could be due to one or more sources: (1) a real difference in risk in the populations studied (perhaps due to higher exposure or uptake of ETS); (2) differences in the way the studies were designed, conducted, or interpreted; or (3) chance occurrence alone. There is suggestive evidence for the first two alternatives. Subjects in the American study were followed for 12 years compared to 16 years in the Japanese study (Hirayama, 1984), so the proportion of subjects with lung cancer would be expected to be lower in the American study. As reviewed in the U.S. SG's report (1986), the relatively high risks observed for nonsmokers whose husbands smoked led to speculation that Japanese women may report themselves as nonsmokers when they actually smoke (also see Lehnert, 1984). However, some reassurance of the validity of self-reported information from Japanese women is provided by the AKIB study, which found strong concordance between self-reported smoking status and the reports from the next-of-kin.

Hirayama has emphasized the importance of properly defining passive smoking. He classifies direct passive smoking as exposure from within approximately 1 to 1.5 meters of the source and indirect passive smoking as exposure from a greater distance (Hirayama, 1984; Lehnert, 1984). Direct passive smoking is of much greater concern than indirect passive smoking (Lehnert, 1984). Japanese wives may experience more direct passive smoking if they tend to be in closer proximity to their smoking husbands than American wives. Related factors that may contribute to a net increase in exposure for Japanese wives relative to their American counterparts include house sizes, the number of smokers per volume of air, proximity of nonsmoking spouse's sleeping area to spouse's smoking area, and the amount of time a nonsmoking spouse is in the home. Hirayama (1981b) notes additional differences between Japan and America that may influence exposure, such as a higher percentage of office workers among females in the United States than in Japan and a higher divorce rate in the United States. Japanese wives may be much less exposed to ETS from sources other than spousal smoking in the home than U.S. wives, i.e., background exposure to ETS may be lower for Japanese wives. (Technical Note: An increase in exposure to household ETS and a decrease in exposure from other sources for Japanese women relative to U.S. women would both contribute toward a higher RR for the Japanese if passive smoking is causally related to lung cancer.) Two additional factors that may affect a comparison between the United States and Japan include total cigarette consumption and lung cancer rates due to causes not related to tobacco smoke.

These differences between the U.S. and Japan weigh heavily in favor of Japan as the more fertile sociological environment for observing an excess risk of lung cancer from passive smoking by means of an epidemiologic study based on spousal smoking. Exposure to household ETS appears to be higher in general, with more direct passive smoking, and exposure from other sources (background exposure) appears to be lower. These factors contribute to a larger relative exposure to ETS between the so-called exposed and unexposed groups. If passive smoking is a

risk factor for lung cancer, then the observed relative risk should be higher when the relative exposure to ETS between the comparison groups is higher (mitigating factors not withstanding). There are also some differences in the methods of analyzing and interpreting data in the two cohort studies, as described in the next section.

3.7.3. Comparative Data Analysis of the Cohort Studies

The measures of risk reported in HIRA(Coh) and GARF(Coh), the odds ratio and the mortality ratio, respectively, are not identical statistics. Neither are the statistical methods to control for age the same. The method applied by Hirayama (Hirayama, 1984) is the Mantel-Haenszel procedure, commonly used to standardize for age and other factors that may have an influence. To control for age by this method, for example, study observations are grouped by time intervals. Comparisons between exposure groups are made at each time interval, and then the results are combined across intervals to test for a difference between exposure groups (the extended M-H procedure). The method of analysis used by Garfinkel (1981) is somewhat different (described more fully in Hammond et al., 1975, 1976). Adjustment for age is handled by assigning weights according to person-years with a smoking husband. The results are analyzed as quantal response data.

The method previously applied to non-ETS data in the American study is used to statistically adjust for potential confounding variables (Hammond et al., 1975, 1976). Groups are formed from the data matched on age, race, highest educational status of the husband or wife, residence, and whether or not the husband is occupationally exposed to dust, fumes, or vapor (Garfinkel, 1981). The ratios of the number of adjusted lung cancer deaths in the low (< 20 cig./day) and high (20+ cig./day) exposure categories to the corresponding number in the control group, i.e., the nonsmoking women with nonsmoking husbands, are reported to be 1.37 and 1.04, respectively, neither of which is statistically significant. Using data from the American

study that includes age at time of death, duration on study, and whether death was due to lung cancer or another cause (supplied by L. Garfinkel), the Mantel-Haenszel method was applied controlling for age and duration on study. Controlling for these two factors simultaneously, however, did not produce statistical significance or otherwise alter previous conclusions.

For further comparison, the descriptive data from GARF(Coh) corresponding to the age groups and exposure classifications of data published for HIRA(Coh) (Hirayama, 1984, Table 1) were placed side-by-side for visual comparison (Table 3-8). Relative to the general pattern of response in the Japanese study, the American data appear to be at greatest variance from what might be expected in the two subgroups at highest exposure (20+ cig./day) in the age classifications 40 to 49 and 50 to 59. Further review of those data for completeness, possible sources of bias, or unanticipated anomalies may be illuminating.

3.8. SUMMARY AND CONCLUSIONS

The primary focus of this chapter has been on hazard identification, in this case a statistical assessment of the combined evidence from 21 case-control studies and three cohort studies of an association between ETS exposure of never-smoking women and lung cancer. The case-control studies vary with regard to inclusion of raw study data, an adjusted statistical analysis (adjusting, or controlling, for covariables in the statistical analysis), and dose-response information to test for upward trend (lung cancer occurrence reported by the amount spouse smokes). The statistical assessment was conducted from these three perspectives. Overall, analysis of unadjusted odds ratios (19 studies) indicated a significant lung cancer relationship ($p \leq 0.001$ for both statistical tests used. The two statistical tests based on authors' adjusted statistical procedures in 11 studies were also significant ($p \leq 0.001$ and $p = 0.014$). To check for an upward trend in response, observed relative risk was plotted against exposure (e.g., number of cig./day smoked by the husband) for the 13 case-control studies reporting these data.

TABLE 3-8. TWO COHORT STUDIES: FEMALE LUNG CANCER DATA FOR SIMILAR AGE AND EXPOSURE GROUPS[1]

Age[3]	Study[4]	Husband's smoking habit[2] Nonsmoker	1-19	20+
40-49	G	9/23,743 (3.8)	6/11,791 (5.1)	12/26,918 (4.5)
	H	4/6,229 (6.4)	14/13,779 (10.2)	16/10,764 (14.9)
50-59	G	31/25,108 (12.3)	25/13,528 (18.4)	21/24,184 (8.7)
	H	10/7,791 (12.8)	28/13,720 (20.4)	24/9,820 (24.4)
60-69	G	23/15,138 (15.2)	16/6,884 (23.2)	20/7,299 (27.4)
	H	18/7,120 (25.3)	37/9,756 (37.9)	23/4,651 (49.4)

[1] Entries are (number of lung cancer deaths)/(number at risk), stated as a percentage (× 100) in parentheses. Data for age 70-79 are omitted because of small sample sizes and small number of lung cancers observed. Data for "G" were supplied by L. Garfinkel. Data for "H" are in Hirayama (1984).

[2] Cigarettes/day.

[3] Women's age for G; Husband's age for H.

[4] G:GARF(Coh) H: HIRA(Coh).

Although outcomes vary, an upward trend was observed in more instances than could be attributed to chance alone. Tabled study characteristics did not suggest common features among the studies that might explain their findings. The statistical results solidly support the conclusion that the observed association between lung cancer and ETS exposure in case-control studies is not attributable to chance occurrence.

The cohort studies were addressed separately from the case-control studies for several reasons. The size of the two major studies, the U.S. study by the American Cancer Society and the Japanese study by Hirayama, might dominate the outcome of some comparisons with case-control studies. Also, the cohort studies differ from the case-control studies in design, execution, and numerous other characteristics. The Japanese cohort study alone provides compelling evidence of a lung cancer risk associated with ETS exposure. Although some corrections to the initial calculations were required, it has withstood extensive critical examination since its appearance in 1981 (see NRC, 1986). Results of the American cohort study are less conclusive. Differences in culture and life-style between the U.S. and Japan suggest that ETS exposure from spousal smoking may be higher, and exposure from background sources lower in the U.S. than in Japan. In view of other study evidence of an upward trend in response, the more pronounced outcome observed in the Japanese study might be anticipated.

Although the American cohort study weakly indicates an increased lung cancer risk from ETS exposure, the data have an observed inversion in dose-response, i.e., lower response at high exposure to spousal smoking than at moderate exposure. Further study of the data to see if the inversion can be explained may be warranted, especially since this study is the largest in the U.S. and is the only U.S. cohort study. A statistical analysis of the data adjusted for survival was not helpful. Consequently, the well-patterned response of lung cancer occurrence by subjects' age and husband's smoking status in the Japanese experience were used as a model to illuminate departures in the American survey. Data in the American study deviate most from what might

be expected in the two subgroups at highest exposure (over 20 cig./day) in age groups 40 to 49 and 50 to 59. Further examination of this subset of the data may be warranted.

Based on the statistical results of this chapter, this report concludes that passive smoking is associated with an increased risk of lung cancer. The stronger conclusion of a causal association, however, is not warranted from these statistical tests alone. Other factors must be considered as well, including the likelihood that the observed association is attributable to systematic bias or the presence of a confounding variable. Further analysis relevant to whether the stronger conclusion of causal association is relevant is given in the next chapter.

4. ASSESSMENT OF LUNG CANCER RISK FROM ETS

4.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that ETS exposure is associated with lung cancer. Statistical tests alone, however, do not generally warrant the conclusion that two variables are causally related, i.e., that one of the variables is a contributing cause of the other. The total weight of evidence needs to be considered. In particular, the likelihood that the observed association is attributable to a confounding variable or a systematic source of bias needs to be considered. If it is concluded that ETS is causally associated with lung cancer, then the next step is to characterize the magnitude of the population risk.

Review and analyses of the epidemiologic studies described in Chapter 3 and supplemented by Appendix A have not indicated a correlate of ETS that may explain the observed association between ETS and lung cancer. Among the potential sources of bias discussed, however, misclassification of smoker status needs to be examined as a possible explanation of the observed effect. Its significance is determined from the remainder of the estimate of overall relative risk after subtraction of an amount attributable to smoker misclassification. A model is implemented to estimate the overstatement of relative risk due to smoker misclassification, the technical details of which are included in Appendix B. The overall relative risk of lung cancer remains significant after adjustment for smoker misclassification. Based on this outcome and other evidence, it is concluded that ETS is causally associated with lung cancer. After numerically adjusting for background ETS (sources other than spousal smoking), the lung cancer risk of ETS from all sources to the U.S. population of nonsmokers

(never-smokers and former smokers of both sexes) is characterized in terms of the number of lung cancer deaths (LCDs) attributable to ETS (estimated at 3800).

Several other authors have estimated the population risk of lung cancer from exposure to ETS also. Two approaches have been used almost exclusively. One analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report. The second approach estimates a dose-response relationship for ETS exposure based on "cigarette-equivalents" determined from a surrogate measure of exposure common to passive and active smoking. Cotinine concentrations in body fluids (urine, blood, or saliva) and tobacco smoke particulates in SS and MS have commonly been used for this purpose. The lung cancer risk of ETS is assumed to be equal to the risk of actively smoking at the rate determined by the cigarette-equivalents.

The NRC report is a good example of the first approach. An overall estimate of relative risk (RR) for never-smokers exposed to spousal smoking is obtained by statistical analysis across all available studies (as in Chapter 3 of this report). Two adjustments are made then to the estimate of RR. The first adjustment accounts for expected bias from former smokers (FS) and current smokers (CS) who may be misclassified as never-smokers (NS) and it results in a decrease in the RR estimate. The second adjustment, an upward correction, takes into account the risk from background exposure to ETS (experienced by a NS whether married to a smoker or not). Population risk can be characterized then by estimating the annual number of LCDs among NS attributable to all sources of ETS exposure (spousal smoking and background). This calculation requires the final-adjusted estimate of relative risk, the annual number of LCDs from all causes in the population assessed (e.g., NS of age 35 or above), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to a background level of ETS.

The cigarette-equivalents approach calculates an estimate of the lifetime excess risk of lung cancer from exposure to ETS, extrapolated from a dose-response curve constructed for dose-response of active smoking. Multiplying this estimate by the size of the population exposed to ETS characterizes the population risk in terms of the excess number of lifetime lung cancers. It is important to note that the population excess risk in the first approach is stated in terms of an annual number of lung cancer cases; in the second approach, population risk is stated in terms of the lifetime excess number of lung cancers. There are variations on the two basic approaches described, but the published literature largely falls into the two camps described—inference from the epidemiologic studies or extrapolation from a dose-response assessment for active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

Examples from the published literature illustrating both approaches and their results are reviewed in Sections 4.2 and 4.3. Section 4.4 describes the risk assessment of lung cancer from ETS exposure for this report, based on epidemiologic data (the first approach described above). The overall relative risk to female NS married to a smoker is estimated from the epidemiologic studies with 95% confidence bounds and then an adjustment for smoker misclassification bias is calculated from an extension of the NRC/Wald formula. Background ETS is taken into account in a second adjustment to RR (implicitly redefining RR at that point to be "relative" to the risk at zero-ETS instead of at an average background level of ETS). The population attributable risk then is estimated to obtain an annual number of U.S. LCDs in never-smoking women attributable to total ETS exposure. The predicted number of LCDs due to ETS is further extended to include male NS and then to include former smokers of both sexes.

4.2. PREVIOUS ESTIMATES OF RELATIVE RISK FROM EPIDEMIOLOGIC DATA

4.2.1. The NRC Report and Wald et al. (1986)

The NRC report follows the construct of Wald and coworkers to adjust for potential misclassification bias. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from spousal smoking is shown in Figure 2 of Wald et al. A similar example is in Table 12-5 of the NRC report. The formula for an extended version of these examples is given in Appendix B (Equation B1), with the required parameters described in Tables B-1 through B-3. The summary relative risks from observed data reported by the NRC are 1.32 (95% C.I. 1.16, 1.51) for females and 1.62 (0.99, 2.64) for males. Both RR estimates apply to NS married to smokers, i.e., the estimates apply to lung cancer risk in exposed NS (actually exposed to spousal smoke and background sources) relative to the risk in unexposed NS (actually exposed to background sources only). The terminology adopted from epidemiologic studies comparing an exposed group with an unexposed group can be misleading when sources of ETS other than spousal smoking are taken into account (i.e., background ETS). Both groups experience background exposure to ETS, so one group is at a higher exposure level (from spousal smoking and background) and the other one is at a lower exposure level (backgound alone).

After adjusting for expected negative (downward) bias in the RR estimates due to smoker misclassification, the NRC concludes that the relative risk for both females and males is likely to be 1.25, and probably lies between 1.15 and 1.35. The "relative" in RR, however, still means relative to the risk from background exposure alone. To estimate the number of LCDs in NS attributable to ETS, risk estimates need to be relative to the risk of lung cancer at zero-ETS exposure instead of at background exposure. This is accomplished in the NRC report by using data on cotinine concentrations to compare exposure to ETS at the higher level (background

plus spousal smoking) with exposure to the lower level (background only). This report uses the same method; it will be discussed in more detail. The resultant estimates of RR apply to exposed persons and to unexposed persons, but are now relative to risk at zero-ETS instead of risk at the background level. This adjustment for background sources changes the NRC estimate of RR for an exposed person to 1.42 ("ranging" from 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS, however, instead of relative to a background level of ETS. Similarly, the RR estimate from background ETS becomes a positive value, since RR now means relative to zero-ETS. The estimates given by the NRC are for both sexes, with the qualification that the adjustment for background and the estimation of LCDs attributable to passive smoking (to be described next) are "crude".

The NRC report estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C). When applied to the ACS's estimate of 6500 (3000) LCDs among NS women (men) in 1988, the number attributable to ETS exposure is 1365 (600), a total of about 2000. To obtain these figures for annual LCDs attributable to ETS in NS requires the RR figure for exposed and unexposed persons obtained from data on married NS. Not all NS are married, of course, and the NRC estimates that 17% of all NS women (married or not) and 12% of NS men (married or not) are exposed to ETS at the higher exposure level (equivalent to background plus spousal smoking); the remaining percentages are assumed to be exposed at the lower exposure level (background ETS only). These exposure percentages are based on a sample of cotinine concentrations. In effect, the NRC is estimating the RR for the population of NS by taking a weighted average of the RR at the higher exposure level and the RR at the lower exposure level, weighted by the proportions of the population at the higher and lower exposures. The population is not bipolarly distributed at two exposure levels, but a judicious assignment of values to the proportions assumed will produce a weighted average that approximates RR for

exposure near the population average. An implicit assumption is that RR is linearly related to ETS exposure between the lower and higher exposure levels.

The remainder of this section discusses details of the NRC and Wald et al. (1986) analyses to adjust the overall RR for bias from smoker misclassification (the first step in the procedure above). In particular, NRC parameter values used for the adjustment are compared with those to be used in Section 4.4 of this report. Both the NRC and Wald et al. assume that 50% of women are NS. Wald et al. assumes that the remaining 50% consists of 35% CS and 15% FS, based on a survey conducted in Britain. Estimates for the U.S. for 1985 from the National Health Interview Survey (NHIS), as reported in the U.S. SG (1989) report, place the percentage of U.S. females who are CS and FS at 27.8% and 16.9%, respectively, for a total of 44.7% ever-smokers (ES) in the U.S. Corresponding values for 1982 from the initial phase of the ACS's Cancer Prevention Study II (CPS-II) are 22.1% and 22.6%, respectively, for the same total percentage (44.7%). Consequently, the 50% value for ES is probably a little high for the U.S., and the composition of female ES in the U.S. between 1982 and 1985 is probably closer to 22% to 28% CS and 17% to 23% FS. In Section 4.4, this report assumes 45% female ES, consisting of 25% CS and 20% FS.

The NRC report estimates that the lung cancer risk of smokers relative to nonsmokers may be as high as 8.0; based on an ACS study in 1966, and the British Physician's Study in 1980, and then allowing for a reasonable increase by the mid-1980s. The initial phase of CPS-II indicates that the relative risk for female CS aged 35 and older has soared from 2.9 between 1959 and 1965 (CPS-I) to 11.9 (95% C.I. 10.0, 14.3) between 1982 and 1986 (CPS-II) (S.G., 1989, p.153). The large change is related to an increase in the number of women who began smoking two to three decades ago, a sufficient period for lung cancers to appear in the mid-1980s. The relative risk reported for female FS in the general population from CPS-II is 4.7 (95% C.I. 3.9, 5.7) U.S. SG, 1989). ES (CS and FS) misreported as NS are assumed to have a

lower risk than correctly reported ES. The NRC report suggests an overall relative risk of two for misclassified ES (but notes that it could be as high as four). Wald et al. adjusts the smoker's relative risk for misreported CS and FS (from eight to two), assuming the misclassification percentage of ES is an aggregate of 2.1% attributable to CS and 4.9% due to FS.

In this report, calculations for the adjustment to relative risk for misclassification are made directly from the specific values assumed for CS, FS, and NS, without combining CS and FS into a common category (ES). This approach is somewhat more general and should provide additional flexibility and accuracy. The extended formula is given in Appendix B. The calculations in Wald et al. and the NRC report are a special case. Wells has undertaken to model the impact of misclassification in further detail by using parameter estimates that are characteristic of the time and place of each study for which a bias is estimated, e.g., in estimates of relative risk for CS and FS. His initial results indicate that the overall relative risk estimate increases with this modification (personal communication from A.J. Wells).

The NRC report and Wald et al. make a correction to the overall relative risk estimate, using identical procedures, to account for background exposure to ETS. Urinary cotinine is used as a surrogate for recent exposure to tobacco smoke in NS. In the study by Wald and Ritchie (1984), the urinary cotinine levels among NS exposed to smoking spouses were three times those of NS married to NS. To make the lung cancer risk to exposure to ETS relative to a zero-exposure group, it is assumed that the excess lung cancer risk from ETS exposure is proportional to urinary cotinine concentration. Note that this assumption does not imply that cotinine (or its precursor nicotine) determines the carcinogenic potential of ETS. The formula to calculate the adjustment is in Equation B2 in Appendix B.

The NRC report calculates the population-attributable risk, assuming that 17% of nonsmoking women and 12% of nonsmoking men are exposed to ETS and that the remaining percentages are exposed to a background level of ETS (NRC, 1986, Appendix C). The exposure

percentages for men (12%) and women (17%) are from a sample of cotinine measurements in men reported in Wald and Ritchie (1984). The 17% is a very low figure for female NS when compared to the percentages exposed in the case-control studies (see Figure 3-1). The 121 married males tested by Wald and Ritchie are not representative of the U.S. population. Wald et al. (1986) assume an exposure percentage of 59% in their example calculation for female NS and the NRC report (p.236) uses an odds ratio of 1.3/3.3 (= 39%) for the exposure of female nonsmokers (NS in this case) in its example. In the analysis of this report in Section 4.4, 60% is assumed, with a plausible range from 45% to 75%. These values are reasonable for the case-control percentages in Figure 3-1.

4.2.2. Other Risk Assessments Based on Epidemiologic Data

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and U.S. SG reports. Like the NRC report, the epidemiologic data for both women and men are considered, for which separate estimates of overall risk and attributable risk are provided. The three cohort studies addressed in the NRC report are also included (no additional ones have appeared). Fourteen case-control studies are analyzed, three of which have appeared in the literature subsequent to the NRC report (Brownson et al., 1987; Humble et al., 1987; Lam et al., 1981; denoted in Table 3-1 as BROW, HUMB, and LAMT, respectively). Other differences compared to the NRC report are: WU (Wu et al., 1985) and the study by Sandler et al. (1985) are included; part of the data of BUFF and KABA are excluded; and CHAN is excluded. The reader is referred to Wells (1988) for discussion of criteria for study inclusion.

Wells calculates an overall relative risk of 1.44 (95% C.I. 1.26, 1.66) for females and 2.1 (1.3, 3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ES is assumed to be 5% (compared to 7% for Wald et al.). Rates were adjusted

for background exposure to ETS except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins [NRC, Appendix D]). The relative risk is calculated under two assumptions regarding risk--constant with age and declining with age, but there is little difference in the two outcomes. A figure of 76% is used for the fraction of female nonsmokers (never-smokers) exposed to ETS, assuming that 60% are exposed to spousal smoking and another 16% are exposed at a comparable level otherwise. The total percentage for males is 61%. The calculation of population-attributable risk applies to FS as well as NS, which is a departure from Wald et al. and the NRC report. The annual number of excess LCDs in the U.S. is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be a best current estimate.

Robins (NRC, 1986 Appendix D) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant assumptions clearly stated. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: 1) adjustment of relative risk for background exposure to ETS independent of age, and 2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. The validity of both assumptions are questioned by the author in later remarks. The age-adjusted population-attributable risk is estimated for females and males separately. (The reader is referred to Robins et al., 1989).

The age-specific fraction of LCDs due to ETS exposure is also required. Data from the controls of one of the case-control studies in the U.S. (Garfinkel et al., 1985) are used for that purpose. The age-specific LCD rates for women are also used in calculating population-attributable risk for males in lieu of no data specific to males. Robins assumes that a relative risk of 1.3 is associated with ETS exposure (1.14, the summary for U.S. studies alone, is also considered). He omits any adjustment for misclassification, but does adjust for background

exposure. In view of the NRC report's emphasis on the potential for misclassification, this omission is surprising. The author estimates lifetime risk of LCD attributable to ETS, but epidemiologic data alone are not sufficient. Further assumptions implying some similar characteristics in lung cancer risk from active and passive smoking are introduced for that purpose.

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time as Wald et al. (1986), the NRC, and the U.S. SG reports appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report (see Table 4-1), except for omission of one cohort study (Gillis et al., 1984), and inclusion of WU, the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. 1.1, 1.5). When the results are combined for high exposure categories, the overall relative risk estimate is 1.7 (1.4, 2.1).

Wigle et al. (1987) apply the epidemiologic evidence to obtain estimates of the number of LCDs in NS due to ETS in the population of Canada. A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually. The percentage of LCDs in NS used in the calculation is 1.6% for males and 12.4% for females, values obtained by pooling results from U.S. and Canadian reports. The fraction of NS with a smoking spouse is estimated from the control groups in two U.S. studies (Dalager et al. [1986] and the case-control study of the ACS reported in Garfinkel et al. [1985]). A pooled prevalence rate of 40% from these two studies is assumed. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and age-specific rates of death from lung cancer attributable to ETS (Repace and Lowrey, 1985).

TABLE 4-1. EPIDEMIOLOGIC STUDIES INCLUDED IN OVERALL RELATIVE RISK IN THIS REPORT (FEMALES ONLY) AND SEVERAL OTHER SOURCES

Study	Sex	Observed relative risk[1]	Sources[2] 1	2	3	4	5
AKIB	F	1.52(0.88,2.64)	F	F	F	F	F
	M	1.80(0.50,5.60)		M	M	M	
BROW	F	1.52(0.39,5.99)			F		F
	M	1.38(- , -)			M		
BUFF	F	0.81(0.34,1.90)		F	F	F	F
	M	0.50(0.20,1.70)		M	M	M	
CHAN	F	0.75(0.43,1.30)	F	F		F	F
CORR	F	2.07(0.82,5.20)	F	F	F	F	F
	M	2.00(- , -)		M	M	M	
GAO	F	1.19(0.82,1.73)					F
GARF	F	1.31(0.87,1.98)	F	F	F	F	F
GENG	F	2.16(1.09,4.28)					F
HUMB	F	2.34(0.83,6.61)			F	F	F
INOU	F	2.55(0.74,8.78)					F
KABA	F	0.79(0.25,2.48)	F	F	F	F	F
	M	1.00(0.20,4.90)		M	M	M	
KOO	F	1.55(0.90,2.67)	F	F	F	F	F
LAMT	F	1.65(1.16,2.35)			F		F

(continued on following page)

TABLE 4-1. (continued)

Study	Sex	Observed relative risk[1]	Sources[2] 1	2	3	4	5
LAMW	F	2.01(1.09,3.71)					F
LEE	F	1.03(0.41,2.56)	F	F	F	F	F
	M	1.30(0.38,4.42)		M	M	M	
PERS	F	1.28(0.76,2.15)	F	F	F	F	F
SVEN	F	1.26(0.57,2.81)					F
TRIC	F	2.13(1.19,3.81)	F	F	F	F	F
WU	F	1.41(0.54,3.67)	F		F		F
GARF (Coh)	F	1.18(0.90,1.54)		F	F	F	F
GILL (Coh)	F	1.00(0.20,4.91)		F	F	F	F
	M	3.25(0.60,17.65)		M	M	M	
HIRA (Coh)	F	1.63(1.25,2.11)		F	F	F	F
	M	2.25(1.04,4.85)		M	M	M	

[1] Figures for case-control studies are as recorded in Table 2-5, with the values calculated in this report from raw data used for females. Figures for cohort studies are taken from NRC (1986). Parentheses contain 95% confidence intervals.

[2] Sources are:

1. Blot and Fraumeni (1986).
2. NRC (1986) and Wald et al. (1986).
3. Wells (1988): includes study by Sandler et al. (1985) on women, and the data for males in HUMB (Humble et al., (1987), both of which contain very few cases of lung cancer.
4. Saracci and Riboli (1989).
5. This report.

Unlike the previous examples discussed, Wigle et al. use the relative risk estimates obtained from a study comparing Seventh-Day-Adventists (SDAs) (Phillips et al., 1980a, 1980b) with a matched group of non-SDAs who are also NS, as reported in Repace and Lowrey (1985). The SDA/non-SDA comparison is used as a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the case-control and cohort studies. It provides an independent source of data and an alternative approach for comparison, to be described further in the review to follow.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. The one based on epidemiologic data estimates the relative risk of LCD from all sources of exposure to ETS, i.e., in the home, at work and elsewhere, in what they describe as a "phenomenologic" approach. A comparison of LCDs in the study by Phillips et al. (1980a, 1980b) referred to above, wherein SDA NS and a demographically/educationally matched cohort of non-SDA NS provides the basic data. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The comparison of two groups of NS is based on the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA groups due to differences in life-style. Relatively few SDAs smoke, so an SDA NS is probably less likely to be exposed at home by a smoking spouse, or in the workplace, or elsewhere if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. reported that the non-SDA cohort experienced an average lung cancer mortality rate equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in lung cancer mortality rates for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million NS in the U.S. in 1979, to obtain a number of LCDs attributable to ETS annually. The result, 4665, corresponds to a risk-

rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1000 people exposed.

A recent article by Vainio and Partanen (1989) assumes that the observed relative risk of 1.3 from Wald et al. (1986) represents a causal effect. No adjustment is made for possible misclassification of subjects. The same correction method for background exposure used by the NRC and Wald et al. is applied to the observed relative risk to yield 1.53. Two calculations are made for population-attributable risk applying an excess risk of 0.53 to the exposed fraction of the population of NS and a value of 0.18 for excess risk from background exposure to the remaining fraction. The two calculations are identical aside from the different values of the fraction exposed: 12% (men) and 17% (women) in one case; 28% (men) and 56% (women) in the other. The first pair of values is identical to the fractions used in the NRC report, as discussed previously in this section. The second set is from one of the case-control studies (Humble et al., 1987). The value for population-attributable risk calculated from the exposure percentages 12%, 17%, 28%, and 56%, are 18%, 19%, 22%, and 27%, respectively, which illustrates only moderate sensitivity of the calculations to the different values assumed for the fraction exposed. Vainio and Partanen use the same excess relative risk for both men and women in their calculations. The authors conclude that the proportion of lung cancer cases among nonsmokers that could reasonably be attributed to ETS is 20% to 30%. This range is consistent with population exposure percentages of 20% to 75%. A plausible range for exposure percentages is about 45% to 75% (Section 4.4.2). The approximate range for PAR concluded by Vainio and Partanen is close to what the calculations in this report would be without a downward adjustment of the RR estimate for smoker misclassification bias.

Saracci and Riboli (1989), of the International Agency for Research on Cancer, review the evidence from the three cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. in the studies to exclude, and add only

one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (1.20, 1.53), is about the same as reported by the NRC, 1.34 (1.18, 1.53). It is not reported how the overall relative risk was calculated.

4.3. APPROACHES TO RISK ASSESSMENT BASED ON CIGARETTE-EQUIVALENTS

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after conversion of exposure to ETS into an "equivalent" exposure from active smoking. For example, suppose the average cotinine concentration in exposed NS is 1% of the average value found in people who smoke 30 cig./day. The lung cancer risk for a smoker of (.01)30 = 0.3 cig./day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both.

A difficultly in assessing this approach lies in evaluating the assumption that apparent differences between passive and active smoking are negligible or have cross-effects that cancel. For example, MS and SS differ in the relative composition of carcinogens identified in tobacco smoke and in their physicochemical properties in general. The lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages. Passive and active smoking also differ in characteristics of intake--intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation. To help illuminate relationships and identify

parameters where additional information would be helpful on this topic, a mathematical model for comparison of dosimetry of passive and active smoking was constructed as a basis for further study (Appendix C).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, concludes "The differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989, p.3) states that "Lacking knowledge of which substances are responsible for the well established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The U.S. SG report devotes a three page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. SG, 1986). It concludes with "These limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well understood. Recent literature raises some questions on this issue (Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a, 1987b; Whittemore, 1988).

The cigarette-equivalents approach has some important limitations, due in large part to limited knowledge regarding similarities and differences between passive and active smoking and how to adjust for them in a risk assessment. Legitimate reservations not withstanding, virtually all analytic approaches bear some assumptions and weaknesses, and most contribute something to our understanding. Further development of the cigarette-equivalents approach and the knowledge base surrounding it may be worthwhile. Three new methods akin to cigarette-equivalents approach are described in Appendix D, with comments and advice solicited. Several

published examples of the cigarette-equivalents approach follow. Although a risk assessment based on the epidemiologic data is preferred in this report, it is worthwhile to consider the spectrum of methods and approaches that have been tried.

Vutuc (1984) estimates that exposure of passive smokers to cigarette smoke is equivalent to 0.1 to 1.0 cig./day actively smoked. This relationship follows Repace and Lowrey (1980), except that Vutuc adjusts their figures to apply to a cigarette with tar content of 16 mg instead of 0.55 mg, as assumed by Repace and Lowrey. For the smoking situations indicated by Repace and Lowrey, who found passive smoking equivalent to actively smoking 5 to 27 cig./day, Vutuc obtains an equivalent of actively smoking 0.2 to 1.0 cig./day.

Citing cigarette-equivalents calculated in other sources, Vutuc assumes a range of 0.1 to 1.0 cig./day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Doll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cig./day give a range in relative risk from 1.03 to 1.36. The author concludes that "As it applies to passive smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." As observed by the author, however, the influence of ETS on lung cancer incidence becomes more marked in the higher age groups, where the carcinogenic effect of tobacco smoke is strongly influenced by the duration of exposure. From Vutuc's Table 1, the increase in incidence (per million) in lung cancer for a smoker of one cig./day is 270 at age 79, 130 at age 70, 40 at age 60, etc. These values of risk slightly exceed the acceptable levels typically used by the EPA and other regulatory agencies in setting standards for pollutants under their authority.

Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. The number of LCDs among NS in the U.S. in 1988 is about 6500 females and 3000 males (personal communication from the ACS). The number of

LCDs in NS attributable to ETS is estimated to range from 240 to 2020 (140 to 1380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among NS in the U.S. These figures are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Methods 2 and 3 of Robins (NRC, Appendix D) are constructs of the cigarette-equivalents approach. In both methods, a range of values is reported corresponding to a range of unknown parameter values. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. The author estimates the number of excess LCDs due to ETS, assuming 7000 and 5200 annual LCDs in female and male NS, respectively. Adjusting his results to 6500 females and 3000 males (for comparison purposes), the range of excess LCDs attributable to ETS is 1650 to 2990 for females and 420 to 1120 for males.

Robins' Method 3 ignores the epidemiologic data on passive smoking entirely and extrapolates from data on active smoking, along with several assumptions. Applying his results to 6500 females and 3000 males, the range of excess LCDs due to ETS is 550 to 2940 for females and 153 to 1090 for males.

Arundel et al. (1987) attribute only five LCDs among female NS to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6500 females and 3000 males). The expected lung cancer risk for NS is estimated by downward extrapolation of the lung cancer risk/mg of particulate ETS exposure for CS. Their premise is that lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase.

Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4000+ deaths/year due to passive smoking, is for all causes of death, not just LCDs.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as well as the procedure described previously. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-6} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that tobacco tar inhaled poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (NS and FS) is attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including FS).

The potential for bias due to misreported smoking habits was apparently first noted by Lee (see discussion in Lehnert, 1984), and has been emphasized by him in several articles, e.g. Lee (1986, 1987a, 1987b). In Lee (1987b), it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported NS in epidemiologic studies. A hypothetical example is first provided to the reader to illustrate that if 5% of reported nonsmokers are actually smokers, and the relative risk of lung cancer of smokers to nonsmokers is 20, then a relative risk as high as 1.75 could be observed for ETS exposure to spousal smoking. The example is a little misleading in view of the discussion that follows in the article on the results of three separate studies aimed at measuring the accuracy of reported current smoking (a cotinine study), the accuracy of reported lifetime smoking (a 1980/1985 follow-up study), and concordance of smoking habits in married couples (a 1985 consumer study). ("Marriage aggregation factor" in NRC [1986] and Wald et al. [1986] is a measure of concordance). All three studies were conducted on British or UK subjects ages 16 and above. Following review of these studies, the author assumes more refined parameter values.

The relative risk for smoking is assumed to be 10 instead of 20. The evidence suggests that about 1.4/2.5 (56%) of misclassified CS may be regarded as "regular smokers" and 1.1/2.5 (= 44%) as only "occasional smokers." The relative risk of the latter is assumed to be 2.5 instead of 10. Based on cotinine measurements, 20 of the 689 self-reported NS (2.9%) are treated as CS, 9 as occasional and 11 as regular smokers. (In the notation of Table B-1, this equates to RR(E/C) = 6.7). The relative risk of misclassified FS is assumed to be 2.0 (giving RR(E/F) = 2.0 in Table B-1). The percentage of reported NS assumed to be FS is 10, equivalent to 21% of the (true) FS. No supporting evidence was found for the 10% figure for FS, but the follow-up study does provide evidence that the percentage may be lower for women than men. Applying an adjustment for women to the 10% and 21% figures above gives 2.8% and 7%, respectively, for

women. (This correction for estimation of risk to women was of little consequence to our calculations.)

The remaining parameter values from Lee (1987b) needed to apply the formula for adjustment to misreporting bias in Equation B1 are as follows, where the variable identifiers are described in Table B-2: (V1,0.336), (V4,0.025; 0.011 for regular smokers plus 0.014 for occasional smokers), (V5,0.483), (V8,0.181), (V11,0.10), (V16,6.7; from a RR of 10 for CS and 2.5 for FS), and (V20,2.0). The observed relative risk for a true value of one from Equation B1 is 1.18. With the correction for women described, 1.18 would be reduced to 1.16. These values are close to what the NRC report and Wald et al. calculated for an expected value of the observed relative risk when the true value is one. The excess above one is the anticipated bias for smoker misclassification.

Assuming that the parameter values specified above accurately reflect the author's description, the method of adjusting for misclassification detailed in Appendix B (adapted in principal from Wald et al. [1986] and the NRC [1986]) does not support the claim that self-reported misclassification would fully account for the excess risk of lung cancer observed in the epidemiologic data. The lower 95% confidence limit on the overall summary observed relative risk of 1.40 is 1.25, and the 99% lower limit is 1.21, still above the range potentially explained by the misreporting of smoking habits alone.

The study results discussed by Lee for setting parameter values need to be included in the larger pool of related information and study evidence available, particularly for inference on U.S. women of age 35+. It appears likely that there are sex-related differences in rate of misreporting, and possibly in other parameters. Age may be a factor. It has not been indicated whether persons of ages 16 to 30, too young to be included in epidemiologic studies, are representative of the older age groups in terms of rates of misreporting and other factors. When

only 20 out of 808 reported nonusers of tobacco are reclassified as CS (11 as regular users at a relative risk of 10 or so), a few subjects may have a large impact on the outcome.

Several further observations on this article may be noted. It is concluded that the overall observed relative risk from spousal smoking to ETS can be explained as bias due to probable overstatement of the number of reported NS. It would follow that the true excess risk is zero. Extrapolation of risk from active smoking using average cotinine concentration in smokers and NS married to a smoker, however, is recommended in place of analysis of the epidemiologic data. It is concluded that there is a positive excess risk to ETS exposed NS (1.02 for women and 1.07 for men). As discussed previously, values in this range cannot be regarded as negligible.

4.4. CURRENT ASSESSMENT OF LUNG CANCER RISK

The data from epidemiologic studies currently available are evaluated for evidence of an elevated occurrence of lung cancer associated with ETS exposure. The methodological approach of Wald et al. (1986) and the NRC report are adapted with two minor modifications. The adjustment for relative risk of ES is calculated by its separate components (CS and FS). The second modification is to distinguish between parameter values for "reported" and "correct" classifications. Some parameter estimates depart from values used by the NRC, largely reflecting more current evidence and information available in some areas (Section 4.4.2). The most significant difference in parameter values is probably in the relative risk of active smoking. The value of eight assumed by the NRC is replaced by 12 (from the ACS's Study CPS-II, as reported in U.S. SG [1989]). Following the adjustment to an overall relative risk estimate for misclassification, a further adjustment is made to account for background exposure, i.e., for exposure to NS aside from spousal smoking, the dominant measure in the epidemiologic studies to distinguish between exposed and unexposed subjects.

The twice-adjusted RR estimate is combined with the percentage of the population exposed to ETS to obtain an estimate of the population-attributable risk (PAR), the proportion of LCDs in female NS of age 35 and older attributable to ETS exposure. Upper and lower confidence limits on the PAR are determined. These limits are conditional on the population exposure percentages assumed. Multiplying the PAR by the number of LCDs in never-smoking women in 1988 estimates the excess number of LCDs attributable to ETS.

In the final section of this chapter the population-attributable risk is calculated separately for each of the 19 case-control studies with data available and the three cohort studies, using the exposed fraction of controls from each study in the calculations. The ordered outcomes provide a basis for reviewing similarities/dissimilarities between studies, such as the country of origin and other study characteristics shown in Chapter 3. Although it is likely that the true differential in ETS exposure for subjects classified as exposed or unexposed is relatively higher in some sampled human environments than others (probably higher in Japan, for example, as discussed by Hirayama and others), comparison of outcomes with study characteristics did not reveal any apparent patterns or study characteristics associated with the findings.

4.4.1. Combining Evidence Across Studies

The overall relative risk estimate for case-control studies is determined by the extended Mantel-Haenzsel procedure. The M-H method was applied to case-control studies in Chapter 3 to test for an association between ETS and lung cancer. This same method is now applied to the raw data of case-control and cohort studies to obtain an overall estimate of RR and confidence interval. The procedure used in the NRC report (1986, Appendix B) is basically this same method (Yusuf et al., 1985). The method of combining cohort studies, and then obtaining an overall value for case-control and cohort studies together, follows the NRC procedure.

The case-control studies included in the analysis and their observed relative risks from raw data are in Table 4-1 (also see Table 3-5). Two studies, SHIM and VARE are excluded because the raw data were not available. The overall estimate of relative risk for the 19 case-control studies and three cohort studies in Table 4-1 is 1.41 (95% C.I. 1.26, 1.57). This value may be compared to 1.32 (1.16, 1.51) in the NRC report for females (three cohort studies and ten case-control studies), and to 1.50 (1.3, 1.8) determined by Wells (1986) from three cohort studies and 14 case-control studies. The shortest confidence interval is for the analysis of this report, indicating that the additional studies since the NRC report have reduced the statistical uncertainty in the estimated RR as would be anticipated. The higher estimate of relative risk in Wells' analysis is largely due to the choice of studies. The study designated as CHAN, reporting a relative risk value of only 0.75, was excluded by Wells but was included in the NRC report and in our analysis.

The summary RR of 1.41(1.26, 1.57) in this report is from the combined values of 1.42 (1.24, 1.63) for 19 case-control studies and 1.39 (1.15, 1.67) for three cohort studies. These figures are almost identical, so the results of one type of study reinforce the outcome from the other type. The consequence of combining the two summary outcomes is essentially just to shorten the confidence interval which is equivalent to reducing the standard error of the estimate of RR. For U.S. studies alone, the RR is 1.25 (1.03, 1.52), the combined RR from seven case-control studies is 1.34 (1.00, 1.79), and GARF(coh) is 1.18 (0.90, 1.54).

Adjustment for smoker misclassification, using the method and parameter values described below, reduces the overall observed relative risk of 1.41 (1.26, 1.57) to 1.28 (1.12, 1.45). Modification for background exposure to ETS raises it to 1.48 (1.21, 1.87). The NRC committee, with eight fewer case-control studies, obtained an overall summary value of 1.34 (1.18, 1.53) for both men and women that was adjusted to 1.25 (with 1.15 to 1.35 possible) for misclassification, and then to 1.42 ("ranging" from 1.24 to 1.61) for background exposure. The

values for women alone should be only slightly lower judging from the initial overall relative risk of 1.32 for women.

4.4.2. Adjustment To Relative Risk for Smoker Misclassification

The reduction formula for misreporting current smokers (CS) and former smokers (FS) as never-smokers (NS) is described in Appendix B. The general equation (B1) is accompanied by a description of parameters in Tables B-1 and B-2. Alternative specification of parameters in terms of "reported" and "correct" values is sometimes useful. The algebraic relationships for this conversion are shown in Table B-3. The description of parameter values used to adjust for smoker misclassification in this report follows, with variable identifiers in parentheses for use with Table B-2.

The percentages of reported CS, FS, and NS are 21.3, 24.0, and 54.7, respectively (V12, V17, V15). These values are obtained from the ACS's study CPS-II (Stellman and Garfinkel, 1986) except that 3% of the reported "never-smoked regularly" (56.4%) were reclassified as FS, leaving 54.7% estimated NS (see footnote d, Table 2, of U.S. SG [1989]). The NRC report and Wald et al. (1986) use 25%, 15%, and 50% for CS, FS, and NS, respectively, from a study of smoking habits in the U.K.

The percentages of reported NS who are misclassified as CS and FS are 2 (1.5, 2.5) and 4 (2, 6), respectively (V1, V2), where the parenthetical values denote a reasonable range. Wald et al. describe evidence to support values of 1.6% and 4.9% for these parameters respectively. Lee (1987b) makes a case for 2.5% (1.1% for regular smokers and 1.4% for occasional smokers) and assumes 10% for misclassified CS and FS, respectively (both males and females.) Adjusting the 10% value to reflect a lower rate of misreporting by females (Lee, 1987b) would make it 2.8%. Cummings (1989b) found that six subjects of a total 669 (1%) reported NS and FS were misreported CS (urinary cotinine above 90 mg/dL). Jarvis et al. (1984) found that 21 of 121

reported nonsmokers (17%) were CS based on biochemical markers. This very high rate was found among elderly patients attending clinics for smoking-related disease, whose doctors had frequently urged them to give up smoking.

The percentages of misclassified CS and FS who are exposed (married to a smoker) are both 82 (71, 92) (V5, V6). These values correspond to an exposure percentage of 60 (45, 75) (V4) for reported NS, and a marriage aggregation factor (MAF) of 3.07 for females (from Lee, 1987b). (The MAF is the ratio of cross-products, i.e., the odds ratio, in a 2-by-2 table of smoking status of subject by smoking status of spouse. The MAF is assumed to be the same for NS compared with either CS or FS). Table 12-7 of the NRC gives MAF = 3.1 for females, a value communicated from Wald et al. The NRC report considers values of 2.5, 3.5, and 4.5, with 3-4 likely.

Evidence suggests that CS and FS who are misclassified as NS are likely to be only light smokers and that misclassified FS have typically stopped smoking several years previously (Wald et al., 1986). Estimates of relative risk for CS and FS (females) are 11.94 (9.99, 14.26) and 4.69 (3.86, 5.70) for 1982-1986 (ACS's CPS-II Study, as reported in U.S. SG [1989]). Our report assumes the relative risks of misclassified CS and FS are 5.95 (5.0, 7.15) and 2.97 (2.7, 3.86) (V7, V8), respectively (discussed and compared with other sources below). If exposed, the values are incremented by the excess risk from exposure to ETS (1-V(9)) to obtain variables V10 and V11. (Technical Note: Equation (B1) is implemented by setting a value for V(9) along with other parameters to obtain a corresponding value of RRO. To find the value of RRM that corresponds to a specific value of RRO may require a few iterations from the starting point chosen for RRM.)

Parameter values for the RR of CS and FS misreported as NS have been determined in other sources from the information available for the relative risk of smokers and FS in general. To compare our parameter values of the RR for CS and FS misclassified as NS with those of

other authors, their formulas for reducing the RR of CS and FS who are misreported NS have been applied to the RR figures from the CPS-II survey given above. For misclassified CS, the results are--NRC (1986): the range from 3.0 to 6.0; Wald et al. (1986): 3.8(3.3, 4.3); Wells (1988): 4.6(4.0, 5.4); and Lee (1987b): 8.0(6.7, 9.6). All but the last entry are below the value 6.0(5.0, 7.2) in this report. For misclassified FS, the figures in these sources would be--NRC: the range from 3.0 to 6.0; Wald et al.: 1.9(1.8, 2.1); Wells: 1.9(1.8, 2.1); Lee: 3.0(2.5, 3.6). The last entry is comparable to 3.0(2.7, 3.9) of this report.

4.4.3. Parameter Sensitivity

For the parameter values described above for this report, a true relative risk of 1.00 corresponds to an observed relative risk of 1.14, a 14% inflation due to smoker misclassification. For each of the parameters with a range of input values (shown in parentheses), the lower and upper values in the parentheses were also applied, leaving the other parameter values fixed. The marriage aggregation factor varied between 2.0 and 4.0 as well. The observed relative risk did not exceed 1.19. The 95% lower confidence limit on the overall observed relative risk from the epidemiologic data is 1.25, still well above the likely range explained by misclassification. (The 99% lower confidence limit is approximately 1.21, still above the explainable range). Only one parameter was set at an extreme value at one time in the sensitivity testing, and it is not improbable that some combination of parameters chosen this way would produce a value exceeding 1.25. But the observed risks from the epidemiologic data appear unlikely to be explained by misclassification alone, and no single parameter within a plausible range alters that conclusion.

4.4.4. Adjustment to Relative Risk for Background Exposure

The relative risk of ETS in epidemiologic studies is relative to the baseline risk of a female NS married to a nonsmoker, who still has some background level of exposure to ETS. Some assumptions are required to approximate the lung cancer risk due to background exposure to ETS. A means of estimating the proportion of total ETS exposure that is due to background in an exposed individual (actually exposed to background and to spousal smoke) is needed. The NRC report compared average cotinine concentrations in exposed and unexposed persons. Assuming that lung cancer risk from passive smoking is linearly related to cotinine concentrations at these low doses, lung cancer risk of passive smoking can be estimated at the higher exposure level (background plus spousal smoking, applicable to an exposed person) and at the lower exposure level (background only, applicable to an unexposed person), with both estimates relative to the risk of lung cancer risk from zero exposure to ETS.

Background ETS appears to constitute about one-third of the total ETS exposure of a NS married to a smoker, if cotinine concentrations are used as an index of total exposure. The ratio of average cotinine concentrations in exposed to unexposed married NS is assumed to be three in the NRC report, based on evidence from Wald and Ritchie (1984). The Wald and Ritchie study applies to men, but Lee (1987b) reports a ratio of 1/.3 (= 3.3) in women and Coultas et al. (1986) report a ratio of 3.41/1.45 (= 2.35) from saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. Three is used in this report (X = 3 in Equation B2), along with the assumption that cotinine is a constant multiple of the carcinogenic potency of ETS at low doses. Applying the method used by the NRC (Appendix B of this report) to take background exposure into account changes the overall RR estimate adjusted for misclassification from 1.28 (1.12, 1.45) to 1.48 (1.21, 1.87) for female NS. It should be noted that the meaning of RR is changed with this adjustment--from meaning relative to the risk from background ETS to meaning relative to the risk at zero-ETS exposure. (Note: There

is an important distinction between the use of cotinine as a surrogate dose for ETS to estimate lung cancer risk from background exposure and its use in the cigarette-equivalents approach (Section 4.3). In the latter, the contention centers around the assumption that cotinine (or anything else, such as respirable suspended particles) is an equivalent dose surrogate for both passive and active smoking, i.e., that equivalent uptake in passive and active smoking implies equivalent carcinogenic risk.)

4.4.5. Population-Attributable Risk and Excess Lung Cancer Deaths

The number of LCDs in U.S. female NS in 1988 is estimated to be 6500 (3000 for male NS). The 6500 figure includes both married and unmarried NS. The ACS's CPS-II Study (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just NS) are: married, 75.3; divorced 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female NS, about 75% of female NS, so it is necessary to consider exposure to ETS in the remaining 25% of unmarried NS.

Cummings (1989b) obtained urinary cotinine levels on a total of 663 self-reported NS and FS. The cotinine levels were only slightly higher in males than females (9.6 and 8.2 ng/mL, respectively), and slightly more than half of the subjects were females. The average cotinine level (in ng/mL) was 10.7 for married subjects if the spouse smoked and 7.6 otherwise (all units in ng/mL). Interestingly, the average cotinine levels reported by marital status are: married, 8.3; never married, 10.3; separated, 11.8; widowed, 10.4; and divorced, 9.2. The study, which includes 7% of age 18 to 29, and 47% of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried NS is probably closer, on average, to a NS married to a smoker (an exposed person) than to a NS married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

The percentage of married female NS who are married to smokers is assumed to be 60, with a plausible range of 45 to 75 (Section 4.4.2.). The choice of exposure percentages is based on the distribution of values observed in the epidemiologic studies (Table 3-2 and Figure 3-1). From the discussion of exposure to unmarried female NS above, it is reasonable to assume that exposure to ETS, on average, is at least as large as the sum of 60% of the higher exposure level (from spousal smoking plus background) and 40% of the lower exposure level (background alone) experienced by a married female NS. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female NS alike, in terms of exposure to ETS (60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level). Alternatively, average exposure in the population of female NS (including marrieds and unmarrieds) is assumed to be at the background level plus 60% of the exposure from spousal smoking. The percentages assumed by others in the literature have varied: 82 (Lee, 1987b), 76 (Wells, 1988), 59 (Wald et al., 1986), and 17 (NRC, 1986). The NRC percentage was taken from a sample of urinary cotinine bioassays appearing in Wald and Ritchie (1984). The 17% figure is likely much too low to be representative of the population of interest.

The population-attributable risk (PAR) for women is the proportion of LCDs in female NS per year associated with exposure to ETS. Multiplying it by the total number of LCDs in female NS gives the number of excess LCDs per year from ETS exposure, i.e., the number attributable to ETS exposure. For calculation of PAR in this report, the percentage of NS exposed to ETS is assumed to be the same for marrieds and unmarrieds (60% as discussed above). The PAR for the 60% assumption in women is 0.27 (95% C.I. 0.14, 0.41). (Technical Note: The calculations are from Equation B3 with P(E/N) = 0.6, RRM = 1.28 and RRB = 1.48. The confidence interval is calculated by using the upper and lower confidence bounds for RRM and RRB in Equation B3. The confidence interval is conditional on the exposure prevalence.)

percentage of 60%). Multiplying the PAR by 6500, the number of LCDs in female NS in 1988, gives 1750 (910, 2660) estimated LCDs in female NS in 1988. The number of LCDs in male NS is probably about one-half the number of females, although the evidence for males is scant in comparison to females. The available data indicate that the risk to male NS is not likely to be smaller than for female NS. Applying the PAR value of 0.27 to the total number of LCDs in male NS (3000), gives an estimate of 810 LCDs per year in male NS due to passive smoking. For both sexes combined, the annual number of LCDs in NS attributable to ETS exposure is about 2500, with a range of 1300 to 4000.

A figure for FS also needs to be included in the estimate of LCDs attributable to ETS since they constitute a large segment of the population. Repace and Lowrey (1985) and Wells (1988b) estimated the risk to FS. Sandler et al. (1985) and Geng et al. (1988) found, respectively, an increased total cancer risk and an increased lung cancer risk in active smokers as a result of passive smoking. Sandler et al. found that relative to active smokers who had no other smokers at home, smokers who had one, two, or three or more smokers at home had increased risks of (total) cancers of 40%, 120%, and 160%, respectively. To calculate the annual number of LCDs in FS attributable to ETS, RR is assumed to be the same for FS and NS. The figure calculated for FS is 1260 (540 women and 720 men), making the yearly total of LCDs attributable to ETS approximately 3800. Data on the number of FS in the U.S. population and the calculational details are included in Appendix B.

The 3800 figure is based on a population exposure percentage of 60, the mid-point in a plausible range of 45% to 75%. The results, however, are not very sensitive to the exposure percentage. If 45% (75%) is assumed instead of 60% in the preceding calculations, then the yearly total of LCDs attributable to ETS is approximately 3500 (4100) instead of 3800. This range, 3500 to 4100, corresponds to the plausible range of the exposure percentage, 45% to 75%, for the estimate of RR after adjustment for misclassification (RRM = 1.28) and correction

for background exposure to ETS (RRB = 1.48). The RRM and RRB figures are based on the epidemiologic studies of female NS married to smokers and the simple linear model using cotinine concentrations to account for background exposure to ETS. Ninety-five percent confidence intervals are available for the population values of RRM and RRB, given by (1.12, 1.45) and (1.21, 1.87), respectively. Calculating PAR from the low (high) value of the plausible range of exposure percentages, 45% (75%), and low (high) values of the 95% confidence intervals for RRM, 1.12 (1.21), and RRB, 1.21 (1.87), provides estimates that are probably too low (high). Using these values to recalculate the population risk provides numerical markers for low and high extremes of the estimated number of LCDs due to ETS. These markers are approximately 1800 and 6100.

In summary, the estimated total number of LCDs per year due to ETS exposure is 3800. It is approximately the sum of estimates for NS females (1750), NS males (810), FS females (540), and FS males (720), assuming a 60% exposure rate. Using the lower (upper) confidence limits for RRM and RRB and the lower (upper) end of the plausible range for exposure percentage gives approximately 1800 (6100) total LCDs per year due to ETS. These low (high) totals consist of NS females 820 (2800), NS males 380 (1290), FS females 250 (860), and FS males 330 (1150). Characterization of the population risk is based on data for female NS from 22 epidemiologic studies of varied design and protocol conducted in numerous locations under ordinary environmental conditions. Extension of these results to the population of all U.S. nonsmokers is not without uncertainty, but is probably conservative. It is unlikely that the true number of LCDs per year in U.S. nonsmokers lies outside the interval defined by the two extreme values, 1800 and 6100.

4.4.6. Adjusted Relative Risk and Population-Attributable Risk by Individual Study

The estimates of RR for lung cancer from ETS exposure have been statistically combined

to give an overall estimate and confidence interval. The overall observed value (RRO) was adjusted for possible misclassification (to be called RRM) and for background exposure to ETS (to be called RRB). The latter "correction" was to make the risk estimates relative to zero-exposure.

Combining results from all studies increases the statistical power to detect an exposure effect on lung cancer. Aside from weighing each study's results according to a measure of statistical uncertainty (influenced but not solely determined by sample size), studies are treated as if they were qualitatively equivalent and as if the "true" RR were the same in all environments studied. Qualitative differences exist in all studies, but there is little basis for quantifying them. The true values of RR being estimated depend on both the study design and protocol. Culture, environment, and life-style would influence inter-study differences. In particular, one might expect these factors to contribute to inter-country variability in the epidemiologic data. To extract this source of variability statistically would require multiple studies, similar in design and execution, from each country. Although there is more than one study from several countries among those analyzed (China [2], Hong Kong [4], Japan [2], Sweden [2], U.S. [8]), the studies are not sufficiently similar within countries to test variability. In particular, there is considerable dissimilarity between the U.S. studies, and this probably contributes to their wide ranging results.

The observed relative risk from each study is adjusted for misclassification and background rate and the PAR is calculated to evaluate the dissimilarity of results. The percentage of exposed NS for a study is taken from the observed percentage among controls of the study (Table 3-2 or Figure 3-1). The exposure percentages for CS and FS are then calculated assuming a marriage-aggregation factor of 3. The same exposure parameters are used in both the calculations of misclassified smokers and the population-attributable risk.

By using 95% confidence limits on the RR estimate for each study in the calculations,

limits are obtained for the PAR. Interpretation of these limits is conditional on the percent exposed, which is a random variable. Aside from the exposure percentages described above, the values and method of calculation are the same as used previously in Section 4.4. The results of adjusting each study's observed relative risk for misclassification are shown in Table 4-2. (Technical Note: The overall observed RR, denoted by RRO, is corrected for misclassification (RRM) and then for background exposure (RRB). The excess RR for background exposure is approximately RRB - RRM, which applies to all NS. The additional excess risk to the proportion of NS exposed to ETS equals RRM-1.) A minus sign (-) in Table 4-2 indicates that the observed excess risk after adjustment for misclassification is negative, i.e., the adjusted RR < 1. The adjustment for misclassification decreases as the observed relative risk increases and is treated as negligible for values above 2.5. The observed value that would correspond to a true RR of one was also calculated for each study. These range from 1.12 (BUFF) to 1.22 (BROW), and cluster from 1.13 to 1.16. The excess risk from background exposure to ETS shown in Table 4-2 was arbitrarily limited to 0.2. When the excess risk after adjustment for misclassification is zero, a correction for background is not appropriate. The values for PAR have associated confidence intervals predominantly with a lower limit of zero (the minimum) and an upper limit in the range 34% to 75%. Exceptions include the case-control studies CHAN and TRIC, and the cohort study HIRA, with percentages of (0,13), (3,58), and (14,49), respectively.

The estimates of PAR and their upper confidence limits are rank-ordered in Table 4-3. Probable values are shown for three studies in which the calculation could not be made due to insufficient data. The studies with a zero estimate of PAR were reviewed to see if some common characteristic might be apparent. Remarks about some of those specific studies follow. The studies with an estimate of zero PAR will serve to indicate some possible sources of disparity in results across other studies as well.

WU includes only patients with adenoma (ADC) or small cell carcinoma (SCC) of the

lung in their case groups. Their results overall are somewhat ambiguous regarding ETS exposure, which the authors attribute to the lesser etiologic role of ETS for ADC compared to SCC. The number of SCC observed, however, was too small to warrant quantitative comparisons. Of 29 ADC cases, 12 are bronchoalveolar cell carcinomas, which Correa et al. (1983) found to have only a weak association with passive smoking. GILL(Coh) reports that insufficient time had elapsed since completion of the recruitment phase of their cohort study to observe a sufficient number of cases to allow firm conclusions. Only six instances of lung cancer in exposed females had occurred. In BUFF, exposure refers to having ever lived with a household member who smoked regularly. Exposure is not limited to spousal smoking, nor to any relative time-frame for duration of exposure. This broad definition of exposure possibly includes subjects who experienced little total exposure from ETS over the past 20 to 30 years. The high percentage of female controls exposed to ETS (84%) leaves a relatively small percentage of unexposed subjects.

KABA is one of the smaller studies in this report (24 cases and 25 controls, total). Exposure refers to current or past smoking of a spouse. SHIM, listed in Table 4-3 as a "probable O" found no association between risk of lung cancer and smoking by husbands, fathers, siblings, or coworkers. A high correlation was observed, however, with smoking by the father-in-law ($p < 0.005$), which the authors describe as plausible in the Japanese society (see Appendix A). The unpublished study by Varela (1987), denoted as VARE in this report, is quite large and warrants further attention. The author detects no effect from exposure to spousal smoking, but does find a significant increase in lung cancer incidence at a very high total exposure to ETS (spouse has smoked 150 person-years, in the author's terminology) (see Figure 3-4). Unfortunately, the pertinent data from this study are not included in the source for this report. Attempts to obtain these data from the authors have been, thus far, unsuccessful.

TABLE 4-2. ADJUSTED RELATIVE RISKS AND POPULATION-ATTRIBUTABLE RISK OF INDIVIDUAL STUDIES (FEMALES)

Study	Percent controls exposed[1]	RR adjusted for misclass.[1,2] (RRM)	Excess RR from background[1,3] (RRB-RRM)	Population attributable risk[1,4]
AKIB	70	1.42(-,2.62)	0.2 (0,0.2)	33(0,57)
BROW	15	1.35(-,5.99)	0.2 (0,0.2)	20(0,49)
BUFF	84	- (-,1.83)	0 (0,0.2)	0(0,47)
CHAN	47	- (-,1.15)	0 (0,0.08)	0(0,13)
CORR	46	2.00(-,5.20)	0.2 (0,0.2)	40(0,68)
GAO	74	1.06(-,1.64)	0.03(0,0.2)	7(0,40)
GARF	61	1.19(-,1.91)	0.11(0,0.2)	18(0,43)
GENG	44	2.10(-,4.28)	0.2 (0,0.2)	41(0,62)
HUMB	56	2.31(-,6.61)	0.2 (0,0.2)	48(0,77)
KABA	60	- (-,2.45)	0 (0,0.2)	0(0,52)
KOO	49	1.44(-,2.67)	0.2 (0,0.2)	29(0,50)
LAMT	45	1.54(1,2.35)	0.2 (0,0.2)	31(0,45)
LAMW	44	2.01(-,3.71)	0.2 (0,0.2)	39(0,58)
LEE	68	- (-,2.56)	0 (0,0.2)	0(0,56)
PERS	43	1.13(0,2.09)	0.07(0,0.2)	6(0,40)
SVEN	66	1.14(-,2.81)	0.08(0,0.2)	15(0,58)
TRIC	43	2.07(1.03,3.81)	0.2 (0.02,0.2)	40(3,58)
WU	63	- (-,3.24)	0 (0,0.2)	0(0,62)
HIRA (Coh)	74	1.53(1.13,2.05)	0.2 (0.07,0.2)	37(14,49)
GILL (Coh)	72	- (-,4.91)	0 (0,0.2)	0(0,75)
GARF (Coh)	72	1.05(-,1.44)	0.03(-,0.2)	7(0,34)

[1] Values in parentheses are calculated from confidence bounds.

[2] Adjustments considered negligible for values of 2.5 or greater. Minus signs indicate a negative excess risk.

[3] Values truncated at 0.2, assumed to be a reasonable upper limit on excess risk for this exercise.

[4] See Appendix B.

TABLE 4-3. POPULATION-ATTRIBUTABLE RISK BY STUDY (FEMALES)

Country	Study	Estimate	Confidence limit
Hong Kong	CHAN	0	13
U.S.	BUFF	0	47
U.S.	KABA	0	52
U.K.	LEE	0	56
U.S.	WU	0	62
Scot.	GILL(Coh)	0	75
Sweden	PERS	6	40
U.S.	GARF(Coh)	7	34
China	GAO	7	40
Sweden	SVEN	15	58
U.S.	GARF	18	43
U.S.	BROW	20	49
Hong Kong	KOO	29	50
Hong Kong	LAMT	31	45
Japan	AKIB	33	57
Japan	HIRA(Coh)	37	49
Hong Kong	LAMW	39	48
Greece	TRIC	40	58
U.S.	CORR	40	68
China	GENG	41	62
U.S.	HUMB	48	77
U.S.	VARE[1]	0	
Japan	SHIM[1]	0	
Japan	INOU[1]	70	

[1] Insufficient information to calculate. Estimate shown is a guess.

Our remarks above pertain to studies that estimate zero attributable risk. It is easier to depict study characteristics that reduce the likelihood of detecting an effect than to speculate why a study may have concluded falsely that there is an effect. A false positive conclusion could result from an undetected causal variable that is correlated with ETS exposure. The likelihood of a false negative conclusion is enhanced if the sample size is small, or the study differentiates poorly between exposed and unexposed subjects.

The cohort study in Japan (HIRA) provides strong evidence of an increased lung cancer hazard associated with ETS exposure. Consideration of plausible confounding factors and covariables has not produced an alternative explanation, and implication of ETS as a causal factor is biologically plausible. The mixed results of epidemiologic studies in the U.S. may be partly due to statistical chance and study differences that affect the power to detect a lung cancer effect from exposure to ETS. There is also evidence to suggest that exposure differentials from spousal smoking may be larger in Japan, and possibly some other countries, than in the U.S. This would make a cancer-related effect more difficult to detect in the U.S. An estimate of U.S. PAR from evidence in Japan alone might lead to an overstatement. Prediction based on the overall summary has the advantages of using all the study data while mitigating but not ignoring the influence of the extreme outcomes.

4.5. SUMMARY AND CONCLUSIONS

The overall summary RR (before adjustments) for female NS obtained by the NRC (for 10 case-control and 3 cohort studies) is 1.32 (95% C.I. 1.16, 1.51). The corresponding value in this report (for 19 case-control and 3 cohort studies) is 1.41 (1.26, 1.57). The effect of nine additional case-control studies in the analysis of this report is to increase the RR from 1.3 to 1.4 and to reduce the width of the confidence interval. (Both changes increase the statistical significance.) The overall RRs for the 19 case-control studies by themselves, and for the three

cohort studies by themselves, are nearly identical, even though the two types of epidemiologic studies have their own strengths, weaknesses, and potential sources of bias. The evidence from the U.S. studies, however, is weaker than for non-U.S. studies. The summary RR from raw data for seven U.S. case-control studies is 1.34 (95% C.I. 1.00, 1.79). For the 12 non-U.S. studies with raw data (all but two studies), the corresponding estimate is 1.45 (95% C.I. 1.24, 1.69). The overall summary RR for all U.S. studies (from seven case-control studies and one cohort study) is 1.25 (1.03, 1.52), which is statistically significant ($p = 0.025$ for a one-tailed test).

The overall RR for women NS is adjusted downward to 1.28 (95% C.I. 1.12, 1.45), using a modeling approach similar to that of NRC/Wald to estimate bias from smoker misclassification. Parameter values for the model were taken from recent sources. The adjusted estimate of RR is still statistically significant ($p < 0.01$). The parameter values also were varied over a plausible range (one at a time, but not jointly), leading to the conclusion that observed values of overall RR of up to 1.19 are consistent with a true RR of 1.0, i.e., could arise from misreporting bias alone. Although possibly substantial, misreporting bias is not sufficient to explain the entire excess risk associated with ETS exposure.

Based on these analyses and following the U.S. EPA guidelines for carcinogen risk assessment (Fed. Reg., 1986), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight of evidence, principally:

- Biological plausibility. ETS is taken up by the lungs and distributed throughout the body. The similarity of carcinogens identified in SS and MS along with the established causal relationship between lung cancer and smoking make it reasonable to suspect that ETS is also a lung carcinogen.

- Consistency of response. The two completed cohort studies and sixteen of the 21 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.

- Upward trend in dose-response. Of the two major cohort studies, the Japanese study (Hirayama) demonstrates a strong association between passive smoking and lung cancer, including an upward trend in dose-response. The upward trend is well supported by the preponderance of evidence in the 13 case-control studies that classified data by exposure level. The Hirayama study has undergone extensive critical review that led to some corrections and revisions but failed to discredit the findings. Differences in life-style and culture may be a factor in the Japanese study reporting a stronger association between ETS and lung cancer than the American study (American Cancer Society).

- Detectable association at environmental exposure levels. Within the population of women who are lifelong nonsmokers, the excess lung cancer risk of those married to a smoker is large enough to be observed. Carcinogenic responses are usually detectable only in high exposure circumstances, such as occupational settings or in highly dosed experimental animals.

- Broad-based evidence. The 21 case-control and three prospective studies provide data from eight different countries and from a wide variety of study designs and protocols conducted by many different research teams. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk from ETS exposure. The evidence remains statistically conclusive, however, after adjustments for smoker misclassification. The summary estimate of relative risk from raw data of both the case-control and cohort studies is 1.41 (95% C.I. 1.26, 1.57) before adjustment for misclassification and 1.28 (95% C.I. 1.12, 1.45) afterward ($p < 0.01$).

To estimate the number of LCDs per year due to passive smoking, a further adjustment to RR is made to correct for background exposure to ETS, i.e., to make the estimate relative to zero ETS exposure. This additional adjustment leaves the overall RR estimate for female NS at 1.48 (1.21, 1.87). This same estimate is assumed for the relatively small number of male NS with a spouse who smokes. The available data on males suggests that the risk is at least as high as for females. It is assumed that 60% of the population of female NS of age 35 and over are exposed to ETS at levels equivalent to being married to a smoker, and that the remaining 40% are exposed to an average background exposure level (equivalently, average ETS exposure in the population of female NS is 60% of the way from the lower exposure level (from background ETS alone) toward the higher exposure level (from spousal smoking and background). It is

estimated that about 27% (95% C.I. 14%, 41%) of annual LCDs in never-smoking women are attributable to ETS exposure. Applied to the ACS's estimate of 6500 such cases in 1988, this percentage equates to 1750 (910, 2660) ETS-related LCDs in never-smoking women. The RR for male NS is likely at least as high as for female NS (NRC, 1986; Wells, 1988b). Applying the RR estimate for females to the ACS estimate of 3000 LCDs of male NS in 1988 gives an estimate of 810 males, making the total estimate 2560 for both sexes.

Compared to the wealth of epidemiologic data on never-smokers, particularly for women married to smokers, the information available for estimation of lung cancer risk in FS is not substantial. The absolute risk is higher in FS than in never-smokers, but the incremental risk from exposure to ETS is essentially unknown. For the purpose of including FS in the calculation of LCDs attributable to ETS, they are assumed to have the same relative risk from exposure to ETS as never-smokers. Based on this assumption and data regarding the number of former smokers in the U.S., the estimated annual number of LCDs due to ETS is 1260 (540 women and 720 men, as calculated in Appendix B). Inclusion of FS brings the estimated total number of LCDs per year from ETS to 3800. The component of this figure for married never-smoking females is based on the large quantity of epidemiologic data that is available. It has been statistically estimated with a 95% confidence interval included to indicate a range of statistical uncertainty. The component terms for unmarried women, for men, and for FS of both sexes are less well substantiated and subject to greater uncertainty.

5. ENVIRONMENTAL TOBACCO SMOKE AND RESPIRATORY DISORDERS IN CHILDREN

5.1. INTRODUCTION

Medical, epidemiological, and experimental research of the past forty years has implicated smoking as a causal factor in an increasing array of diseases and detrimental health conditions. A recent workshop (Speizer, 1989) describes chronic obstructive pulmonary disease (COPD) as a heterogeneous group of disorders with the common element of obstructive airways disease. It concludes that over the last 25 years there has been a drastic and relatively sharp rise in COPD, particularly in men, and that much of the increase is associated with temporal trends in cigarette smoking. As knowledge unfolds an increasing breadth and severity of health effects related to smoking, the potential implications for passive smokers expand as well.

Unlike studies testing for a link between ETS and lung cancer, only a few studies have used adult subjects to test for respiratory symptoms. Infants and small children generally have been preferred because of better study control for exposure to ETS and confounding substances and because of the greater likelihood of an observable response due to their higher susceptibility. Children are more susceptible to respiratory disorders because their immunologic and respiratory systems are immature and pulmonary function is still developing (NRC, 1986; WHO, 1986). Also, "doses" of ETS are larger relative to their body size. Very young children experience prolonged exposure since they spend much of their time at home, and they are not exposed socially or occupationally to ETS or potential confounding agents. On the negative side, regular active smoking and experimentation become potential confounding factors in children at about age seven that may be understated by either parental or self-reporting. At early ages, particularly up to one or two years when study results of some health effects are most consistent, in utero exposure to products of tobacco smoke is another potential

confounding variable. Finally, children are also relevant study subjects because of their population size. The number of American children less than five years old living in homes with at least one smoker probably exceeds nine million (American Academy of Pediatrics, 1986).

As observed in the report of the Canadian Pediatric Society (1986), the results of epidemiologic surveys on the potential effects of parents' smoking on their children were initially equivocal because it was often asked if either parent was a smoker. Only when the mother's and father's smoking habits were considered separately did it become evident that the mother's smoking habit was more important. It is not surprising that maternal smoking is more significant than paternal smoking in studies involving infants and young children. The predominant effect of maternal smoking, however, further complicates differentiating the influence of maternal smoking during pregnancy and during the postnatal period. A large study by Chen et al. (1988) has found increased respiratory illness in infants of nonsmoking mothers but with ETS exposure from other household smokers after birth. This somewhat discounts the role of the potential confounding effect of in utero exposure to tobacco products from the mother's smoking during pregnancy.

This chapter focuses on the evidence for an association of ETS exposure with chronic respiratory symptoms, acute lower respiratory illnesses, and impaired pulmonary function in children, with emphasis on epidemiologic studies that have appeared since the reports of the NRC and the U.S. SG in 1986. Studies on related topics are discussed in the last section, including the exacerbating effects of household ETS on asthmatic children and the potential association of parental smoking with the prevalence of additional respiratory disorders--asthma, upper-respiratory-tract infections, and middle ear effusion (an indicator of chronic middle ear disease).

5.2. EXPOSURE OF CHILDREN

Biochemical data indicating *exposure* to ETS are predominantly assay results of cotinine concentrations in urine, saliva, or serum. Nearly all of the studies on adverse *health effects*, however, have relied on verbal reports of parental smoking or some other measure of exposure. Two exceptions have related health risks to cotinine concentrations. Strachan et al. (1989), who found a positive association between passive smoking and middle ear effusion in seven-year-old children, evaluated exposure to ETS by assaying salivary cotinine. The authors note that cotinine concentrations were related to the number of smokers in the household. Schwartz-Bickenbach et al. (1987) observed urinary cotinine concentrations in infants as a measure of exposure to nicotine and cotinine in breast milk and to nicotine in ETS. As noted by Jarvis (1989), the implicit assumption in utilizing cotinine concentrations as a measure of ETS exposure, i.e., as a dose-surrogate, to detect detrimental health effects that may be associated with exposure to ETS, is that cotinine concentrations are directly proportional to the uptake of risk-relevant compounds in ETS. Which compounds are risk-relevant to a particular detrimental health effect is generally unknown, however, and uptake may vary between individuals. Cotinine concentration appears to be the most promising internal measure of recent exposure to ETS. Studies that have addressed the validity or reliability of cotinine as an indicator of exposure to ETS are described next.

Jarvis et al. (1985) found saliva cotinine concentrations in nonsmoking schoolchildren to be related to smoking within the family. A clear increase in cotinine concentration was observed across the categories (1) neither parent smokes, (2) father only smokes, (3) mother only smokes, and (4) both parents smoke. Pattishall et al. (1985) measured serum cotinine in young children (6 to 12 years of age) and found a direct correlation with the number of smokers in the home, the amount smoked by the mother, and the amount smoked by others in the home. Coultas and colleagues (1987) surveyed salivary cotinine levels in children and adults. Similar to the study by

Pattishall and colleagues, the major determinants of a detectable level of cotinine in children were the mother's smoking, father's smoking, and smoking of other household members. Henderson et al. (1987) found urinary cotinine to be a more sensitive indicator than serum cotinine among exposed children of day-care age. Both measures of cotinine, however, were significantly correlated with ETS exposure in the home as determined by levels of nicotine recovered from air samples and by the number of cigarette butts collected. Henderson et al. (1989) notes that urinary cotinine/creatinine ratios were remarkably stable in preschool children over a one-month period, and Jarvis et al. (1987) reports that cotinine measures were reasonably stable over one year in nonsmoking adolescent girls. The cotinine/creatinine levels of nine children (9 months to 3.5 years of age) exposed to 26.4 micro-grams/m^3 of nicotine from SS peaked at 4 hours and the elimination half-life was 29 hours (Goldstein et al., 1987). Greenberg et al. (1989) studied a representative sample of 433 healthy neonates in central North Carolina. Sixty-four percent lived in households with smokers or had contact with nonhousehold smokers. Urinary cotinine was found in 60% of all study infants. Seventy-five percent of smoking mothers smoked near their infants. The amount smoked in the infants' presence was the most significant correlate of cotinine concentration.

The cotinine studies clearly demonstrate uptake, metabolism, and systemic distribution of ETS in infants and implicate mothers' smoking as a principal source of exposure in their own children. There are indications of substantial host-related differences in cotinine concentrations among children, i.e., in experiments with controlled exposure to ETS, cotinine concentrations vary between individuals experiencing the same airborne concentration of ETS. Benowitz and Jacobs (1984) reported similar results for studies of cotinine in adults. To our knowledge, no researchers have estimated the component of variability due to inter-individual differences of absorption and metabolism in studies comparing cotinine levels with airborne concentrations of SS.

5.3. RECENT EPIDEMIOLOGIC EVIDENCE

Studies that have appeared subsequent to the NRC and U.S. SG reports of 1986 are displayed in Table 5-1. They have largely taken potential biasing factors into account in the study design, protocol, or data analysis. It is often not feasible to measure and control for all the variables of potential interest, however, and it is difficult to do so perfectly when attempted. For example, active smokers among study subjects have generally been identified by self-reporting or parental reporting. Although there is no evidence to suggest that this method has been inadequate, the possibility of classification bias cannot be fully excluded. Other examples of variables to be considered include parental social class (Chen et al., 1988; Somerville et al., 1988; Willatt, 1986); heating and cooking fuels (Chen et al., 1988); parental illness that could either cross-infect their children or make the children genetically vulnerable (Chen et al., 1988; Willatt, 1986); and illnesses in the children that could mimic the effects of ETS (Chen et al., 1988; Geller-Bernstein et al., 1987). Typically these variables have been entered into a multiple regression or logistic regression model for statistical analysis or a method of stratification has been applied.

The epidemiologic studies emphasized in the U.S. SG and NRC reports on the health hazards of ETS to children between birth and adolescence are shown in Tables 5-2 to 5-4 for respiratory symptoms, respiratory illness, and pulmonary function. About 30 additional studies have appeared since the two major reports of 1986. Recent studies' characteristics are listed in Table 5-1, which includes a few entries for ailments in addition to respiratory symptoms, respiratory illness, and pulmonary function. Those last three categories, however, are the principal focus of this report and the topics of the next three sections. The general formats of the sections are similar: summary conclusions and issues from the NRC and U.S. SG reports are reviewed; selected recent studies are described that may bear on the weight of evidence and relevant issues; implications of the recent studies for the results and conclusions of the NRC and

TABLE 5-1. EVIDENCE OF RESPIRATORY DISORDERS RELATED TO ETS EXPOSURE FROM SELECTED STUDIES SUBSEQUENT TO THE U.S. SG AND NRC REPORTS OF 1986.

Study	Age of subjects	Section reference	Reaction to ETS exposure
Chan et al., 1989	Children (7)	5.4.3 and 5.4.4	Wheeze in low-birth-weight cohort; cough in controls.
Charlton and Blair, 1989	Adol. (12-13)	5.4.1 and 5.7.5	Increased school absenteeism.
Chen et al., 1988	Infants	5.1, 5.3, 5.5.3, 5.5.4, and 5.7.3	Increased hospitalization.
Chen, 1989 (same sample data as entry above)	Infants	5.5.3 and 5.5.4	Synergism of passive smoking and artificial feeding on hospitalization.
Evans et al., 1987	Chil./adol. (4-17)	5.7.4	Increased emergency room visits; no increase in hospitalizations; no effect on pulmonary function.
Fleming et al., 1987	Infants/ chil. (0-5)	5.7.2	Increased upper respiratory tract infection.
Geller-Bernstein et al., 1987	Infants/ chil. (0-5)	5.3 and 5.7.3	Persistent wheezing in atopic children who were bottle fed.
Hinton, 1989	Infants/chil.	5.7.1	Higher chance of hospital admission for grommet insertion (middle ear).
Kallail et al., 1987	Children	5.7.1	No association with middle ear problems.

(continued on following page)

TABLE 5-1. (continued)

Study	Age of subjects	Section reference	Reaction to ETS exposure
Kauffmann et al., 1989	Children (6-10)	5.4.4, 5.6.3, and 5.6.4	Maternal (but not paternal) smoking associated with decrease in FEV_1 and FEF_{25-75}, but not in FVC.
Lebowitz and Holberg, 1987	Chil./adol./ adult (5-25)	5.6.3 and 5.6.4	Long-term effect on children'spulmonary function.
Marks, 1988	Children (5)	5.4.3 and 5.4.4	More likely to cough or wheeze during physical exercise.
Martinez et al., 1988	Children (9)	5.7.3	Increased frequency of bronchial responsiveness and atopy in males but not females.
Masi et al., 1988	Adol./adults (15-35)	5.6.3 and 5.6.4	Exposure during lung growth period may affect males permanently.
McConnochie and Roghmann, 1986	Children (6-10)	5.4.3 and 5.4.4	Predicts wheezing only if family history is positive for respiratory allergy.
Murray and Morrison, 1989	Chil./adol. (1-17)	5.7.4	More severe asthma symptoms, especially in males.
Neuspiel et al., 1989	Inf./chil. (0-10)	5.4.3, 5.4.4, and 5.7.3	Increased incidence of post-infancy wheezy bronchitis.
Ogston et al., 1987	Infants	5.5.3 and 5.5.4	Increased incidence of alimentary and respiratory illnesses.

(continued on following page)

TABLE 5-1. (continued)

Study	Age of subjects	Section reference	Reaction to ETS exposure
Ostro, 1989	Chil./adults (0-6)/(18-65)	5.7.5	Increased respiratory restricted days in adults, and bed disability days in young children.
Park and Kim, 1986	Children (0-14)	5.4.3 and 5.4.4	Dose-response relationship observed for cough, except with family history of cough or phlegm.
Reed and Lutz, 1988	Children	5.7.1	Dose-response relationship observed.
Somerville et al., 1988	Children (5-11)	5.3, 5.4.3, 5.4.4, 5.5.3, 5.5.4, and 5.7.3	Associated with wheeze, day and night cough, and bronchitis attacks. Asthma and morning cough increased, but not statistically significant.
Stern et al., 1987	Infants (0-2)	5.4.3, 5.4.4, 5.5.3, 5.5.4, 5.6.3, 5.6.4, and 5.7.3	Increased hospitalization for chest illness; cough, phlegm and asthma more frequent.
Strachan et al., 1989	Children (7)	5.2, 5.4.4, and 5.7.1	Relation between salivary cotinine and middle ear effusion.
Teculescu et al., 1986	Adol. (10-16)	5.4.3, 5.6.3, and 5.7.2	More prevalent respiratory symptoms and upper airway infections; decreased forced expiratory flow. Effects more marked in males.
Willatt, 1986	Chil./adol. (2-15)	5.3 and 5.7.2	Associated with sore throats.

U.S. SG reports are discussed. The recent evidence largely corroborates and strengthens the support for the similar conclusions of the two reports.

5.4. RESPIRATORY SYMPTOMS

The studies on respiratory symptoms cited in the 1986 reports of the U.S. SG and the NRC are listed in Table 5-2.

5.4.1. The U.S. Surgeon General's Report on Respiratory Symptoms

Children whose parents smoke were found to have a 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The results of some of these studies may have been confounded by the child's own smoking habits (Colley et al., 1974; Bland et al., 1978; Kasuga et al., 1979). The association with parental smoking was not statistically significant for all symptoms in all studies (Lebowitz and Burrows, 1976; Schilling et al., 1977; Schenker et al., 1983). However, the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home.

Although misclassification of smoking children as nonsmokers must be considered, many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. In addition, several studies (Bland et al., 1978; Weiss et al., 1980; Charlton, 1984; Schenker et al., 1983; Dodge, 1982; Burchfiel et al., 1986) found significant effects of parental smoking after adjusting for active smoking by the children. Acute respiratory symptoms represent an immediate health burden for the child. However, the long-term significance of chronic respiratory symptoms for the health of the child is unclear.

TABLE 5-2. STUDIES ON RESPIRATORY SYMPTOMS REFERENCED IN THE U.S. SG AND NRC REPORTS of 1986

Study	Age of subjects	U.S. SG	NRC
Bland et al., 1978	Children/adol. (12-13)	X	
Bland et al., 1958	Children (12)		X
Charlton, 1984	Children/adol. (8-19)	X	
Colley, 1974	Children (6-14)	X	X
Dodge, 1982	Children (8-10)	X	X
Ekwo et al., 1983	Children (6-12)	X	
Kasuga et al., 1979	Children (6-11)	X	
Lebowitz and Burrows, 1976	Children (< 16)	X	X
Schenker et al., 1983	Children (5-14)	X	X
Schilling et al., 1977	Children/adol. (< 16)	X	X
Tager et al., 1979	Children (5-19)		X
Ware et al., 1984	Children (6-13)		X
Weiss et al., 1980	Children (5-9)	X	X

5.4.2. The National Research Council Report on Respiratory Symptoms

Almost all of the cross-sectional studies that have compared children of parents who smoke with the children of parents who do not smoke have reported increased prevalence of respiratory symptoms, usually cough, sputum, or wheezing, in the children of smoking parents. Some studies, including some that have not found a statistically significant increase in the prevalence of respiratory symptoms in ETS-exposed children, observed an increase in prevalence of respiratory symptoms as the number of household smokers increases.

Three problems related to interpretation of results are particularly relevant to studies of respiratory symptoms in children--underreported active smoking on the part of the children, recall bias leading to overreporting of symptoms by parents, and the confounding variables of infections in parents. All three may lead to overestimation of symptom prevalence among children of smokers. It has been observed that parents, especially mothers who have a history of severe respiratory illness, report higher rates of respiratory symptoms in their children (Schenker et al., 1983; Ferris et al., 1985).

Lebowitz and Burrows (1976), reporting on children in the Tucson Epidemiologic Study of Obstructive Lung Disease, emphasized the need for controlling for parental symptoms. Ferris et al. (1985) have argued, however, that correcting for parental symptoms represents an overcorrection for respiratory symptoms in children since it also corrects for the parents' smoking habits. In the Harvard Air Pollution Respiratory Health Studies (Six-Cities Study) of children ages 6 to 9 years, the variable indicating whether the parent had a history of bronchitis, emphysema, or asthma was found to be a highly significant risk factor for cough and wheeze and a history of respiratory illness among children.

In both the Lebowitz and Burrows and Ferris et al. studies, adjustment for parental symptoms or respiratory illness decreased the strength of the apparent association between exposure to ETS and respiratory symptoms but did not eliminate it. This finding leads to the

reasonable conclusion that the exposures typical of ETS are sufficient to cause respiratory symptoms in some children. The increase in frequency of cough was 20% to 50%, and as high as 90%, when there were smoking parents. The increased frequency of wheezing was more variable, which may indicate the difficulty in assessing this symptom. Furthermore, there appears to be a dose-response relationship between exposure and the likelihood of the child's developing respiratory symptoms or a respiratory illness.

5.4.3. Recent Studies on Respiratory Symptoms

Studies in Table 5-1 that address respiratory symptoms vary by objective and methodological approach. For discussion they are categorized roughly by age of the study subjects. Age is an important factor for several reasons. Susceptibility and the manifestation of symptoms may be related to duration of exposure or to developmental growth and maturation. It is also of interest to identify respiratory symptoms in infancy that may be predictive of chronic respiratory disorders or impaired lung function in later years. As noted previously, evidence of smoking in the home is more clearly differentiated between subjects in the first few years of life where there is little exposure to ETS and confounding substances outside the home. For this age group, maternal smoking has historically been more strongly related to respiratory symptoms and illnesses in early childhood than have paternal smoking or other more general measures of household exposure. This outcome is consistent with what would be anticipated if ETS exposure is causally linked to an increased incidence of symptoms.

A further reason for considering age relates to the potential sources of bias, mentioned above and discussed further in the summary and discussion to follow (Section 5.4.4.). Since smokers tend to have more respiratory symptoms than nonsmokers, it has been claimed that parents may overstate (or understate) their own children's symptoms. It seems unlikely, however, that parental perceptions of their children's health are sufficiently distorted or

influenced by their own health conditions to have a broad-based influence across numerous studies. Perhaps of greater significance is the potential for unknowingly treating active smokers as passive smokers. Children of parents who smoke are more likely to become smokers than children of nonsmokers. Consequently, subjects who smoke but are misreported as nonsmokers may be more likely to be included with those exposed to ETS at home. If a subject's own smoking contributes to respiratory symptoms, then the adverse effects of passive smoking may be overstated. As noted previously, children may become smokers as young as 10 years of age, and experimentation with cigarettes may start younger.

Of the studies examined in this report, one is on infants; four are on children of primary school age (5, 7, 5-11, and 6-10); one is on adolescents (10-16); two cover a wide age range from birth (0-14 and 0-10). Virtually all of the investigators report some adverse outcome associated with ETS exposure (except possibly Park and Kim, 1986, for ages 0 to 14). Statistical significance is not always achieved, however, and it is not always clear if the findings reported include all symptoms investigated. Nevertheless, the evidence is very substantial. If there were no effects of ETS exposure on respiratory symptoms, then the outcomes would be equally likely to produce an observed increase or decrease in relation to ETS exposure. This is clearly not the case for the published studies.

Stern and colleagues (1987) evaluated the effects of infant exposure to maternal smoking in a cohort of over 4000 Canadian schoolchildren. Cough and phlegm were more frequent symptoms in children whose mothers smoked during the child's first two years. (Cough was also more common in children whose mothers smoked during pregnancy, which is a potential confounding variable.)

Increased occurrence of cough and wheeze was commonly reported to be associated with ETS exposure in studies of children in the next higher age group (5, 7, 6-10, 5-11). Specifically, Marks (1988) conducted a multiethnic study of inner-city preschool 5-year-olds. Children living

in smoking households were more likely to experience coughing or wheezing during physical exercise, although cigarette smoke exposure did not appear to influence other respiratory symptoms. The effect of passive smoking on respiratory symptoms of children ages 5 to 11 years was investigated in over 4000 English children and nearly 800 Scottish children participating in the National Study of Health and Growth in 1982 (Somerville et al., 1988). A number of statistically significant positive associations were found between respiratory conditions, including wheeze and cough, in English children and the number of cigarettes smoked per day at home by their parents. Only wheeze was significant for Scottish children. Frequent "cough first thing in the morning" showed a positive but not statistically significant association in English children.

McConnochie and Roghmann (1986) explored the effects of passive smoking and non-breast-feeding on wheezing in children ages 6 to 10. Maternal smoking, lack of breast-feeding, and two measures of genetic tendency (family history of respiratory allergy and male sex) predicted wheezing in children with a mean age of 8.4 years. Passive smoking determined wheezing only among children whose family history was positive for respiratory allergy. The final study in this age category is by Chan and associates (1989) who found evidence that low birth weight children of age seven experience wheezing when exposed to ETS. In a comparison of 121 seven-year-old English children with a history of low birth weight (< 200 g) and an unselected reference group of schoolchildren of the same age, the investigators reviewed hospital charts at discharge after birth; administered questionnaires on family, social, and clinical history; and performed tests for lung function, bronchial reactivity, and allergies. Multiple logistic regression was used to control for socioeconomic status, neonatal oxygen scores, atopy, and family history of asthma. In the reference group, daytime (but not nocturnal) cough was weakly associated with maternal smoking but not with smoking by other household members. Maternal smoking was associated with wheeze but not cough in the low birth weight cohort.

The two studies of children in the age ranges 0-10 and 0-14 are by Neuspiel et al. (1989) and Park and Kim (1986), respectively, both of whom utilized large samples. The former studied the effect of parental smoking on wheezing in 9670 British children. Children of smoking mothers had a significantly increased cumulative incidence of post-infancy wheezing to ten years of age, but it was confined to an increase in wheezy bronchitis. (The authors note that some investigators have suggested that wheezy bronchitis is clinically and pathologically indistinguishable from asthma, so this study is referenced in Section 5.7.3. as well.) There was a 14% increase in childhood wheezy bronchitis when mothers smoked over four cigarettes per day and a 49% increase at 14 cigarettes per day after adjustment for covariables. The covariables controlled in the analysis (multiple logistic regression) include paternal smoking, social status, sex, history of family allergy, crowding, breast-feeding, gas cooking and heating, and bedroom dampness. Some of the observed effect was explainable by maternal respiratory symptoms and maternal depression, but not by neonatal problems, the child's allergic symptoms, or paternal respiratory symptoms. Passive smoking was related only to wheezy bronchitis and not to parent-reported asthma or wheezing for other reasons.

The Park and Kim (1986) survey of 3651 Korean children from 0 to 14 years of age was conducted to ascertain if coughing is related to ETS exposure. A rural area was selected for the survey where adult smokers showed a similar life-style and spent much of their time at home. The prevalence and frequency of coughing was found to increase with the number of adult household smokers and with the number of cigarettes smoked in an analysis unadjusted for covariables. Smoking by children is unlikely to be a confounding factor as smoking is seldom seen in children below 15 years of age in Korea. Data on 21 extraneous variables were collected in the study. When included in an adjusted statistical analysis, the presence of coughers in the family was found to be an explanatory variable of some importance. The association of ETS exposure with increased coughing may be due to the indirect effect of family smoking through

coughers in the family, or a direct consequence of exposure to ETS. The mechanism by which adult household smoking is related to increased coughing in children was not investigated.

Teculescu et al. (1986, in French) conducted a relatively small study that compared 46 nonsmoking children ages 10 to 16 years whose parents smoke with an identical number of children matched for sex, age, and height whose parents were nonsmokers. Passive exposure to parental tobacco smoke was associated with a higher prevalence of respiratory symptoms.

5.4.4. Summary and Discussion of Respiratory Symptoms

Studies on the relationship of ETS exposure and respiratory symptoms appearing subsequent to the U.S. SG and NRC reports of 1986 provide additional support to those reports' conclusions. Increased cough has been observed in a range of ages, including 0 to 2, 5 to 11 and 0 to 14 (Stern et al., 1987; Somerville et al., 1988; and Park and Kim, 1986, respectively). The last reference, however, found that the substantial dose-response observed could be largely (but not totally) explained by a family history of cough or phlegm. Similarly, McConnochie and Roghmann (1986) found that ETS exposure predicts wheezing only in families with a history of respiratory allergy. The cumulative incidence of post-infancy wheezy bronchitis through 10 years of age increased with the amount mothers smoked, in the large study by Neuspiel et al. (1989). They found that some of the effects could be explained by maternal respiratory symptoms. These results are consistent with the explanatory effect of parental symptoms found in the studies by Lebowitz and Burrows (1976) and Ferris et al. (1985) (Section 5.4.2). A weak association of wheezing was reported in seven-year-olds of low birth weight (Chan et al., 1989). Marks (1988) observed increased wheezing and coughing in exposed children of age five following physical exercise.

Family history of respiratory symptoms and disease appears to be a confounding variable for the interpretation of data. As noted in the remarks from the NRC report (Section 5.4.2),

bias may be introduced by parents who have a history of respiratory illness for several reasons. They may be overstating their children's symptoms, or their children may actually have more respiratory symptoms and illness. The latter possibility could be the result of intra-family correlation of susceptibility (referred to as familial resemblance in Kauffmann et al., 1989) or may be attributable to contagion between members of the same household. The conclusion is simply that family history has been shown to be a confounding variable in some studies showing an association of respiratory symptoms in children with parental smoking. This means that family history, as well as any other factors correlated with parental smoking, is a candidate for causally contributing to the occurrence of respiratory symptoms in children. When data have been collected on family history one has the option of attempting to adjust for its effect statistically. How meaningful the results are, however, depends on how confounded family history is with parental smoking. Correlation between family history (as reported in the data, whether biased or not) and household exposure to ETS will tend to lead to an understatement of the statistical significance of ETS after adjustment for family history and conversely, regardless of which (if either) is causally related to the observed increase in respiratory symptoms. This difficulty has been noted in the literature (Section 5.4.2.).

Some additional precautions to those already discussed are in order. Controlling for active smoking becomes an issue for subjects at about age ten (some evidence suggests seven or eight years of age) depending on the culture, even though it may be light smoking. Most researchers have been aware of the potential confounding effect of smoking and have attempted to control for it. Some studies have excluded persons who smoke, and others have made them a separate group for comparison. A greater difficulty probably lies in the potential for misreported smoking habits. Young persons may be reluctant to admit to smoking cigarettes, especially if they have been experiencing respiratory maladies. Data are often obtained from parents, who may not be aware of a child's smoking. Future studies may include cotinine tests

to confirm the reported smoking status (as in Strachan et al., 1989). Of course, misreported smoking status would not explain the observed relationship between ETS exposure and respiratory symptoms in infants and children up to the middle years of primary school.

In conclusion, there is no apparent single source of systematic bias that might explain the substantial evidence accumulating across the multiple age groups, investigative approaches, and environmental and cultural conditions studied. Family history may cause overstatement of conclusions when it is not taken into account in the analysis of data, but it may only indicate that ETS is related to increased respiratory symptoms indirectly, or both directly and indirectly. It is reasonable to conclude that parental smoking increases the incidence of respiratory symptoms from infancy well into primary school years and probably through the adolescent years. Misreported smoking status may have some influence in studies of older children. Results in the higher age group, however, are not inconsistent with findings at other ages. In addition to the unlikelihood that bias significantly distorts the overall results, several other factors are supportive: (1) evidence that maternal smoking tends to be more of a factor than paternal smoking in the first one to two years of life; (2) an observed dose-response function in numerous cases; and (3) the biological plausibility given the increased incidence of respiratory symptoms in adult smokers.

5.5. ACUTE RESPIRATORY ILLNESS

References to the evidence on acute respiratory illness in the reports of the U.S. SG and the NRC of 1986 may be found in Table 5-3. As in Section 5, conclusions of the U.S. SG and NRC reports are summarized, subsequent evidence is addressed, and the overall implications for exposure to ETS are assessed in a summary and discussion section.

TABLE 5-3. STUDIES ON RESPIRATORY ILLNESS REFERENCED IN THE U.S. SG AND NRC REPORTS OF 1986

Study	Age of subjects	U.S. SG	NRC
Cameron et al., 1969	Children (6-9)	X	
Colley, 1971	Infants	X	
Colley, 1974	Infants		X
Dutau et al., 1981	Infants/children (0-6)		X
Fergusson et al., 1981	Infants	X	X
Harlap and Davies, 1974	Infants	X	X
Leeder et al., 1976b (also see Colley, 1974, and Leeder et al., 1976a)	Infants	X	X
Pedreira, 1985	Infants	X	X
Pullen and Hey, 1982	Children	X	
Rantakallio, 1978	Infants/children (0-5)	X	X
Said et al., 1978	Children/adol. (10-20)	X	X
Sims et al., 1978	Children	X	
Speizer et al., 1980	Children (6-10)	X	X
Ware et al., 1984	Children (5-9)	X	

5.5.1. The U.S. Surgeon General's Report on Acute Respiratory Illness

The results of these studies show excess acute respiratory illness in the children of parents who smoke, particularly in children under two years of age. This pattern is evident in studies conducted with different methodologies and in different locales. The increased risk of hospitalization for severe bronchitis or pneumonia associated with parental smoking ranges from 20% to 40% during the first year of life. Young children appear to represent a more susceptible population for the adverse effects of involuntary smoking than older children or adults. The time-activity patterns of infants, which generally place them in proximity to their mothers, may lead to particularly high exposure to ETS if the mother smokes.

The possibility of bias due to the respiratory status of the reporting parent(s) must be considered for the studies that have used questionnaires to measure illness experience. In all studies in which potential reporting bias was examined, control for parents' status reduced, but did not eliminate, associations of involuntary smoking with health outcomes (Colley et al., 1974; Leeder et al., 1976a,b; Schenker et al., 1983; Ware et al., 1984). Further, the consistency of these studies, in spite of differing study populations and methods, weighs against bias as the sole explanation. Acute respiratory illnesses during childhood may have long-term effects on lung growth and development. It may possibly increase the susceptibility of the lung to the effects of active smoking and to the development of chronic obstructive lung disease (Samet et al., 1983; U.S. DHHS, 1984).

5.5.2. The National Research Council Report on Acute Respiratory Illness

There is now strong evidence that bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur more frequently (at least during the first year of life) in children who have one or more parents who smoke. Bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur up to twice as often during the first year of life in children who have one or more parents

who smoke than in children of nonsmokers. All the studies that have examined the incidence of respiratory illnesses in children under the age of one year have shown a positive association between such illnesses and exposure to ETS. There is a dose-response relationship that relates more to maternal smoking than to paternal smoking as the source of ETS exposure.

The association between ETS exposure and increased occurrence of respiratory illnesses in children is very unlikely to have arisen by chance. It may represent a direct association between ETS exposure and disease (a causal explanation) and/or an indirect one (noncausal) arising because children living in homes of smokers are at risk of such diseases for other reasons. Some of the studies have examined the possibility that the association is indirect by allowing for confounding factors--such as social class, parental respiratory illnesses, and birth weight--and have concluded that such factors do not explain the results. This argues, therefore, in favor of the causal explanation. Such an explanation is also supported by the evidence of a dose-response relationship specific for respiratory disease. Regardless of the mechanism, however, the exposure of small children to smoking in the home appears to put them at risk of respiratory illness.

5.5.3. Recent Studies on Acute Respiratory Illness

Four of the studies that have appeared subsequent to the U.S. SG and NRC reports deal with the potential relationship between exposure to ETS and lower-respiratory-tract illness (excluding the study on asthmatics for now and counting Chen, 1989 and Chen et al., 1988 as one study). All four reports indicate an association between ETS and increased respiratory illness, although the approaches and health-related endpoints are varied. Three studies pertain to infants. The remaining one applies to the age range 5-11.

Chen and his colleagues (1988) investigated the relationship between passive smoke exposure and hospitalization for bronchitis and pneumonia by 18 months of age in a study of

2227 Chinese children. The results indicated a significant dose-response relationship of household smoking to hospitalization for respiratory illness during the child's first 18 months. No confounding variables were discovered. Further analyses indicated that infants who were less than six months of age, had low birth weight, or were artificially fed were relatively more susceptible to the effects of tobacco smoke. Moreover, the cumulative incidence of bronchitis and pneumonia increased significantly with increased smoking of family members. This result persisted when sex, birth weight, nursery care, father's education, coal for cooking, and cases of adult chronic respiratory disease were taken into account. An interesting and important aspect of this study is that of 1746 smoking families, there were no mothers who smoked. Presuming that the reporting of smoking habits is accurate, or nearly so, smoking during pregnancy is unlikely to confound postnatal exposure to ETS. In a later publication based on the sample described above, Chen (1989) reported that among artificially fed infants the frequency of hospitalization for respiratory illness was 2.5 times greater when more than 20 cig./day were consumed in the home. The frequency dropped to 1.7 times greater if 1 to 19 cig./day were consumed. Chen also concluded that passive smoking and artificial feeding work synergistically, producing a detrimental effect much greater than that produced by their separate actions. Thus, infants may be at greater risk from ETS exposure if bottle fed.

Further evidence of a relationship between passive smoking and respiratory illness in the child's first year is provided by Ogston et al. (1987). These investigators conducted a prospective study of 1565 infants involved in the Tayside Morbidity and Mortality Study. Health visitors interviewed parents to gather data on social class, age of parents, method of heating and cooking, father's and mother's smoking habits, and the presence of upper- or lower-respiratory-tract infections (later confirmed by medical diagnosis). Parents were classified simply as smokers or nonsmokers. Multiple logistic regression indicated that respiratory illness during the first year of life was predicted by parental smoking. Moreover, a trend indicated increasing

incidence from (a) nonsmoking families to (b) only father smoking, to (c) mother or both parents smoking.

A cohort study of 4099 Canadian children, 7 to 12 years of age, corroborates the findings described above. Stern and associates (1987) found that children whose mothers smoked during the first two years of their life were significantly more likely to have been hospitalized at least once before the age of two years for a respiratory illness than children of nonsmoking mothers. Moreover, ETS-exposed children hospitalized in their first two years of life were six times more likely to be hospitalized for chest illness than unexposed children. Similar results were reported for children whose mothers smoked during pregnancy, however, so in utero and postnatal exposure to products of tobacco smoke may be partially confounded.

A study demonstrating a dose-response relationship between passive smoking and respiratory illness in children 5 to 11 years old was conducted by Somerville and associates (1988). The sample consisted of 4000 English and 800 Scottish children from the National Study of Health and Growth. Data on each child's respiratory symptoms, parental smoking, and family background were obtained from a self-administered questionnaire completed by the mother. Passive smoking was assessed by the total number of cigarettes smoked each day by the mother and the father. Multiple regression analysis indicated that the number of cigarettes smoked by English parents was significantly associated with bronchitis attacks within the last two months. Neither household crowding, parents' education, father's occupation, nor age or sex of the child confounded this result.

5.5.4. Summary and Discussion on Respiratory Illness

As in the discussion of respiratory symptoms (Section 5.4), the respiratory status of parents is a factor to be considered in interpreting the results on respiratory illness. As the U.S. SG report notes, there is the possibility of biased reporting from parents who smoke and may be

more subject to respiratory ailments than normal. All of the studies reviewed used questionnaires or interviews. The questions dealing with respiratory illness tend to be rather specific, requiring little subjective judgment. For example, the number of hospitalizations for respiratory or chest illness during the first year or two of life, and the number of doctor-diagnosed cases, were indexes of health (Chen et al., 1988; Chen, 1989; and Stern, 1987). Ogston et al. (1987) confirmed reports of respiratory infections by medical diagnosis. Consequently, the potential for biased reporting from parents who smoke may be less of an issue for evaluation of respiratory illness than for respiratory symptoms.

The consistent association between respiratory illness and ETS exposure in the home over all studies to date, especially in studies of infants, is unlikely to be attributable to a confounding factor. Such a factor would have to be consistently operative over the broad spectrum of countries, cultures, and age groups studied and of substantial influence on respiratory health. Most researchers have attempted to control for potential confounding factors, although only one study has controlled for in utero exposure (Chen et al., 1988). The dose-response relationships, reported in recent studies (Chen et al., 1988; Somerville et al., 1988; Ogston et al., 1987) and in previous evidence assessed by the NRC and U.S. SG committees, are consistent with a causal association; a plausible explanation in terms of systematic bias or a confounding factor is less apparent. These arguments and the biological plausibility that ETS exposure increases the incidence of lower-respiratory-tract illnesses in the first one-to-two years of life provides some support for a causal relationship. The influence of potential sources of bias and confounding factors, however, cannot be adequately assessed to conclude a causal association between ETS exposure and the increased incidence of respiratory illnesses in young children. The consistency of the conclusions across the cumulative recent and previous studies, however, cannot be statistically attributed to chance occurrence; it is only the explanation behind the association that is uncertain.

The implications of early childhood respiratory illnesses for health in later years is an important related issue that is difficult to study. Stern et al. (1987) concluded that the strong relationship between hospitalization before the age of two years for a chest illness and subsequent respiratory symptoms and decreased pulmonary function later in childhood suggests that there are definite carryover effects of early acute respiratory illness. In a study not directly related to passive smoking, Barker and Osmond (1986) found a strong geographical relation between death rates from chronic bronchitis and emphysema in 1959 to 1978 and infant mortality from bronchitis and pneumonia during 1921 to 1925 for regions in England and Wales. The authors concluded that this relation provides strong evidence of a direct causal link between lower respiratory infection in early childhood and chronic bronchitis in adult life. Although these studies contribute some evidence of the potential for long-term effects from childhood exposure, further support is needed for a conclusion. Long-term implications have been expressed as a major concern by numerous authors. Chronic respiratory ailment or permanently impaired lung function has largely been speculated from the results of multiple studies over various age groups. No major longitudinal study following subjects from infancy through adolescence has been conducted.

5.6. PULMONARY FUNCTION

Studies on pulmonary function referenced in the 1986 reports of the U.S. SG and the NRC are displayed in Table 5-4. Conclusions of the U.S. SG and NRC reports are summarized, and studies appearing since the U.S. SG and NRC reports are reviewed. The current state of evidence on the potential association of ETS exposure with pulmonary function are summarized and discussed.

TABLE 5-4. STUDIES ON PULMONARY FUNCTION REFERENCED IN THE U.S. SG AND NRC REPORTS OF 1986

Study	Age of subjects	U.S. SG	NRC
Berkey et al., 1986	Children (6-10)	X	X
Brunekreef et al., 1985	Adults	X	
Burchfiel et al., 1986	Infants/children (0-10)	X	
Chen and Li, 1986	Children/adol. (8-16)	X	X
Comstock et al., 1981	Adults	X	
Dodge, 1982	Children (8-10)	X	X
Ekwo et al., 1982	Children (6-12)	X	
Ferris et al., 1985	Children/adol.		X
Hasselblad et al., 1981	Children (5-13)	X	X
Kauffmann et al., 1983	Adults	X	
Kentner et al., 1984	Adults	X	
Lebowitz, 1984	Families	X	
Lebowitz and Burrows, 1976	Children/adol. (< 16)	X	X
Pimm et al., 1978	Adults	X	
Schilling et al., 1977	Children/adol. (< 16)	X	X
Shepard et al., 1979	Adults	X	

(continued on following page)

TABLE 5-4. (continued)

Study	Age of subjects	U.S. SG	NRC
Sims et al., 1978	Children	X	
Tager et al., 1979	Children (5-19)		X
Tager, 1983	Children (5-9)	X	X
Tashkin	Children	X	
Vedal et al., 1984	Children (6-13)	X	
Ware et al., 1984	Children (6-13)		X
Weiss et al., 1980	Children (5-9)	X	X
White and Froeb, 1980	Adults	X	

5.6.1. The U.S. Surgeon General's Report on Pulmonary Function

Cross-sectional studies have demonstrated lower values on tests of pulmonary function (FEV 75%, FEV_1, FEF_{25-75}, and flows at low lung volumes) in children of mothers who smoked compared with children of nonsmoking mothers. Longitudinal studies confirm the cross-sectional results and provide some insight into the implications of the cross-sectional data. Dose-response relationships have been found in both cross-sectional and longitudinal studies (Tager et al., 1979; Weiss et al., 1980; Ware et al., 1984; Berkey et al., 1986); the level of function decreases with an increasing number of smokers in the home. As would be anticipated from the mother's greater contact time with the child, maternal smoking tends to have a greater impact than paternal smoking. Younger children seem to experience greater effects than older children (Tager et al., 1979; Weiss et al., 1980), and in older children the effects of personal

smoking may be additive with those of involuntary smoking (Tager et al., 1979, 1985). Some studies have reported greater effects on flows at lower lung volumes in girls than in boys (Burchfiel et al., 1986; Tashkin et al., 1984; Yarnell and St. Leger, 1979; Vedal et al., 1984). Flows at higher lung volumes seem to be more affected in boys (Burchfiel et al., 1986; Yarnell and St. Leger 1979; Berkey et al., 1986; Tashkin et al., 1984). It is unclear whether these sex effects represent differences in exposure, differences in susceptibility to environmental cigarette smoke, or differences in growth and development. The observed reduction in lung function of children associated with maternal smoking is small, on the average. Some children may be affected to a greater extent, however, and even small differences may be important for children who become active smokers in adulthood.

5.6.2. The National Research Council's Report on Pulmonary Function

It is often difficult (but not impossible) to measure lung function in young children, and it is also hard to dissect out the relative contribution of ETS and that of natural variation and the effect of respiratory infections to pulmonary damage. The most important contributors to variation in lung function among children are size-related factors such as sex, age, and height. These account for about 50% to 60% of the variation (Comroe et al., 1962). Nevertheless, a majority of the studies has shown a small decrease (up to 0.5% of FEV_1 per year) in rate of increase in lung function associated with normal growth in children living with one or more parents who smoke compared with those living with nonsmoking parents. These differences have usually been statistically significant. Although the mean effect is small, there are individuals in each study who have large decrements in growth of lung function. Some studies have found a dose-response relationship with the number of smokers in the home or the amount smoked (Hasselblad et al., 1981). In most studies, only the maternal effect was statistically significant. It is not possible to determine whether ETS is directly causing the decreased lung

function observed in children of smoking parents or if an increased infection rate in these children is responsible for the decrease.

The annual small decrease in FEV_1, which is related to exposure to ETS, is unlikely to be clinically significant. However, the effect may be important in two respects. First, the existence of statistically significant differences related to parental smoking leads to the conclusion that there are pathophysiologic effects of exposure to ETS in the lungs of the growing child. It may be an in utero effect, an effect on the growing and remodeling of the lung, or both. Second, it raises the question of whether the child who is adversely affected by parental smoking may be at increased risk for the development of chronic airflow obstruction in adult life. An accelerated decline in lung function could increase the risk of chronic pulmonary disease (Samet et al., 1983). An important unanswered question is whether exposure to ETS affects the way the lungs grow and develop during childhood.

5.6.3. Recent Studies on Pulmonary Function

Kauffmann et al. (1989) asked what factors related to lung function may be correlated between parents and their offspring between 6 and 10 years of age. A total of 1160 children were included in the study whose parents had been examined in the 1975 French PAARC Cooperative Study. Positive correlations between parent and child of FVC, FEV_1, and FEF_{25-75} were observed and exhibited an increasing temporal trend with increasing age of the children. Comparisons between siblings of the opposite sex suggest that different growth patterns between boys and girls may be a factor in lung function. Maternal, but not paternal, smoking was associated with a significant decrease in FEV_1 and FEF_{25-75}, but not with FVC.

Masi et al. (1988) suggest that passive smoking during the growth period of the lungs in early life permanently affects their mechanical properties in young men. They collected mail-in questionnaire data on lifetime exposure to ETS. The exposure estimates were compared with

pulmonary data previously collected as part of a cross-sectional study of the evaluation of lung function from adolescence to early adulthood. FEF_{25-75} was inversely related to ETS exposure estimates before age 17 in males, but not in females.

A longitudinal study of pulmonary function between the ages of 5 and 25 supports the hypothesis that childhood respiratory illnesses have implications for pulmonary development (Lebowitz and Holberg, 1987; also, Lebowitz et al., 1987). A total of 1502 observations were made between 1972 and 1983 on 362 subjects 6 to 15 years of age when initially tested. Follow-up averaged about 9 years. Measures of pulmonary function included FVC, FEV_1, flow at 50% of FVC($\dot{V}_{max}$ 50%), and flow at 75% of expired FVC($\dot{V}_{max}$ 75%). The study includes active smokers as well as nonsmokers, which complicates analysis and interpretation of the data. The statistical models assumed describe the data well, but the technical details are sketchy. The authors conclude that respiratory illnesses and smoking had the biggest negative impact on growth of lung function, using FVC, FEV_1, $\dot{V}_{max}$ 50%, and size-compensated flows ($\dot{V}_{max}$ 50%/FVC). Further negative impacts were due to parental smoking, especially as it interacts with active smoking and respiratory disease. Measures of flow ($\dot{V}_{max}$ 50%, $\dot{V}_{max}$ 50%/FVC) were more sensitive than FEV_1 to the effects of concurrent disease and smoking and were better indicators of a long-term effect persisting into early adulthood.

Stern and colleagues (Section 5.4.3.) found a statistically significant 0.7% decrement in FEV_1 associated with maternal smoking during the first two years of life, but no effect on FVC was observed. The small study by Teculescu and others (Section 5.4.3.) also reported a significant decrease in forced expiratory flows, with effects more marked in boys. The single-breath nitrogen washout test, a sensitive test of small airways obstruction in adults, did not detect any effect of passive smoking in this limited sample (46 nonsmokers of ages 10 to 16 whose parents were smokers).

5.6.4. Summary and Discussion of Pulmonary Function

The NRC report has previously noted the difficulties in measuring lung function in small children and then sorting out the effect attributable to ETS exposure. Height, age, and sex are factors to control in tests of pulmonary function. Factors related to familial resemblance (Kauffmann et al., 1989), such as parental smoking and lung function, temporal trends in parent-child correlations as a child's age increases, and different growth patterns between boys and girls are further complicating factors. The evidence suggests that any effect of passive smoking on lung function is likely small. In view of these conditions, it is not surprising that study results have been somewhat mixed and difficult to assess overall.

If a health effect is associated with ETS, it is generally more apt to be observed if the differential exposure to ETS between study subjects being compared is large than if it is small. This is particularly true when factors affecting the variability of study data are poorly controlled and difficult to assess. This observation may be particularly relevant for studies of pulmonary function, as illustrated by comparative analyses of two major longitudinal studies. Lebowitz and Holberg (1988) and Tager et al. (1987) both reanalyzed the longitudinal data from the East Boston Study and the Tucson Study. The former study found an effect of maternal smoking on FEV_1 and the latter did not. Both reviews concluded that the disparate results were not attributable to the different methods of analysis originally used. The difference in ETS exposure between the "exposed" and "unexposed" groups appears likely to be much larger in one study than in the other, attributed (at least in part) to the differences in climate (which affects the amount of ventilation from outdoor air).

Differences between studies that affect exposure levels and the influence of host-related variables affecting measured responses that cannot be fully controlled make it difficult to assess the overall evidence from studies on pulmonary function. In reviewing previous studies, Tager (1986) notes that some consistency emerges if one focuses on FEV_1 and FEF_{25-75}. The recent

study of Kauffmann et al. (1989) found that maternal smoking was related to FEV_1 and FEF_{25-75} but not to FVC, consistent with Tager's observation. Two other conclusions that appear frequently in the cumulative studies on lung function are the greater susceptibility of boys and the significance of age in subjects up to adulthood.

Recent studies provide additional information on the question of whether childhood exposure to ETS has implications for long-term effects in lung function. As noted by the NRC, it is not possible to determine whether ETS is directly causing the decreased lung function observed in children of smoking parents or if an increased infection rate in these children is responsible for the decrease. Epidemiologic data of Paoletti et al. (1989) support the hypothesis that childhood history of respiratory infection (prior to age 12) and adolescent-adult history are related to increased prevalence of a number of detrimental health conditions in adulthood, including reduced lung function and chronic obstructive lung disease (independent of whether parental smoking is implicated in the childhood history of respiratory illness). Stern et al. (1987) conclude that the strong relationship between hospitalization before the age of two years for a chest illness and subsequent respiratory symptoms and decreased pulmonary function later in childhood suggests that there are definite carryover effects of early acute respiratory illness. The longitudinal study of Lebowitz and Holberg (1987) links early respiratory disorders with long-term pulmonary effects, specifically in the small airways. The study of Masi et al. (1988) suggests a permanent affect in young men (but not women). If passive smoking in childhood is causally associated with respiratory illness (only "association", not "causal association", is concluded in this report), then these studies support the hypothesis of a long-term effect on lung function.

Based on the cumulative evidence available, this report concludes that passive smoking in early childhood is associated with decreased lung function in childhood and with a small reduction in their rate of pulmonary growth and development.

5.7. RELATED RESULTS

A number of studies have investigated the potential for health hazards to children from parental smoking that have not been described under the sections on respiratory symptoms, respiratory illness, or pulmonary function. In most cases there is less evidence on these health related endpoints, but that does not imply that they are necessarily less important--just less thoroughly studied at this time. Some of these studies and their topics of inquiry are summarized in this section. This report concludes that household smoking is associated with excess incidence of middle ear effusion (Section 5.7.1.), but no further conclusions are drawn from the study results described. There is increasing evidence that maternal smoking may be associated with increased prevalence of asthma, particularly before the age of one year. Potential bias in parent-reported data and confounding by in utero exposure, however, are difficult to assess. Based on the overall statistical evidence, it appears unlikely that maternal smoking has a very large effect on asthmatic conditions in children. No conclusions are warranted, however, as study results have been inconsistent and ambiguities complicate comparisons.

5.7.1. Middle Ear Effusion

The U.S. SG report includes reviews of five studies that demonstrate an excess of chronic middle ear disease (including middle ear effusion, a sign of chronic middle ear disease) in children exposed to parental cigarette smoke. A causal mechanism is unknown, however, and potential confounding factors may be important. The long-term implications of excess middle ear disorders need further study. The U.S. SG and NRC reports are similar on this topic; neither draws a firm conclusion.

Additional study data subsequent to these two reports adds to the weight of evidence. In particular, a dose-response relationship is reported by Reed and Lutz; Strachan and coworkers

have shown a relationship with salivary cotinine concentrations. Based on the cumulative evidence, this report concludes that parental smoking is associated with increased incidence of middle ear effusion. Recent studies are described below.

Reed and Lutz (1988) evaluated the association between middle ear effusion and household smoke exposure in children seen in an outpatient office. They reported an increasing percentage of middle ear effusion in children with progressive levels of smoke exposure. Strachan and colleagues (1989) assayed saliva of 7-year-olds for cotinine concentrations (apparently the first study to use biochemical data to evaluate exposure to ETS in primary schoolchildren). They concluded that about one-third of the cases of middle ear effusion were statistically attributable to exposure to tobacco smoke. By contrast, Kallail et al. (1987) found that exposure to cigarette smoke apparently was not a risk factor for middle ear problems in a survey of primary schoolchildren. The discrepancy in conclusions is possibly attributable to study differences. Kallail and colleagues grouped children according to outcomes on a school's hearing test. All members of the experimental group were diagnosed by a physician as manifesting a middle ear problem. By contrast, Reed and Lutz (1988) and Strachan et al. (1989) both addressed a specific middle ear problem (effusion) as indicated by abnormal tympanograms.

The association of passive smoking with middle ear effusion is further supported by Hinton (1989), who conducted a study to ascertain whether there is any relationship between parental smoking and various factors in children undergoing surgery for otitis media with effusion. That study included 115 children of ages 1 to 12 years who were admitted for grommet insertion. The admission rate for grommet insertion was statistically higher for children with at least one parent who smokes.

5.7.2. Acute upper-respiratory-tract illness

Risk factors for acute upper-respiratory-tract disease in childhood were evaluated in a population-based sample of the Atlanta metropolitan area by Fleming and colleagues (1987). Mothers of children less than 5 years of age were questioned about upper-respiratory-tract infection and ear infection occurring in their children during the preceding two weeks. Maternal smoking was a risk factor for a child's having upper-respiratory-tract infection (odds ratio = 1.7, $p = 0.01$). The small study by Teculescu and colleagues (Section 5.4.3.) found that children of parents who smoke had more frequent upper airway infections.

A study by Willatt (1986) found that sore throats were predicted by maternal passive smoking in children of ages 2 to 15 years. A regression model indicated a dose-response relationship between sore throats and the number of cigarettes the mother smoked. The author noted that active smoking in the older children could not account for these results since the relationship between sore throats and smoke exposure was strongest for children under the median age of 6.9 years. As the author also observes, few studies have looked at the effects of passive smoking on children's upper respiratory tract.

5.7.3. Asthma

The two central issues related to ETS and asthma in children are whether parental smoking increases the prevalence of asthma cases and whether passive smoking exacerbates conditions in asthmatic children. The populations differ with regard to these two questions so the first issue is discussed in this section and the other one is addressed in the next section.

The U.S. SG report found no consistent relationship between the report of a doctor's diagnosis of asthma and exposure to ETS. It noted that the variability in results may reflect differing ages of the children studied, differing exposures, or uncontrolled bias. Recent studies

offer some additional evidence suggesting increased prevalence of asthma in children with smoking parents, but the cumulative evidence remains inconclusive.

Stern and coworkers (1987) found that asthma is more prevalent before the age of two in smoking households. Somerville and colleagues (1988) reported increased asthma attacks and morning cough in children 5 to 11 years old, but the results were not statistically significant. Chen et al. (1988) found that asthma was reported more frequently for children in smoking families, but the increase was not statistically significant.

A very recent article by Weitzman et al. (1990) reports significant increase in childhood asthma with maternal smoking. Data from the Child Health Supplement to the 1981 National Health Interview Survey were analyzed with information about 4331 children aged 0 to 5 years to study the relationship between maternal smoking. It was found that maternal cigarette smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease, independent of a number of potentially confounding variables. Children whose mothers smoke one-half pack or more per day are twice as likely to have asthma and are four times as likely to use asthma medications as children of mothers who do not smoke. The authors caution that all information in the study is based on parents' reports (which may be a source of bias as discussed previously).

A study relating bronchial responsiveness in parental smoking was conducted by Martinez and colleagues (1988). Questionnaires were administered to parents of 172 Italian children 9 years old regarding parental smoking habits, the child's and family's history of respiratory illness and symptoms, the number of persons living in the house, the number of rooms in the house, and the type of heat. Skin prick tests and a flow-volume spirometric test were also administered. Male children with smoking parents had a statistically significant increase in bronchial responsiveness (BR) when compared to those whose parents did not smoke (odds ratio, OR = 4.3). No significant increase in BR was found in female children of smoking

parents (OR = 0.5). The relationship between BR in children and smoking in parents was stronger in asthmatics (p = 0.02) and remained significant after controlling for asthma and atopy. BR was significantly correlated with atopy. This was also true for nonasthmatic children and for both males and females separately. Male children of smoking parents had increased reactivity to allergens as assessed by the skin prick test index (p = 0.001). It was hypothesized that passive smoking, by increasing the frequency of BR and of atopy, may increase the risk of asthma in childhood, particularly in boys.

The following study by Geller-Bernstein et al. (1987) is included in this section on asthma because, as the authors discuss, atopic children with post-infancy wheezing often suffer from asthma throughout childhood. The authors recorded the clinical course and sequential IgE values in a 4-year prospective study of 80 atopic wheezing children between the ages of 6 months and 5 years. Although there was no correlation between increase of IgE levels and type of feeding or exposure to cigarette smoke, statistical data confirmed that bottle feeding and parental smoking lead to persistent wheezing in atopic children.

Neuspiel et al. (Section 5.4.3.) found no evidence of increased prevalence of asthma in children of mothers who smoke, but did find a significant increase in wheezy bronchitis in those children up to 10 years of age.

5.7.4. Symptoms in Asthmatics

The U.S. SG and NRC found some evidence that ETS exposure may increase the frequency or severity of attacks of bronchoconstriction in asthmatic children, but results have been inconsistent and difficult to compare. The stability and the mechanisms of bronchoconstriction differ among asthmatics and study populations have not always been fully characterized. The NRC notes several unresolved issues. For instance, what proportion of a clearly defined population of asthmatics do react to ETS? If the patients are selected according

to methylcholine or histamine responsiveness, criteria should be given for the extent of responsiveness since it is a continuum. These issues remain unresolved, although recent studies contribute additional results to the accumulating evidence on this general topic.

Murray and Morrison (1989) reported in a previous article (1986) that asthmatic children with mothers who smoke have substantially reduced lung function compared to those whose mothers do not smoke. Their current study of 415 nonsmoking asthmatic children found that asthma symptoms (based on an asthma score) were more severe if the mother smoked, with boys apparently more affected than girls. Compared to boys with nonsmoking mothers, there was also a significant decrease in FEV_1, FEF_{25-75}, and PC_{20} in boys with mothers who smoke. Maternal smoking was not significant for lung function tests in girls. When analyzed by age categories, 1 to 6, 7 to 11, and 12 to 17, an age effect became apparent. In the youngest category, there was no significant effect of maternal smoking nor any indications of asthma severity. In the intermediate age category, there was a significant difference in asthma severity (as measured by an asthma score) but not in FVC, FEV_1, FEF_{25-75}, or PC_{20}. In the oldest category, however, maternal smoking was significant for all but FVC. These results are in contrast to those for asthmatics with nonsmoking mothers where lung function improved significantly with age.

Evans and colleagues (1987) evaluated 276 asthmatic children for association of ETS exposure with frequency of emergency room visits, hospitalizations, and impaired pulmonary function. Although a strong association was found for emergency room visits, no association of passive smoking was detected for hospitalizations or abnormalities of pulmonary function (FEV_1, FEF_{25-75}, and PEFR). The analysis of data from the National Health Interview Survey by Weitzman et al. (Section 5.7.3.) found no relationship between maternal smoking and hospitalizations of asthmatic children up to five years of age.

5.7.5. Non-Specific Ailments

Ostro (1988) reviewed five years of data from the annual Health Interview Survey (conducted by the National Center for Health Statistics) and found that the number of bed disability days for children of age 0 to 6 years is 20% higher in households with a pack-a-day smoker. A similar result was obtained for adult nonsmokers with a spouse who smokes. (The author notes that the use of disability days in bed as an indicator of acute morbidity is not a strict measure of respiratory impairment.)

Charlton and Blair (1989) found that children's absence from school for minor ailments (e.g., colds, flu, tonsillitis) could be predicted on the basis of their own and their parents' smoking habits four months earlier. The sample consisted of 2885 English children, 12 to 13 years old. Passive smoke exposure was defined as neither parent smoked, only the father smoked, only the mother smoked, or both parents smoked. Logistic regression indicated that whatever the children's smoking habits, the proportion who were absent was higher when both parents or at least the mother smoked. For children who never smoked the proportions absent were 17% if neither parent or only the father smoked vs. 21% if both parents or only the mother smoked. When children smoked "regularly," the proportion absent was 37% if neither parent smoked vs. 46% if both or only the mother smoked. Sex and social background had little effect. Although the authors relate absenteeism to ETS exposure, the evidence for a causal relationship is not apparent.

APPENDIX A

SUMMARY DESCRIPTIONS OF ELEVEN CASE-CONTROL STUDIES

BROW. The case-control study of risk factors for adenocarcinoma by Brownson et al. (1987) includes 23 never-smoker cases (19 females) among the 102 cases interviewed. All subjects were white, had microscopically confirmed cancers incident from 1979 to 1982, and were identified through the Colorado Central Cancer Registry which covers the five county Denver metropolitan area. In the study as a whole, interviewed cases represented 68.5% of the 149 cases meeting eligibility criteria. Controls were chosen from persons with cancer at sites unassociated with cigarette smoking and were matched to the cases on age and sex. Of the 169 eligible controls, 131 (77.5%) were interviewed. Sixty-nine percent of the cases and 39% of the controls required surrogate respondents.

Passive smoke exposure was analyzed both as a dichotomous variable based on the smoking status of the spouse and as a stratified variable based on the hours per day that the subject was in the presence of persons smoking. Other variables pertain to previous smoking, education, income, occupation, and residence history as an indirect measure of exposure to total suspended particulates.

The relative risk for adenocarcinoma among female never-smokers exposed four or more hours per day relative to a lower exposure was 1.68 (95% C.I. = 0.39 - 2.97) after adjustment for age, income, and occupation. Similar nonsignificant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. The high proportion of surrogate source data led the authors to conduct parallel analyses limited to self-reported data. Results from those analyses were described as highly comparable and indicated possibly higher risks than those reported for all respondents.

Note: The number (19 female cases) of never-smokers in this study is much too small to make even a large observed odds ratio (1.68) statistically significant. Further, combining ever-smokers and never-smokers (possibly to increase the sample size) makes the results difficult to compare with previous findings.

GAO. Gao et al. (1987) report the results of a large (1407 subjects) population-based case-control study of lung cancer etiology in Shanghai China, where lung cancer rates for women are among the highest in the world. Potential cases included all female patients with newly diagnosed primary lung cancer incident between February 1984, and February 1986, who were 35 to 69 years of age at the time of diagnosis and were residents of urban Shanghai. After exclusion of 93 patients who died, the remaining 672 cases were interviewed. Eighty-one percent were diagnosed by tissue biopsy or cytology and 19 percent by repeated x-ray. Adenocarcinoma was the predominant (61%) diagnosis. Controls were frequency-matched within five-year age strata and randomly selected from the general population of the Shanghai urban area. Of the total of 735 controls interviewed, only 9.7% were secondary controls, chosen mainly because the first selected control had moved from the Shanghai urban area or was found to be outside the eligible age range. The study includes 246 cases and 375 controls who were nonsmokers (presumably had never smoked cigarettes). Logistic models were used to estimate relative risks of disease adjusted for other study factors.

Among all subjects no significant increase in risk was observed for overall ETS exposure during childhood (OR = 1.1, 95% C.I. = 0.7 - 1.7) or adult life (OR = 0.9, 95% C.I. = 0.6 - 1.4). For these calculations, exposure was said to have occurred if the subject had ever lived with a smoker. However, when exposure was defined in terms of husbands' smoking and the analysis was limited to nonsmoking women, lung cancer risks tended to increase with the number of years of exposure, with the highest observed risk (OR = 1.7, 95% C.I. = 1.0 - 2.9)

occurring in the comparison of those with 40+ years of exposure to those with 20- years exposure, after adjustment for age and education (Table II). The relative risk in this comparison was higher (OR = 2.9, 95% C.I. = 1.0 - 8.9) for squamous- and oat-cell carcinoma alone. No test for trend over levels of ETS exposure was reported.

In the discussion of the results, the authors note the upward trend in risk associated with increasing years of exposure among nonsmoking women married to smokers. They conclude that ETS may be a contributing causative agent, but that other factors need to be considered as well, e.g., pre-existing lung disease, hormonal conditions, and especially exposure to cooking oil vapors.

Note: The study was not undertaken specifically to look at ETS lung association. Despite the large number of nonsmokers, it was not possible (or the authors chose not) to use women married to nonsmokers as a comparison group in their Table II. That may have been necessitated by the high prevalence of cigarette smoking among Chinese males.

GENG. In a brief article describing work similar in design and purpose to Gao et al, Geng et al. (1987) report the results of their study of lung cancer risk factors among women living in Tianjin, where the rates of lung cancer mortality are the highest in China. All 157 female cases were resident in Tianjin for at least ten years and were pair-matched to 157 controls by sex, race, age (within 2 years), and marital status. Diagnosis was predominantly by histologic or cytologic review (84.7%), although computerized tomography (10.8%) and clinical or x-ray (4.5%) methods were also used to identify cases. The authors describe the case group as representative of Tianjin female lung cancer patients in terms of age and distribution of residents. They further state that the prevalence of smoking among the controls (40.8%) is similar to that seen among the Tianjin adult female population. The participation rates for cases and controls is not given, but other studies from China have reported very high response rates.

The study report available in the literature is fairly brief. Neither the method for assigning ETS exposure nor information about personal smoking status are discussed. Both multiple conditional regression and stratified analytic techniques were used to calculate reported risk estimates, but the authors do not stipulate which variables were controlled for in the analyses.

The authors report that among the odds ratios of passive smoking from husbands, fathers, mothers, and colleagues, only that from husbands is significant. However, it is not clear whether this applies to smokers and nonsmokers combined in the same analysis or whether the analyses of ETS were restricted to nonsmokers only. The authors do explicitly state in Table 5 that the odds ratio for lung cancer in nonsmoking women married to smokers is 2.16 (95% C.I. = 1.05 - 4.53), but it is not clear why this estimate differs from the odds ratio of 1.86 for nonsmoking wives with smoking husbands in Table 7. The odds ratios for lung cancer increase with the number of cigarettes smoked per day by the husband and the duration of exposure to the husband's smoking (Table 6). No tests for trend are provided, however, and whether these findings apply to all subjects as a group or only to the nonsmokers is not clear.

One interesting finding in Table 7 of this brief report is the similarity of estimated effects associated with ETS exposure from a husband only (OR = 1.86, 95% C.I. = 1.04 - 3.5) and active smoking by the wife only (OR = 2.61, 95% C.I. = 1.4 - 4.6). Further, these independent risks can be seen to interact on a multiplicative scale among smoking women married to smoking husbands (OR = 4.9, 95% C.I. = 1.8 - 9.5). The authors did not state whether these estimates were adjusted for other factors.

HUMB. The study by Humble and colleagues (Humble et al., 1987) includes 28 incident cases described by interview to be lifelong nonsmokers (8 men, 20 women). Cases were identified through the population-based New Mexico Tumor Registry while controls (130 men, 162

women) were chosen through randomly generated phone numbers and Health Care Financing Administration rosters of Medicare participants. Controls were frequency-matched to cases by ten-year age groups and by sex. Subjects were the nonsmoking subset in a larger study of lung cancer risk factors in which 88.5% of cases and 83.1% of controls eligible for interview had participated. Of the 28 lung cancers among nonsmokers, 24 had a histologic diagnosis in the Tumor Registry record. However, in a separate review of histologic materials for 17 of these cases, only eight cell types concurred with the Registry.

Subjects or their proxies were interviewed regarding their personal smoking habits, smoking by their spouses, and their occupational exposures. Surrogate interviews (usually with the spouse) were necessary for 19 of the 28 cases, but for only 13 of the 292 controls. No effect of information source was noted when analyses were run separately for self-reported and surrogate-reported cases using self-reported controls as the comparison group. Small numbers precluded a separate reporting of the OR for males.

An elevated risk of lung cancer was reported for all subjects combined and for females separately. Logistic models, which included adjustment for age and ethnicity and sex when appropriate, calculated ORs of 2.6 (90% C.I. = 1.2 - 5.6) for all subjects and 2.2 (90% C.I. = 0.9 - 5.5) for females. Risk increased with the duration of spousal smoking (chi-squared statistic for linear trend equals 2.01 for all subjects and 1.23 for females alone) in cross-tabular analyses, but not in results from multiple logistic models. No trend was seen over the average number of cigarettes smoked per day by the spouse. Separate analyses for current and former smokers revealed no increased risk associated with marriage to a smoker.

Cell-line specific analyses were precluded by the small number of cases with histologic confirmation of their diagnosis, the poor concordance of histologic designations in the Registry file, and the special review. The high proportion of cases with surrogate respondents may actually have improved the quality of data regarding exposure to a spouse's cigarette smoking, as

spouses were the principal source of surrogate data. Exclusion of four former smokers (by information from other sources) did not alter the results. Size of the case series allowed only crude stratification of duration and amount when testing for trends, and may explain the marginal significance of findings reported separately for women.

INOU. In a case-control study of smoking and lung cancer in two Japanese cities, Inoue and Hirayama (1987) identified 37 women who died with lung cancer. Twenty-eight of these women (75.7%) were nonsmokers (definition not given). Cases were matched for age, year of death (within 2.5 years), and residential district to 74 controls who had died of cerebrovascular disease. Sixty-two (83.8%) of the controls were nonsmokers. Husbands' smoking status was available for 29 of the 37 cases and 54 of the 74 controls. Interviews were used to gather data for analysis, but the authors do not describe the characteristics or degree of relatedness of the surrogate respondents. Neither do they describe the degree of cooperation among the study subjects.

The Mantel-Haenszel procedure was used to estimate the relative risks of disease associated with ETS, adjusted for age alone and for age and residential district (due to differences in socio-economic status of the two areas). The odds ratios, stratified by age and district, are 2.58 (90% C.I. = 0.44 - 5.7) when husbands smoked less than 19 cigarettes a day, and 3.09 (90% C.I. = 1.04 - 11.81) when husbands smoked 20 or more cigarettes a day. The chi-squared test for trend is significant ($p < 0.05$).

LAMT. The large case-control study by T.H. Lam and colleagues (Lam et al., 1987) assessed the respective roles of active and passive smoking in lung cancer etiology among women living in Hong Kong. Only patients with a pathologist's confirmation (98% by histological or cytological review) were included. Those with rare tumors, e.g., carcinoids, were excluded. Women were interviewed in the hospital and then age-matched to healthy female controls selected from

within their own neighborhoods. Interviews took place between 1983 and 1986 and approximately 99% of all eligible subjects responded. Never-smoker status for both subjects and their husbands was defined as having never smoked as much as one cigarette a day, or its equivalent in other tobacco products, for at least one year. A woman was considered exposed to her husband's tobacco smoke if she had lived with her smoking husband in the same household continuously for at least one year. If the husband was an ever- smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. Never-married women were included as nonexposed to ETS. The authors describe the results of separate analyses on cigarettes only and on all forms of tobacco as similar and only report the latter. RR and 95% confidence intervals were calculated for each level of ETS exposure. The Fisher's Exact Test (two-sided) was used to check whether the RR was significantly different from unity. Multivariate methods do no appear to have been used.

Among the total of 444 cases and 443 controls were 199 cases and 335 controls who had never smoked and for whom data on husbands' smoking were available. For never-smokers the RR for lung cancer of all types from ETS exposure is 1.65 (95% C.I. = 1.16 - 2.35); for adenocarcinoma the RR is 2.12 (95% C.I. = 1.32 - 3.39). The risks for small and large cell carcinomas are 3.00 and 3.11, respectively, but these estimates are not statistically significant. Trends in relative risk for cancer at all sites, and for adenocarcinoma by the amount of tobacco smoked daily by the husband, are both significant with $p < 0.001$. The authors discount the possibility that misclassification bias could have lead to the observed results, given the low prevalence of smoking (4.1%) among women in Hong Kong and the strength of the findings in the present study.

LAMW. The dissertation of Lam (Lam, 1985) was the third case-control study of risk factors for lung cancer among females in Hong Kong. The nonsmoker cases, all with histologic or

cytologic confirmation of adenocarcinoma, were part of a larger case series of 161 interviewed Chinese female lung cancer patients diagnosed at a large, regional general hospital between January 1981 and April 1984. Fifteen cases with three other lung cancer histologies, as well as any patients with metastatic disease, were not included. Nonsmoking controls (n = 144) were part of a larger series of 185 Chinese, mostly lower income female patients admitted to the orthopedic wards between 1982 and 1984. Cooperation of potential subjects exceeded 99%.

There was little difference in the ages, occupations, years of schooling, or recent residences of the 161 cases and 185 controls, so the author deemed it unnecessary to control for (stratify on) these variables in the analysis of the 60 nonsmoking cases with adenocarcinoma and 144 nonsmoking controls. Exposure to ETS was categorized separately for husbands and other sources, e.g., cohabitating relatives or coworkers. Subjects were also queried regarding exposure to smoke from kerosene stoves and incense. The author interviewed all cases and, with a single research assistant, all controls. Thus, one may assume that interviews were not "blind."

The strongest and most statistically significant associations of ETS were with peripheral adenocarcinoma, with the highest odds ratio (2.64) occurring when exposure was based solely on husbands' smoking behavior. Estimates of relative risks of 1.6 and 1.7 were found for centrally located tumors when ETS was based on the husband's habits and total exposure to passive smoking, respectively. When data from Table 7.5 of the study are summed over sites, relative risks of approximately 2.0 are obtained with $p < 0.05$, regardless of exposure classification scheme. All odds ratios appear to be unadjusted for any other study factors. No statistically significant risks from kerosene or incense were found. The author concludes that the small sample size and use of only a single hospital source for subjects are limitations. Logistic regression was used in the statistical analysis, along with Bayesian risk-ratio procedure.

SHIM. Shimizu and his colleagues (Shimizu et al., 1988) use a hospital-based case-control study of lung cancer in women to examine the effect of involuntary exposure to tobacco smoke from a variety of sources. Among 118 female patients with histologically confirmed lung cancer, 90 reported having never smoked cigarettes. Cases were matched on hospital, age (within 1 year), and date of admission to patients being seen for conditions generally unrelated to tobacco use. All subjects were asked to complete a questionnaire about occupational history, kinds of fuels used for cooking and heating, and smoking habits, including number of cigarettes smoked daily by parents, siblings, the husband, and the husbands' parents in the home, as well as the amount of time spent in the same room with the husband, and the duration of marriage. ETS exposure at work was simply categorized by presence or absence of smokers.

No association was observed between risk of lung cancer and smoking by husbands, fathers, siblings, or coworkers. However, increased odds ratios were seen for smoking by subjects' mothers (OR = 4.0, $p < 0.05$) and by their husbands' fathers (OR = 3.2, $p < 0.005$). Dose-response relationships were not apparent for exposure by the mother or the husband's father, but the authors suggest that subjects may have been unable to recall the exact number of cigarettes in some cases (especially in childhood).

It is not clear whether variables such as occupational exposure to iron and other metals, or type of heating fuel, were assessed. Neither is there mention of cooperation rates by cases and controls. Adjustment of odds ratios for smoking by mother, smoking by husbands' father, and occupational exposures to iron and other metals, caused modest reductions in the point estimates, although smoking by husband's father in the home, (adjusted OR = 3.2) is still significant with $p < 0.005$. The authors describe this association as plausible since a high proportion of Japanese wives live with their in-laws after marriage and their father-in-law may have already retired.

SVEN. The study of lung cancer etiology in women who had never been regular smokers by Svenson et al. (1988) includes 34 cases with microscopically confirmed non-carcinoid cancer. Cases were patients referred to one of four clinical departments that diagnose or treat lung cancer in Stockholm county, Sweden. Only patients who would not benefit from specialist care, or who were not in physical or mental condition to allow an interview, were excluded from eligibility. Cases were matched on age using random selection from the population register in Stockholm County. Only seven subjects refused to be interviewed, resulting in a sample of 210 cases and 209 controls. Cooperation of nonsmoking cases and their matched controls was presumably high as well.

Four physicians completed all interviews using a structured questionnaire that included ETS exposure during childhood, as well as domestic and work environment exposure during adulthood. Other questions concerned the consumption of foods rich in vitamins A and C, and information about the dwellings where a subject had lived for more than two years. No surrogate sources of information were used and squamous/small cell carcinomas constituted 57.9% and 20.6% of the case histologies, respectively.

Women who lived with a smoking mother as children (RR = 3.3), or were exposed to ETS both at home and at work (RR = 2.1), or were exposed both as children and as adults (RR = 1.9), showed the highest risks. However, all estimates had very wide confidence intervals owing to the small sample size, and tests of association between ETS exposure and lung cancer incidence and tests for trend were all nonsignificant.

The authors describe the results for ETS as inconclusive, but note that most estimates of relative risk are greater than unity. The statistical power to detect an increased risk of 50% from exposure to ETS was only about 0.1. The author suggests that information bias may have precluded the identification of statistically significant small increases in risk. Specifically, no information on the duration or intensity of ETS exposure was obtained in the study, so it was

difficult to assess the relative importance of domestic and workplace exposures. Several statistical methods were applied to the data, including stratified analyses and multiple logistic regression.

VARE. The case-control study described by Varela in his 1987 dissertation (Varela, 1987) is based on 439 histologically confirmed primary lung cancer cases incident in nonsmokers over an 18-month period in upstate New York. Sample size requirements were set large enough that detection of a relative risk of the size reported by Hirayama and Trichopoulos would be likely. However, to reach the calculated requirement of 450 matched case-control pairs, it was necessary to include former smokers (55% of sample) in addition to never-smokers. Cases were identified through a special rapid reporting system in all participating hospitals and through periodic review of the New York State Cancer Registry. Controls were matched to cases on residence, age (within 5 years), sex, smoking history, and whether the interview was with the subject (67%) or with a surrogate (33%). Standardized interviews were conducted to collect data describing exposure to a spouse's cigarette smoke in terms of cig./day, total years of smoke exposure, and total cigarettes smoked during the marriage. Information was also collected on total exposure from all smokers in the household, from coworkers on the job, and from exposure in social circumstances. The potentially confounding variables considered in the analysis include religion, income, marital status, other occupational exposures, and number of cigarettes smoked/day for former smokers. The study's total of 439 cases represents a cooperation rate of 84% among those selected for interviews.

The author provides a systematic and exhaustive analysis based on linear logistic models for pairwise matched data. These data were collected as continuous values to allow analysis by source of exposure, e.g., spouse, other household smokers, coworkers, and social encounters, using methods for both continuous data and for categorical data. Analysis of household exposure

was further complicated by the use of two alternative assumptions regarding missing data for exposure at previous residences.

After extensive analyses no index of exposure to spouse's tobacco or smoking by coworkers was associated with an increased risk for lung cancer. However, person-years of total exposure from all smoking household members showed a statistically significant linear trend. When exposure was fitted as a continuous variable, the unadjusted odds ratio associated with 150 person-years of exposure was 1.86 (95% C.I. = 1.22 - 2.83). Adjustment for the potentially confounding variables listed above reduced the OR for 150 person-years of exposure to 1.56 (95% C.I. = 1.00 - 2.41). Exposure to passive smoke in social situations showed an anomalous protective effect in both adjusted and unadjusted models (Tables 20 to 22 and Figures 25 to 28).

Note: The study contains extensive statistical analyses of which only a small part have been described here. When a large number of tests are made, the likelihood that one or more statistically significant results will occur by chance alone increases. This can cause results to be interpreted as more significant than may be justified.

The author suggests that his own finding of no effect from exposure to spouses' smoke is understandable because the smoking habits of a spouse may not accurately describe true exposure to passive smoke. By contrast, the household exposure variable which was designed to more fully capture exposure in the home was the only index that was associated with increased risk of disease in this study. The greater association of household exposures with epidermoid and small cell histologies (Tables 12, 13, 15, 16) is not inconsistent with the apparent specificity of effect observed in PERS and GARF. One difficulty with comparing the Varela study with other case-control studies is the inclusion of either males with females or ex-smokers with never-smokers, in the reported results. Although the analysis is very comprehensive, no reports for the risk of female never-smokers alone were found. The author suggests that differences in past smoking habits of cases and controls may have a confounding effect. Although identical

proportions of cases and controls were former smokers, cases had smoked a larger number of cig./day (28.9 vs. 23.8, p = 0.0002). Former smokers were not included, however, unless they had stopped smoking at least ten years prior to the interview. The author questions the validity of an apparent significant protective association from ETS in social circumstances, suggesting the possibilities of biased reporting and questionnaire artifacts as alternative explanations for this finding.

WU. Wu and her coauthors (Wu et al., 1985) report the effects of ETS exposure as part of a larger study of determinants of lung cancer among white women living in Los Angeles County. Eligible cases included only patients with microscopically diagnosed primary adenocarcinoma (ADC) or small cell carcinoma (SCC) of the lung, incident between April 1, 1981, and August 31, 1982. Subjects also had to be English-speaking residents and less than 76 years old at the time of diagnosis. One neighborhood control was individually matched to each interviewed case using date of birth (within five years).

From a total of 490 eligible cases (smokers and nonsmokers), 190 were dead or too ill to participate, eight could not be located and 44 refused to be interviewed, leaving 220 (44.9%) as the interviewed case group. After replacement of 85 potential controls who refused to participate, 220 controls were also interviewed. Surrogate respondents were not used because they were thought to be an unreliable source of information for ETS exposures and dietary practices in childhood. this article reports 29 cases (ADC) with 62 controls, but does not include the percentages exposed to spousal smoking. Also, it is noted that 15 pairs of the ADC were deleted from the analysis because either the case or control was never married.

Cases and controls were interviewed by telephone regarding personal smoking habits, exposure to ETS, history of lung diseases, dietary intake of vitamin A, types of heating and cooking fuels used, and reproductive history. Information obtained about childhood exposure to

ETS included the amount and years of smoking by fathers, mothers, and other household members. Questions on exposure in adulthood pertained to smoking habits of spouses and other household members.

Study data were adjusted for potential confounding variables by application of logistic regression. Estimates for the relative risk of ADC are provided separately for nonsmokers, ex-smokers, and current smokers, but a small number of occurrences precluded the corresponding calculations for SCC. For ADC and SCC among smokers and nonsmokers combined, no significantly increased risks were observed due to smoking by the subject's mother, father, spouse, or coworkers after adjustment for personal smoking habits. For the 29 nonsmoking ADC cases exposed to passive smoke, no significant elevated risk was associated with ETS exposure from a mother who smoked, a father who smoked, a spouse who smoked, or from the workplace. The observed relative risk for ADC increases with the number of years of adult ETS exposure from spouse(s) and coworkers, but a test for trend is not statistically significant. The authors attribute the ambiguous nature of their results to the lesser etiologic role of ETS for ADC compared to SCC. Further, 12 (41%) of the 29 ADC cases are bronchoalveolar cell carcinomas, which Correa et al. (1983) found to have a relatively weaker association with passive smoking.

APPENDIX B

MATHEMATICAL FORMULAS AND RELATIONSHIPS

ADJUSTING RELATIVE RISK FOR SMOKER MISCLASSIFICATION AND BACKGROUND ETS EXPOSURE

The formula relating observed relative risk (RRO) and the value after adjustment for misclassification (RRM) is shown in Equation B1 below, with terms described in Tables B-1 and B-2. The calculational procedure is similar to that of Wald et al. (1986), except that separate terms for former smokers and current smokers are retained (instead of being combined into a single term for ever-smokers) and distinction is made between "correct" values and "reported" values, e.g., for the number of never-smokers. It may be noted that an assumption of additive risks due to current or former smoking, and exposure to spousal smoke, is implicit.

$$RRO = UY/VX \qquad \text{(B1)}$$

where $U = [(C_c-C_r)/N_r]P(E/C)RR(E/C)$

$+ [N_c/N_r]P(E/N)RR(E/N)$

$+ [(F_c-F_r)/N_r]P(E/F)RR(E/F),$

V is The same as U with the terms for RR omitted,

$X=[(C_c-C_r)/N_r]\ [1-P(E/C)]\ RR(E/C)$

$+ [N_c/N_r]\ [1-P(E/N)]\ RR(E/N)$

$+ [(F_c-F_r)/N_r]\ [1-P(E/F)]\ RR(E/F),$

Y is The same as X with the terms for RR omitted,

RR(E/N) = RRM, the relative risk after adjustment for misclassification, and

RR(E/C)=RR(U/C) + (RRM - 1),

RR (E/F) = RR (E/F) + (RRM - 1).

TABLE B-1. DEFINITION[1] OF TERMS IN EQUATION B1 RELATING OBSERVED RR (RRO) AND ITS VALUE ADJUSTED FOR MISCLASSIFICATION (RRM)

Term	Description
N_r	Reported number of NS (never-smokers)
N_c	Correct number of NS (never-smokers)
C_r	Reported number of CS (current smokers)
C_c	Correct number of CS (current smokers)
F_r	Reported number of FS (former smokers)
F_c	Correct number of FS (former smokers)
P(E/N)	Proportion of NS exposed[2]
P(E/C)	Proportion of CS exposed[2]
P(E/F)	Proportion of FS exposed[2]
RR(E/N)	Risk of lung cancer death (LCD) for NS exposed, relative to NS unexposed[3]
RR(E/C)	Same as RR(E/N) except for CS exposed[3]
RR(E/F)	Same as RR(E/N) except for FS exposed[3]
RR(U/C)	Same as RR(E/N) except for CS unexposed[3]
RR(U/F)	Same as RR(E/N) except for FS unexposed[3]

[1] Table applies to marrieds.

[2] "Exposed" means married to a smoker.

[3] RR(E/N) equals RRM in the text notation.
RR(U/C) is the relative risk of smoking, a parameter value.
RR(U/F) is the relative risk of former smoking, a parameter value.
RR(E/C) = RR(U/C) + (RR(E/N) - 1). Assumes relative risk of exposed smoker is the sum due to smoking and spousal exposure to ETS.
RR(E/F) = RR(U/F) + (RR(E/N) - 1). Same assumption as for RR(E/C) except applied to former smokers.

TABLE B-2. PARAMETERS AND THEIR ALTERNATIVE SPECIFICATIONS REQUIRED FOR EQUATION (B1)

Parameter Identifier	Appears in (B1) ?	Parameter[1]	Description
V1	Y	$(C_c-C_r)/N_r$	Proportion of reported never-smokers (NS) who are current smokers (CS)
V2	Y	$(F_c-F_r)/N_r$	Proportion of reported NS who are former smokers (FS)
V3	Y	N_c/N_r	Proportion of reported NS who are NS
V4	Y	P(E/N)	Proportion of NS exposed (married to a smoker)
V5	Y	P(E/C)	Proportion of CS exposed
V6	Y	P(E/F)	Proportion of FS exposed
V7	Y	RR(U/C)	Risk of misclassified CS, not exposed, relative to NS, not exposed
V8	Y	RR(U/F)	Risk of misclassified FS, not exposed, relative to NS, not exposed
V9	Y	RR(E/N)	Risk of NS, exposed, (=RRM) relative to NS, not exposed
V10	Y	RR(E/C)	Risk of misclassified CS, exposed, relative to NS, not exposed
V11	Y	RR(E/F)	Risk of misclassified FS, exposed, relative to NS, not exposed
V12	N	C_r/T	Proportion of subjects reported to be CS
V13	N	C_c/T	Proportion of subjects correctly classified CS
V14	N	$(C_c-C_r)/C_c$	Proportion of CS reported to be NS
V15	N	N_r/T	Proportion of subjects reported to be NS
V16	N	N_c/T	Proportion of subjects correctly classified as NS
V17	N	F_r/T	Proportion of subjects reported to be former smokers
V18	N	F_c/T	Proportion of subjects correctly classified FS
V19	N	$(F_c-F_r)/F_c$	Proportion of FS reported to be NS

[1] "T" is the total number of subjects.

RRO is just a ratio of weighted relative risks. The term U/V applies to exposed subjects and X/Y applies to unexposed subjects. To make the relationship more transparent, consider the special case where the proportion of all subjects (regardless of their own smoking habits) married to a smoker is one-half and there is no misclassification of former smokers. Then RRO can be written as RRO = A/B, where A = (no. of misclassified CS exposed) times (their relative risk) + (no. of correctly classified NS exposed)times(their relative risk) and B is the same as A except with "exposed" replaced by "unexposed." All of the relative risk terms are relative to the same value (the lung cancer risk in unexposed never-smokers) so the ratio A/B is the risk observed in exposed subjects relative to the risk observed in unexposed subjects.

The terms in expression Equation B1, stated as proportions of the number of reported never-smokers (N_r), may need to be converted from alternative parameter specifications. For example, the misclassification rate of current smokers, $(C_c - C_r)/C_c$), may be specified instead of the proportion of reported misclassified current smokers, $(C_c - C_r)/N_r$). In the literature, "misclassification" is usually referred to as a percentage or proportion of a reference group, but authors do not all have the same reference group in mind. Conversion of parameters make some values more interpretable, as well. Formulas for conversion of parameters between reported and correct classifications are given in Table B-3.

The procedure used to account for ETS exposure from sources other than spousal smoking is described in the NRC report (1986). It is assumed that lifetime lung cancer risk from exposure to ETS is linear in the range of environmental exposures to ETS. RRM is the risk of never-smokers (NS) exposed (e.g., married to smoker) to ETS relative to unexposed NS (e.g., married to a never-smoker). Both the exposed and unexposed NS experience ETS from sources other than what differentiates their classification in epidemiologic studies (typically, "exposed" means married to a smoker).

The terms RRB and RRM denote the risk of exposed NS relative to NS with zero exposure to ETS, and relative to an unexposed NS, respectively, where an "unexposed" NS is not married to a smoker but experiences ETS from other sources collectively referred to as background sources.

TABLE B-3. CONVERSION OF PARAMETERS BETWEEN REPORTED AND CORRECT CLASSIFICATIONS

From Correct Values to Reported Values

Let $W = (V13)(V14) + V16 + (V18)(V19)$

$V1 = (V13)(V14)/W$

$V2 = (V18 + V19)/W$

$V3 = V16/W$

From Reported Values to Correct Values

$$V14 = \frac{(V1)(V15)}{(V1)(V15) + V12}$$

$V16 = V15 - (V1)(V15) - (V2)(V15)$

$$V19 = \frac{(V2)(V15)}{(V2)(V15) + V17}$$

If R(E), R(U), and R(TU) denote the absolute risk (lifetime probability of lung cancer) for exposed, unexposed, and truly unexposed (no background exposure to ETS) NS, respectively, then RRM = R(E)/R(U), RRB = R(E)/R(TU), and R(U)/R(TU) = RRB/RRM.

Let Z be the ratio of (1) the excess risk of exposed NS relative to truly unexposed NS, and (2) the excess risk of unexposed NS relative to a truly unexposed NS. Then, Z = (1)/(2) = (RRB-1)/(RRB/RRM - 1). In this report, Z = 3 is assumed (see Section 4.4.4). RRM is the observed relative risk (RRO) after adjustment for smoker misclassification. For values of Z and RRM,

$$RRB = (1 - Z)/(1 - Z/RRM) \qquad (B2)$$

POPULATION-ATTRIBUTABLE RISK (PAR)

Let RRB and RRM be as defined previously. The population-attributable risk is the ratio of the excess risk due to ETS exposure to the total risk from all sources.

$$PAR = \frac{P(E/N)(RRM - 1) + (RRB-RRM)}{P(E/N)(RRM - 1) + (RRB-RRM) + 1} \qquad (B3)$$

where P(E/N) is the proportion of NS exposed to ETS. Note that all NS are at risk from background exposure (the term RRB - RRM) and the exposed persons have an additional risk from ETS exposure (the term RRM - 1).

LUNG CANCER DEATHS IN FORMER SMOKERS ATTRIBUTABLE TO ETS

It is assumed that the RR of lung cancer from exposure to ETS is the same for former smokers (FS) and never-smokers (NS). The number of lung cancer deaths per year in FS due to ETS exposure is approximated from the ratio of the number of FS to the number of NS in the U.S. population times the estimated number of lung cancer deaths for NS (1750 women, 810 men). The number of NS (FS) in the 1985 U.S. population is 55.4 million (17.1 million) women

and 32.8 million (29.1 million) men (Table 2, U.S. SG [1989]). The estimated number of lung cancer deaths in FS is 540 women and 720 men, for a total of 1260.

APPENDIX C

DOSIMETRY OF ENVIRONMENTAL TOBACCO SMOKE

C.1. INTRODUCTION

The biological relationship between exposure to tobacco smoke and lung cancer risk has been the subject of much research. The constituency of tobacco smoke is a complex mixture of chemicals, a number of which have been classified as carcinogens, with varying weights-of-evidence. Research continues toward identifying the agents of tobacco smoke, and their combinations, that account for the carcinogenic risk to the lung and other organs. In addition to knowledge of the chemical agents of interest, a part of the biological puzzle concerns the intake, uptake and organ deposition of the chemicals. Once organ dose is determined, the problem concerns the process by which dose poses a cancer risk. In this last step, pharmacological research, dose-response data from animal or epidemiological studies, and quantitative models all contribute toward estimating the magnitude of increased cancer risk associated with environmental exposure levels. The following discussion addresses the second of the three steps above, the determination of target organ dose (or surrogate) of chemicals present in tobacco smoke, in particular the dose to the lung. A general mathematical framework is given that applies to both active and passive smoking. It will be helpful first to review briefly the current knowledge base regarding carcinogens in tobacco smoke.

The constituents of tobacco that have been identified as carcinogens, largely in animal studies, are discussed in several sources, e.g., NRC, 1986; U.S. SG, 1986; IARC, 1987; Hoffmann and Hecht, 1989. The relative concentrations in sidestream (SS) and mainstream (MS) smoke vary over a range of severalfold, for both the particulate and vapor phases. Hoffmann and Hecht (1989) classify the tumorigenic agents in tobacco and tobacco smoke as polycyclic aromatic hydrocarbons (PAH), aza-arenes, N-nitrosamines, aromatic amines, aldehydes,

inorganic compounds, and miscellaneous organic compounds. Particularly relevant to active smoking are the PAH, N-nitrosamines (notably NNK or NNK-4-(methyllnitrosamino)-1-(3-pyridyl)-1-butanone), and the aldehydes. Based on animal bioassays, the levels of exposure to active smokers of PAH and NNK are sufficient to be potential causative agents of respiratory tract cancer. More specifically, likely causative agents for cancers of the lung or larynx from active smoking include: PAH, with enhancing agents catechol (a cocarcinogen) or a weakly acidic tumor promoter; NNK, with enhancing agents acrolein or crotonaldehyde (some uncertainty in the latter); acetaldehyde; formaldehyde; and Polonium-210, a minor factor (Table 4, Hoffmann and Hecht, 1989).

Of course it is unknown exactly which constituents of tobacco smoke, active separately or in combination, account for the lung cancer risk in active smoking and may pose a risk to passive smokers. It is unlikely that causative agents are exclusive to either the particulate or vapor phase, so both phases need to be considered. The level of detail that can be included in modeling lung exposure requires knowledge of parameter values and information on biological mechanisms to describe them by equations. The most refined level, biologically-based modeling, potentially provides a sensitive means by which to compare and contrast features of active and passive smoking. This is particularly relevant because active smoking has been the subject of much research in the past. Typical exposure levels to environmental tobacco smoke (ETS) can be evaluated under suitable models, the sensitivity of selected parameters tested, and parameters identified that may help to characterize potentially hypersusceptible subpopulations. Aside from the differences in the composition of SS and MS smoke, active and passive smoking ostensibly differ in fundamental ways that must be considered. Active smokers are exposed to high concentrations of inhaled smoke for short durations while passive smokers are exposed to lower concentration at their typical volumetric breathing rate over a more extended time period. Additionally, the active smoker is generally a passive smoker as well.

There are some common features of intake, uptake, and lung deposition for agents in the particulate phase of tobacco smoke that depend on particle size and density. This makes it useful to consider the particulate and vapor phases separately in a mathematical model. Unlike the particulate phase, constituents of the vapor phase may not have any parameter values in common and thus have to be treated individually. When a chemical occurs in both phases, the biokinetics are determined separately for the two phases, at least prior to entry into cells and tissues.

For the general framework described in the next section to be useful for cancer risk assessment, it is necessary to assume that the contribution of ETS to cancer risk in the lung depends primarily on dose to the lung (although host factors will modify this risk). The model identifies the parameters needed for dose determination and their interrelationship. Since values for parameters, or data from which to estimate them, are not always available in practice, several measures related to exposure are provided to accomodate the level of detail in the information available. These include, in increasing order of refinement and information required: exposure concentration (in room air), cumulative exposure, lung intake, lung uptake, lung burden, lung dose, and dose distribution in systemic organs.

Although many aspects of the biokinetics of passive smoking and active smoking are not fully understood, much is known about critical and separate features of passive and active smoking. Quantitative modeling reveals the structure and interrelationship of the basic biokinetic features, serves to identify areas of research needed, and shows where assumptions are required to bridge current gaps in knowledge regarding mechanisms or chemical properties. In this sense a quantitative model that integrates the current knowledge base over several disciplines is a useful guide to the current state-of-knowledge and future research needs. It also contributes to evaluation of dose surrogates for ETS and the potential comparative basis for lung cancer risk from active and passive smoking.

C.2. GENERAL ISSUES

C.2.1. The Lung

Suppose we are interested in a mixture of chemicals such as ETS, where these chemicals may exist either in the vapor or particulate phase. In general, the vapor phase chemicals are inhaled and absorbed in the lung with characteristics specific to that chemical, i.e., the diffusion coefficient and solubility coefficient for that chemical in lung tissue. The chemicals existing in the particulate phase, however, are inhaled and deposited with characteristics specific to the particle size with which the chemicals are associated. For this reason, it is necessary to understand the aerodynamic properties of inhaled particles. To differentiate between the vapor and particulate phase of a chemical, the subscript v (for vapor) will be employed, while the subscript d (for the particle's aerodynamic diameter) will be employed for the particulate phase chemicals.

The simplest, but most approximate, measure of dose from a chemical is its concentration in air. This concentration typically is referred to as the exposure intensity and denoted by C. An index i will refer to the i^{th} chemical of a mixture contained in ETS. The subscripts v and d will denote the vapor phase and particle phase, respectively, with d taking a particular value for particle diameter. For example, $C_{N,0.5}$ is the concentration of the N^{th} chemical, e.g., nicotine (g/m^3), attached to aerosol particles of diameter 0.5μ. Then $C_{N,v}$ would denote the concentration of nicotine (also in g/m^3) in the vapor phase. The total exposure intensity for nicotine would be the sum of $C_{N,0.5}$ and $C_{N,v}$, although this should not be interpreted as a reduction of the two phases to a common measure of dose. The subscripts for chemical and vapor phase will be omitted for ease of reading, except as needed. Since the incidence of effect per unit concentration can be quite different for these two components, total exposure intensity may act as a poor measure of risk.

The cumulative exposure, ψ, over a time interval [0, T] is

$$\psi(T) = \int_0^T C(t)dt, \tag{1}$$

where C(t) is the concentration of the chemical in air at time t. At constant concentration C,

$$\psi(T) = C \times T. \tag{2}$$

The total cumulative exposure over [0,T] is obtained by summing all contributions from the various phases in units of gram-days per liter of air (g-d/L).

The total amount of inhaled chemical will be referred to as the lung intake, I. Let V be the volumetric breathing rate (L/min), which equals the product of the tidal volume (L) and the breathing frequency (min^{-1}). The value of V may change with age (Crawford-Brown, 1987), in which case the dependence of V on an individual's age can be made explicit in the notation. The lung intake for the i^{th} chemical during an interval of length T is

$$I(T) = V \times \psi(T). \tag{3}$$

The intake is in grams of the chemical considered.

With the exception of radionuclides, an inhaled chemical must deposit onto the walls of the lung to yield damage. The quantity of a chemical deposited in the lung over a time period [0,T] is the lung uptake, U(T). Typically, the relationship between intake and uptake will vary dramatically between the phases of a chemical due to differences in deposition and absorption processes. The uptake to the lung equals the product of the intake and the fraction "f" of the chemical deposited onto the surface of the lung. The total uptake to the lung then is

$$U(T) = f \times I(T). \tag{4}$$

For the vapor phase, the value of "f" depends on the specific chemical and often is unknown (although it may be infered from solubility coefficients if these are developed in future studies). For the particulate phase, the dominant environmental factor affecting f is the aerodynamic diameter, d, of the particle. In general, f_d will also be a function of the age of the individual, the state of activity, i.e., whether resting or working, the hygroscopicity of the particles, i.e., their ability to grow by gaining water in the lung, and the state of health of the individual. The uptake U is in grams of the chemical considered.

Lung uptake must be refined further in order to account for the structure (anatomy) of the lung. As described elsewhere (Weibel, 1963), the lung may be depicted as a series of bifurcating passageways that branch into smaller passageways as one moves from the proximal (near the mouth) to the distal (deep lung) locations in the lung. A simplified version of this branching scheme has been adopted by the International Commission on Radiological Protection (ICRP) in its report on lung modeling (ICRP, 1966). The ICRP model divides the lung into three distinct subsections or regions, each with a specific value of f. These regions are the naseopharyngeal (NP) region, consisting of the nose and pharynx; the tracheobronchial (TB) region, which extends from the trachea down to the terminal bronchioles; and the pulmonary (P) region of the lung, where gas exchange occurs between the alveolar sacs and the bloodstream. A schematic of the lung is shown in Figure C-1.

The value of f differs between the three regions of the lung due to differences in airflow and the size of passageways. To reflect this situation, let f_{NP}, f_{TP}, and f_P be the deposition fractions in the NP, TB, and P regions, respectively. Their values will depend upon the phase of the inhaled chemical. The uptake in each of the three regions over [0,T] is obtained from Equation 4

$$U^P(T) = f_P \times I(T) \qquad (5)$$

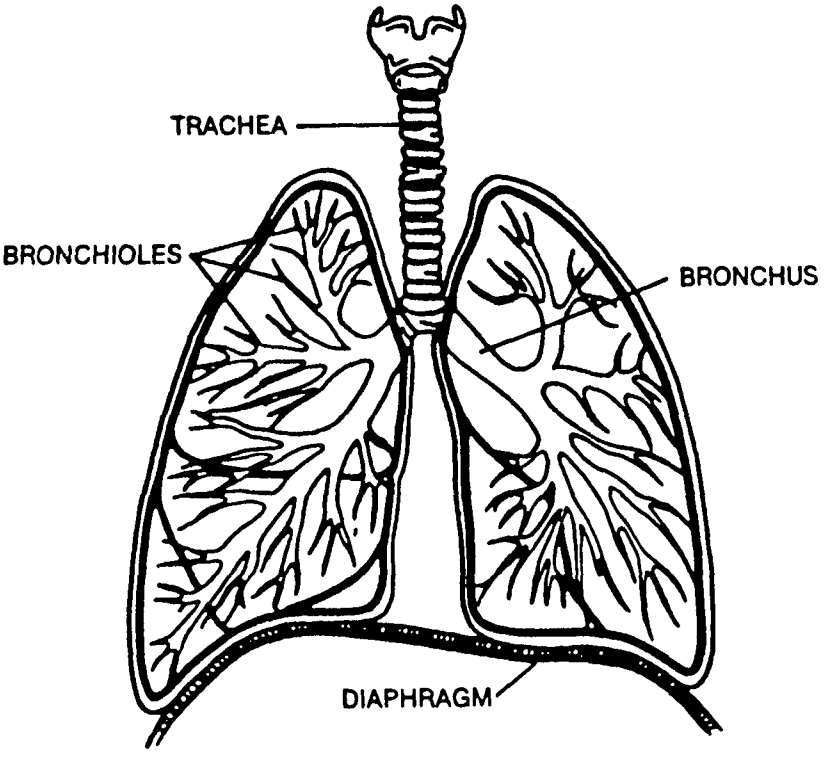


FIGURE C-1. THE GENERAL ANATOMY OF THE LUNG FROM THE TRACHEA DOWN TO THE DISTAL BRONCHIOLES

$$U^{TB}(T) = f_{TB} \times I(T) \tag{6}$$

$$U^{NP}(T) = f_{NP} \times I(T). \tag{7}$$

Each term may be subscripted further to indicate the chemical and its phase. The total lung uptake equals the sum of Equations 5 through 7, although this sum should not be construed as an appropriate measure of risk to specific cells of the lung.

After deposition in the lung tissue, a chemical must interact with the cells in order to produce an effect. In general, the probability of this interaction increases as the residence time of the chemical in the tissue increases. Because of this factor, it is necessary to specify a retention function R(t), describing the fraction of a chemical remaining in that tissue at a time, t, after uptake. For the pulmonary region, R(t) results from the translocation of the chemical across the alveolar membrane and into the bloodstream (with some contribution by engulfment into macrophages). For the TB and NP regions, R(t) is controlled by the movement of the mucociliary blanket towards the esophagus and, ultimately, into the gastrointestinal (GI) tract.

For the TB region, the retention can be influenced by the particular pattern of deposition within the separate generations of that region. A further complication arises due to the possibility of enhanced deposition at the bifurcations of airways (Martonen and Hoffmann, 1986), where movement of the mucociliary blanket will be slower. We will assume that a chemical deposited in the TB region may be characterized by a single retention function, however, since more refined characterizations are not feasible at present.

The amount of a chemical present in a region of the lung at time, t, is the *organ burden*, B(t). For the case of an acute, i.e., instantaneous, uptake denoted by U_0, the burden is

$$B(t) = U_0 \times R(t), \tag{8}$$

where the unit of B(t) is grams. The quantities B, U, and R may be subscripted by chemical and phase, and may be divided into the three separate regions of the lung.

For protracted exposures over a time interval of length T > 0, the calculation of B(T) requires a convolution integral (Checkoway et al., 1989). The burden of a chemical in the lung regions is described by

$$B^{P}(T) = \int_0^T \dot{U}^{P}(t) R_P(T-t)dt, \tag{9}$$

$$B^{TB}(T) = \int_0^T \dot{U}^{TB}(t) R_{TB}(T-t)dt, \tag{10}$$

and

$$B^{NP}(T) = \int_0^T \dot{U}^{NP}(t) R_{NP}(T-t)dt. \tag{11}$$

In these equations $\dot{U}$ is the rate of uptake into the separate lung regions. When concentration C is constant over time, simplifications follow as demonstrated earlier. The unit of burden in the lung region of interest is grams. Further subscripting to account for chemical and phase continues to be omitted.

The rate at which damage is produced in a tissue at time t is assumed to be proportional to the *dose-rate*, $\dot{D}(t)$, in the tissue (Checkoway et al., 1989), and the dose-rate is assumed to be proportional to the burden, B(t). Under these assumptions,

$$\dot{D}(t) = K \times B(t), \tag{12}$$

where K is a proportionality constant that depends upon the particular chemical and tissue. In essentially all cases, with the exception of radionuclides, it is not possible to specify a value of K for chemicals because the important molecular damage is neither specified nor measured.

Unfortunately, not knowing the value of K for different chemicals precludes combining burdens from across chemicals to yield a single estimate of the dose-rate from ETS.

The total *dose* to an organ (or lung region) is the integral of the dose-rate over the time interval of interest

$$D(T) = \int_0^T \dot{D}(t)dt. \tag{13}$$

Substituting Equations 9, 10, or 11 into Equation 12, and substituting this into Equation 13, yields

$$D(T) = K \times V \int_0^T \int_0^T C(\tau) f R(t - \tau) d\tau dt, \tag{14}$$

which for cases of constant concentration in air reduces to

$$D(T) = K \times C \times V \times f \int_0^T \int_0^t R(t - \tau) d\tau dt. \tag{15}$$

Again, all terms may be subscripted by chemical, phase, and lung region. The units of dose are gram-days in the lung region of interest. When K is unknown (as is true for ETS), it is ignored and the dose is replaced by the integral of the organ burden, IB.

Retention functions can take on a variety of forms that depend upon the physical processes involved in removal from an organ. These functions, however, usually are approximated by an exponential function or a sum of such functions

$$R(t) = e^{-\lambda t}, \tag{16}$$

where λ is the removal rate constant (unit of time^{-1}) from the organ or region of interest. Substitution of this retention function into either of Equations 9 through 11 for constant concentration C gives

$$D(T) = C \times V \times f \int_0^T e^{-\lambda t} dt = \frac{C \times V \times f \times (1-e^{-\lambda T})}{\lambda}, \quad (17)$$

ignoring the subscripts for lung region. The dose may be obtained by substituting Equation 17 into Equation 12, and then inserting Equation 12 into Equation 13:

$$D(T) = \int_0^T \frac{K \times C \times V \times f \times (1 - e^{-\lambda t})dt}{\lambda} = \frac{K \times C \times V \times f \times (T - (1 - e^{-\lambda T})/\lambda)}{\lambda} \quad (18)$$

As before, the integral organ burden over T is obtained by ignoring K in Equation 18.

An additional complication arises in distinguishing between an organ burden (or dose) and a biologically active organ burden. For some chemicals, e.g., nicotine, biotransformation may occur in the body (see, e.g., Jacob et al., 1988; Hoffmann and Hecht, 1989; Hoffmann et al., 1987; Hoffmann and Wynder, 1986). The chemical form of a substance may be altered, producing a new molecule (such as cotinine) of either greater or lesser potential for harm. In that case, the burden (or dose) of interest would be the one from the active form of the chemical. This form may or may not be the form present in the environment. The biologically active burden B_B, will be equal to the burden of inhaled material, B, times a scaling factor, k_A, for activation of that material. When the rate constant for activation is small compared to the rate constant for elimination of the active form, it may be necessary to perform specific calculations of B_B. In general, k_A will be the fraction of the inhaled chemical biotransformed into the active form. Similarly, D_B will equal the *biologically active dose* and is obtained by multiplying D by k_A (or by calculating D_B directly). For most chemicals (particularly those in ETS), k_A is unknown and B_B or D_B must be approximated by B or D as described earlier. An exception is the conversion of nicotine to cotinine.

C.2.2. Translocation to Systemic Organs

As shown in Figure C-2, the lung is coupled to the other organs of the body through the bloodstream and the GI tract. Material deposited in the P region of the lung tends to be translocated into the bloodstream, where it is carried to the systemic organs or excreted, primarily in the urine. This process may be viewed as essentially catenary (Crawford-Brown, 1984), in which a chemical moves from the lung, into the blood, into an organ, and then into the urine. Flow is assumed to be unidirectional, avoiding the complications introduced by recirculation and exchange between organs.

Material deposited in the NP region is removed primarily to the G.I. tract, with little absorption of ETS chemicals directly into the bloodstream (Wald et al., 1981). For deposition in the TB region, there is evidence of high absorption of nicotine into the blood, at least in dogs (Herrmann et al., 1989). From the G.I. tract, the chemicals are absorbed to a limited degree into the bloodstream, where they are expected to behave in a manner similar to the material entering the blood from the P region. Slight differences can occur due to the proximity of the liver to the G.I. tract, but there is not sufficient information available to consider that further. Chemicals unabsorbed by the GI tract will be excreted in the feces.

Let $f_{P,b}$ equal the fraction of a chemical leaving the P region and entering the blood. This fraction is determined with respect to the uptake and not the intake. Similarly, let $f_{TB,b}$ and $f_{NP,b}$ be the fraction leaving the TB and NP regions, respectively, and entering the blood. The latter fraction will be quite small and is ignored here. The fractions $f_{TB,GI}$ and $f_{NP,GI}$ represent the fraction of regional uptake entering the G.I. tract. The latter fraction is assumed to equal unity here. The term $f_{GI,b}$ equals the fraction of a chemical in the G.I. tract which crosses into the bloodstream. The total uptake of a chemical entering the bloodstream is

$$U^b = U^P f_{P,b} + U^{TB} f_{TB,b} + (U^{TB}(1-f_{TB,b}) + U^{NP} f_{NP,GI}) f_{GI,b} \qquad (19)$$

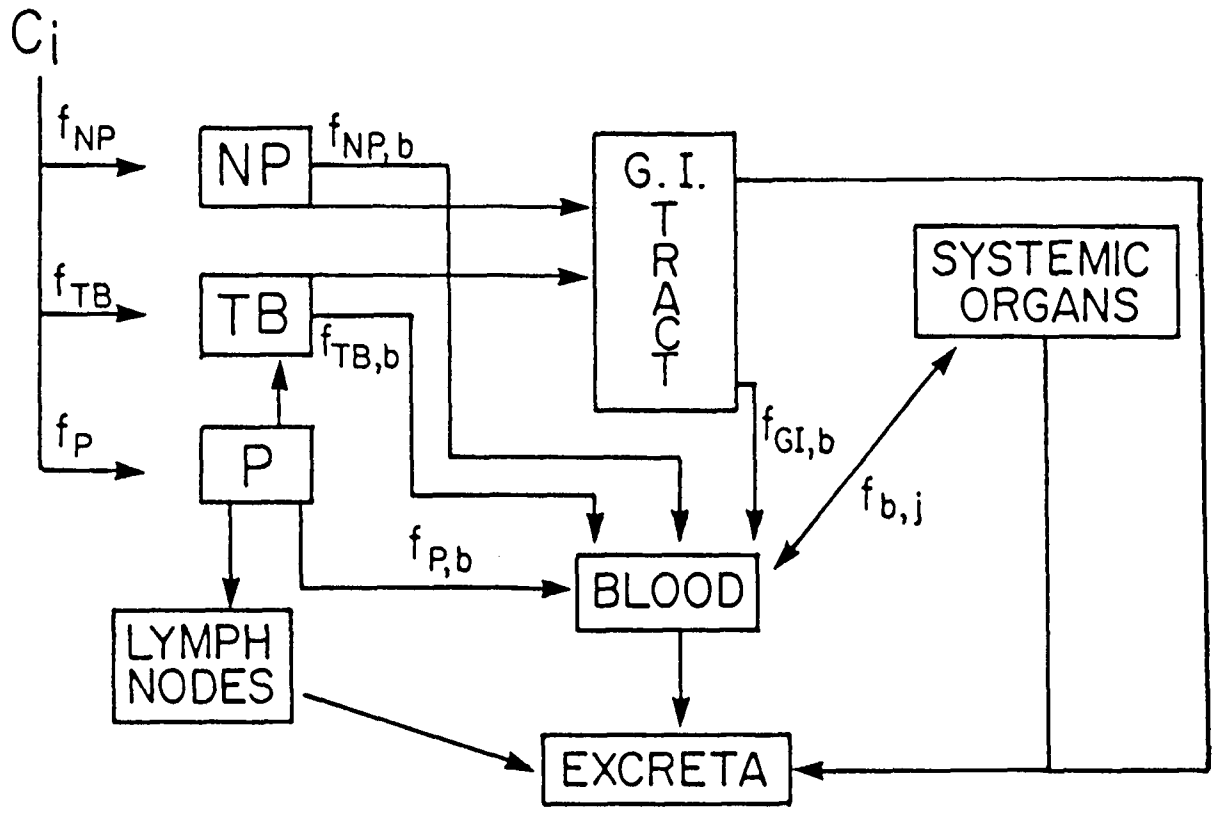


FIGURE C-2. A COMPARTMENTAL MODEL OF THE HUMAN BODY, DISPLAYING ORGANS, TISSUES, FLUIDS, AND THEIR INTERCONNECTIONS

The expressions for U^P, U^{TB} and U^{NP} may be found in Equations 5 through 7.

Material in the blood is cleared into the systemic organs. The fraction of material moving from the blood into a specific organ, indexed by j, will be denoted by $f_{b,j}$. Its value is assumed to be independent of the route into the blood, although this assumption is untested at present. The uptake into organ j is described by

$$U^j = U^b \times f_{bj}, \tag{20}$$

where U^b is given by Equation 19.

The retention function for a substance in organ j is given by $R_j(t)$. The dose to an organ following an acute uptake to the organ then is

$$D^j = K \times U^j \times \int_0^T R_j(t)dt. \tag{21}$$

This dose may be converted to a biologically active dose by multiplying Equation 21 by k_A (unknown at present). Since K also is unknown, D must be replaced by the integral organ burden.

For protracted exposure to a chemical at a constant concentration, C in air, uptake to organ j in the time interval [0,T] is

$$D^j(T) = K \times C \times V \times [f_R f_{P,b} + f_{TB} f_{TB,b} + f_{NP} f_{NP,GI} f_{GI,b}] f_{bj} \times \int_0^T \int_0^t R_j(t - \tau)d\tau dt. \tag{22}$$

Implicit in the equation is the assumption that material clears rapidly from the lung and into organ j, at least with respect to the interval of exposure. If it is assumed that the NP region does not contribute significantly to systemic doses, due to low values of $f_{GI,b}$ Equation 22 reduces to:

$$D^j(T) = K \times C \times V \times [f_R f_{P,b} + f_{TB} f_{TB,b}] \times f_{bj} \times \int_0^T \int_0^t R_j(t - \tau)d\tau dt. \tag{23}$$

If it is assumed further that $R_j(t)$ is a single exponential function with rate constant, λ, then:

$$D^j(T) = K \times C \times V \times [f_R f_{P,b} + f_{TB} f_{TB,b}] \times f_{b,j} \times (T - (1-e^{-\lambda T})/\lambda)/\lambda. \quad (24)$$

Unfortunately, organ specific values for $f_{b,j}$ are not known for the chemicals in ETS. There are, however, limited data concerning the distribution of nicotine, a component of ETS, within various tissues. The steady-state distributions of nicotine in those organs will be approximately proportional to the dose-rate and, hence, the dose. The measurements, taken from a report by the U.S. Surgeon General (U.S. DHHS, 1988) are displayed in Table C-1. It will be noted that nicotine accumulates primarily in the kidney, followed by the liver, heart, brain, muscle and adipose tissue. If the dose to the blood is calculated for nicotine, therefore, the dose to other organs or tissues may be obtained by multiplying by the ratios in Table C-1. It is unlikely, however, that the same ratios will apply to other chemicals in ETS.

C.2.3. Summary

A measure of exposure to a given *chemical* in ETS could take several forms:

1) Exposure Intensity, C, in units of g/m^3.

2) Cumulative Exposure, ψ, in units of $g\text{-days}/m^3$ (see Equations 1 and 2).

3) Lung Intake, I, in units of grams of chemical (see Equation 3).

4) Total Lung Uptake, U, or Uptake to the P region, U^P, TB region, U^{TB}, or NP region, U^{NP}, in units of grams of chemical (see Equations 4-7).

5) Total Lung Burden, B, or Burden in the P region, B^P, TB region, B^{TB}, or NP region, B^{NP}, in units of grams of chemical (see Equations 8-11).

6) Integral Organ Burden, IB, in units of gram-days of chemical.

7) Total Lung Dose, D, or Dose to the P region, D^P, TB region, D^{TB}, or NP region, D^{NP}, in units of gram-days of chemical.

TABLE C-1. STEADY-STATE RATIO OF CONCENTRATIONS OF NICOTINE IN BODY TISSUES OR ORGANS

Tissue	Ratio*
Blood	1.0
Brain	3.0
Heart	3.7
Muscle	2.0
Adipose	0.5
Kidneys	21.6
Liver	3.7
Lung	2.0
Gastrointestinal	3.5

*Relative to blood.

Source: U.S. Surgeon General (1986).

obtained from Intake or Uptake (above) or:

8) Blood Uptake, U^b, in units of grams of chemical (see Equation 19).

9) Organ Uptake, U^j, in units of grams (see Equation 20).

10) Integral Organ Burden, IB^j, in units of gram-days of chemical (see Equations 21-24 divided by K).

11) Organ Dose, D^j, in unit of gram-days of the chemical in the organ (see Equations 21-24). This generally will not be possible to calculate.

12) Biologically Active Organ Dose, D_B^j, in units of gram-days of the biologically active form. This generally will not be possible to calculate.

The measure of exposure to a chemical depends upon the level of available information. In cases where parameter values are unknown, it will not be possible to calculate values that depend upon those parameters. In such cases, the measure further "upstream" in the chain of calculations must be used. For example, the retention functions for many of the chemicals in ETS are not available at present. For these chemicals, uptake is the most highly developed measure of dose possible. For vapor phase chemicals, the deposition fractions or equilibrium concentration ratios (tissue:air) have not been measured to date, leaving intake as the best available measure of exposure.

C.3. ASSUMED EXPOSURE CONDITIONS AND INTAKES

Exposure to ETS may vary widely due to differences in cigarette type, rate of smoking, ventilation conditions, room volume, etc. No attempt is made here to develop calculations under the immense range of conditions likely to be found in society. Instead, calculations are presented for a simplified case that is typical of exposure conditions. The exposure duration, T, for both active and passive smokers is taken to be one day, with exposure to ETS at a constant concentration, C (see the equations in Section 2 of this report). Of interest is the dose

delivered to tissues as a result of this single day of exposure. Predictions at any other concentration, C*, and any other exposure length, T*, may be obtained by multiplying the reported value by:

$$\frac{C^*}{C} \times \frac{T^*}{T}$$

For this example it is assumed that an active smoker smokes one pack (20 cigarettes) in a structure of volume 150 m^3 over a one day period with a passive smoker present. The NRC (1986) reports an average of 26 mg of respirable suspended particulate (RSP) matter per cigarette in the sidestream smoke (SS), giving an emission rate of 22 mg/hour. With an air exchange rate of 1 per hour, an approximate U.S. average, in a room volume of 150 m^3, the concentration of RSP in the air will be approximately 200 $\mu g/m^3$ (see Figures 5-4 and 5-6 in NRC, 1986). Assuming a tidal volume of 750 mL and a breathing frequency of 15 per minute (Crawford-Brown, 1987), the total daily intake of RSP for the passive smoker will be approximately 3 mg.

Rickert et al. (1984) measured the RSP in mainstream smoke (MS) and found a range of 0.7 to 17 mg per cigarette, for cigarettes primarily low in tar. By contrast, the NRC (1986) report 15 to 40 mg for non-filter cigarettes. A moderate value of 12 mg will be assumed here. The daily intake of RSP for an active smoker of 20 cig./day will be 240 mg. The values of 240 mg in the active smoker and 3 mg in the passive smoker correspond to values assumed by Wells (1988).

The distributions of chemicals by mass in the MS from one nonfilter cigarette are displayed in Table C-2 by vapor and particulate phase (NRC, 1986). In this table, a representative value from the NRC report (1986) is reported. Also shown in the table are the ratios of the amount of each chemical leaving the cigarette in diluted SS and in MS. The total

TABLE C-2. APPROXIMATE COMPOSITION OF MAINSTREAM (MS) AND DILUTED SIDESTREAM SMOKE (SS) FROM ONE NON-FILTER CIGARETTE*

Constituent	Average MS	Average SS/MS
Vapor Phase in MS		
Carbon monoxide	15 mg	3
Carbon dioxide	30 mg	10
Carbonyl sulfide	30 μg	0.1
Benzene	30 μg	8
Toluene	150 μg	7
Formaldehyde	85 μg	20
Acrolein	80 μg	12
Acetone	175 μg	3
Pyridine	30 μg	13
3-Methylpyridine	25 μg	13
3-Vinylpyridine	20 μg	10
Hydrogen cyanide	450 μg	30
Hydrazine	30 μg	3
Ammonia	90 μg	110
Methylamine	20 μg	5
Dimethylamine	9 μg	4
Nitrogen oxides	400 μg	7
N-nitrosodimethylamine	30 ng	60
N-nitrosodiethylamine	20 ng	30
N-nitrosopyrrolidine	20 ng	18
Formic acid	350 μg	1.5
Acetic acid	500 μg	3
Methyl chloride	350 μg	2.5
Particulate Phase in MS		
RSP	24 mg	1.5
Nicotine	14 mg	3
Anatabine	10 μg	0.3
Phenol	100 μg	2.5
Catechol	200 μg	0.7
Hydroquinone	200 μg	0.8
Aniline	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine	2 ng	30
4-Aminobiphenyl	5 ng	31
Benz(a)anthracene	50 ng	3

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TABLE C-2. (continued)

Constituent	Average MS	Average SS/MS
Benzo(a)pyrene	30 ng	3
Cholesterol	20 μg	0.9
λ-Butyrolactone	15 μg	4
Quinoline	1 μg	10
Harman	2 μg	1
N-nitrosonornicotine	1500 ng	2
NNK	500 ng	3
N-nitrosodiethanolamine	50 ng	1
Cadmium	100 ng	7
Nickel	50 ng	20
Zinc	60 ng	7
Polonium-210	0.1 pC_i	3
Benzoic acid	20 μg	0.8
Lactic acid	100 μg	0.6
Glycolic acid	100 μg	0.8
Succinic acid	120 μg	0.5

*Adapted from Table 2-2 of NRC (1986).

RSP inhaled in one day by the passive smoker in our example is proportional to its concentration in air of 200 $\mu g/m^3$. As noted above, using that value and Table C-2, the concentration of other chemicals inhaled from SS can be obtained from the relation

$$C_i = 200 \times \left[\frac{M_i}{M_{RSP}}\right] \times \left[\frac{R_i}{R_{RSP}}\right], \qquad (25)$$

where C_i is the concentration of chemical i in the room air ($\mu g/m^3$), M_i is the average mass of chemical i in MS and M_{RSP} is the mass of RSP in MS (both taken from Table C-2), R_i is the ratio SS/MS for chemical i from Table C-2 and R_{RSP} is the ratio SS/MS for RSP. Computed values of C_i and the intakes for the passive smoker and the active smoker are shown in Table C-3 for known carcinogens in tobacco smoke.

The calculations in Table C-3 presume fresh diluted SS, which ages over time. This aging may change the physicochemical properties of the ETS due to plating, ventilation, metabolism, etc. (NRC, 1986). Little is known, however, about the effect of aging. For reference, the average concentration of several airborne components of ETS measured under diverse environmental conditions are shown in Table C-4 (adapted from Repace, 1987).

Since the results in Table C-4 were obtained under such a wide range of conditions, absolute concentrations of chemicals in aged air are difficult to specify for the environmental conditions assumed in this report. Still, a limited comparison of relative values can be made by focusing on nicotine, benzene, N-nitrosodimethylamine and N-nitrosodiethylamine, since these measuresurements were made under roughly similar conditions in a room with a large number of smokers (Badre et al., 1978; Brunnemann et al., 1978; Stehlik et al., 1982). From these measurements, the relative concentrations of nicotine: benzene: N-nitrosodimethylamine: N-nitrosodimethylamine are 1:0.2:0.0002:0.0001. These values may be compared against the predictions using fresh diluted SS in Table C-3, which suggest values of 1:0.06:0.00004:0.0001. The relative concentrations of these four chemicals, therefore, do not appear to have been significantly affected by aging, with the possible exception of benzene. The reason for the increase in benzene after aging is unknown. The benzene estimate is based on a single small sample, which may be a factor. Subsequent calculations will use the concentrations and intake values in Table C-3 based on fresh diluted SS. There is need for more research on the effects of aging for ETS.

TABLE C-3. SUMMARY OF CONCENTRATIONS AND DAILY INTAKES FOR CONSTITUENTS OF CIGARETTE SMOKE, ASSUMING FRESH SS

Constituent*	C_i^{**}	$I_p^{\dagger}$	$I_p^{\dagger\dagger}$
Benzene	1.3 $\mu g/m^3$	21 μg	300 μg
Hydrazine	0.5 ng/m^3	8 ng	300 ng
N-nitrosodimethylamine	30.0 ng/m^3	160 ng	300 ng
N-nitrosodiethylamine	3.0 ng/m^3	48 ng	200 ng
N-nitrosopyrrolidine	2.0 ng/m^3	32 ng	200 ng
RSP[a]	200.0 $\mu g/m^3$	3 mg	240 mg
Nicotine[b]	23.0 $\mu g/m^3$	370 μg	14 mg
2-Naphthylamine[a]	0.3 ng/m^3	5 ng	20 ng
4-Aminobiphenyl[a]	0.9 ng/m^3	14 ng	50 ng
Benz(a)anthracene[a]	0.8 ng/m^3	13 ng	500 ng
Benzo(a)pyrene[a]	0.5 ng/m^3	8 ng	300 ng
λ-Butyrolactone[a]	0.3 $\mu g/m^3$	5 ng	150 μg
N-nitrosonornicotine[a]	17.0 ng/m^3	270 ng	15 μg
N-nitrosodiethanolamine[a]	0.3 ng/m^3	5 ng	500 ng
Nickel[a]	6.0 ng/m^3	96 ng	500 ng
Polonium-210[a]	2.0 nC_i/m^3	32 nC_i	1 pC_i

* Only constituents listed as human carcinogens, suspected human carcinogens or animal carcinogens (NRC, 1986) are listed, with the exception of nicotine (a precursor to carcinogens).

** For passive exposures only.

† Intake for passive exposure.

†† Intake for active exposure.

[a] Chemicals located in the particulate phase for both active and passive smokers.

[b] Nicotine is assumed to be entirely in the particulate phase for active smokers and entirely in the vapor phase for passive smokers.

TABLE C-4. MEASUREMENTS OF ETS CONSTITUENTS IN ENVIRONMENTAL SETTINGS*

Constituent	Setting	Average concentration	Reference
Acrolein	Varied	0.1 mg/m^3	Badré et al., 1978
	Varied	8.0 ppb	Fischer et al., 1978, and Weber et al., 1979
Benzene	Varied	0.1 mg/m^3	Badré et al., 1978
Toluene	Varied	1.0 mg/m^3	Badré et al., 1978
Benzo(a)pyrene	Arena	10.0 ng/m^3	Elliot and Rowe, 1975
	Restaurant	6.0 ng/m^3	Galuskinova, 1964
	Coffeehouses	5.0 ng/m^3	Just et al., 1972
	Restaurant	10.0 ng/m^3	Husgafvel-Pursiainen et al., 1986
	Public places	100.0 ng/m^3	Perry, 1973
Carbon monoxide	Varied	20.0 ppm	Badré et al., 1978
	Varied	8.0 ppm	Chappell and Parker, 1977
	Rooms varied	5.0 ppm	Coburn et al., 1965
	Taverns	12.0 ppm	Cuddleback et al., 1976
	Planes	3.0 ppm	USDOT, 1971
	Arenas	15.0 ppm	Elliott and Rowe, 1975
	Restaurant	3.0 ppm	Weber et al., 1979
	Restaurant	5.0 ppm	Fischer et al., 1978
	Varied	10.0 ppm	Godin et al., 1972

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TABLE C-4. (continued)

Constituent	Setting	Average concentration	Reference
	Office	5.0 ppm	Harke, 1974
	Car	40.0 ppm (peak)	Harke and Peters, 1974
	Train	20.0 ppm	Harmsen & Effenberger, 1957
	Public places	8.0 ppm	Perry, 1973
	Rooms	15.0 ppm	Portheine, 1971
	Varied	10.0 ppm	Stebben et al., 1977
	Conference rooms	8.0 ppm (peak)	Slavin and Hertz, 1975
	Offices	3.0 ppm	Szadkowski et al., 1976
Nicotine	Varied	100.0 $\mu g/m^3$	Badré et al., 1978
	Submarines	30.0 $\mu g/m^3$	Cano et al., 1970
	Train	2.0 $\mu g/m^3$	Harmsen & Effenberger, 1957
	Varied	6.0 $\mu g/m^3$	Hinds & First, 1975
	Restaurants	15.0 $\mu g/m^3$	Muramastu et al., 1984
N-nitrosodi-methylamine	Varied	100.0 ng/m^3	Brunnemann & Hoffmann, 1978, and Brunnemann et al., 1978
	Restaurants	25.0 ng/m^3	Stehlik et al., 1982

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TABLE C-4. (continued)

Constituent	Setting	Average concentration	Reference
RSP	Varied	200.0 $\mu g/m^3$	Repace and Lowrey, 1980
	Varied	300.0 $\mu g/m^3$	Repace and Lowrey, 1982
	Coffeehouses	1000.0 $\mu g/m^3$	Just et al., 1972
	Hospital	30.0 $\mu g/m^3$	Neal et al., 1978
	Residences	60.0 $\mu g/m^3$	Spengler et al., 1981
	Offices	130.0 $\mu g/m^3$	Weber and Fischer, 1980
	Offices	50.0 $\mu g/m^3$	Nelson et al., 1982
	Restaurants	1000.0 $\mu g/m^3$	Husgafvel-Pursiainen et al., 1986
	Houses	150.0 $\mu g/m^3$	Brunekreef and Beleij, 1982
	Tavern	600.0 $\mu g/m^3$	Cuddleback et al., 1976
	Residences	30.0 $\mu g/m^3$	Dockery and Spengler, 1981
	Arenas	400.0 $\mu g/m^3$	Elliott and Rowe, 1975
Acetone	Varied	1.0 mg/m^3	Badré et al., 1978
Sulfates	Residences	5.0 $\mu g/m^3$	Dockery and Spengler, 1981

*Adapted from Repace (1987).

Application of the dosimetry model of ETS beyond the initial step of predicting inhalation becomes hampered by the large amount of detailed biological information required for the carcinogens in tobacco smoke. This limitation is more applicable to the vapor phase, however, than to the particulate phase. In the latter case, many of the dosimetric characteristics are largely dependent on the distribution of the size and density of particulates rather than chemical-specific properties. To continue illustration of our example as possible, and also to identify where information is available and where it is needed, we will consider the particulate phase further but not the vapor phase. The information available for calculation by lung regions is disparate, so assumptions will be made explicit as required to complete calculations for lung dose from the particulate phase for our example. We have stopped short of introducing assumptions that do not seem "reasonable," however, simply for the sake of illustration. The calculated values may be viewed as approximations, vis-a-vis the assumptions used. In any event, intake of vapor phase components is included in Table C-3.

Fortunately, one of the major constituents of interest in tobacco smoke, nicotine, has been sufficiently studied that much of the information required for prediction of lung and systemic organ dose of nicotine and the metabolite cotinine can be calculated for our example, including both the vapor and particulate phases for active and passive smoking. Nicotine dosimetry is particularly relevant because it is the addictive factor in active smoking and is a pre-cursor of tobacco specific nitrosamines, at least one of which (NNK) is a potent carcinogen (Hoffmann and Hect, 1989). Also, nicotine forms the tobacco-specific metabolite cotinine, widely considered to be the preferred biomarker for ETS exposure. Calculations for nicotine/cotinine are in Section C.6.

C.4. UPTAKE OF PARTICULATE PHASE CHEMICALS.

Due to lack of data on uptake of vapor phase components by lung tissue, only the uptake of particulate phase chemicals can be considered here. For chemicals in the vapor phase, the proportionality constant to convert from intake to uptake may differ between chemicals. The lack of chemical-specific data on uptake from the vapor phase is a major limitation for comparison of carcinogenicity of tobacco smoke to active and passive smokers. There is a pressing need for research on concentration ratios (air:tissue) for vapor phase components of ETS.

In calculating uptake of particulate phase chemicals, it is necessary to specify regional deposition fractions (Equations 5 through 7). A primary environmental determinant of these fractions is particle diameter. The mean diameter for MS has been reported to range from 0.1μ to 1μ (Carter and Hasegawa, 1975; Hiller et al., 1982), and from 0.01μ to 0.8μ for SS. For the calculations reported here, a Mass Median Aerodynamic Diameter or MMAD of 0.7μ is used for MS (Stöber, 1984) and a MMAD of 0.4μ is assumed for fresh diluted SS (Wells, 1988). The particle diameters are assumed to be distributed lognormally with a geometric standard deviation (GSD) of 1.5 (Stöber, 1984).

Aged air, however, may contain a different distribution of aerosol sizes. Several authors (Keith and Derrick, 1960; Wynder and Hoffman, 1967; Ingebrethsen and Sears, 1985) have demonstrated that the MMAD for cigarette smoke decreases by a factor of 2 to 3 due to aging. This appears to be due to the loss of large particles from the suspended aerosol, as may be seen in the measured and predicted distributions published by Nazaroff and Cass (1989). An additional factor may be the "boiling off" of chemicals from the RSP. The present report, therefore, assumes that the MMAD for aged ETS is on the order of 0.15μ, and that for direct smoking is 0.7μ.

Total deposition of smoke in the lung has been reviewed by Stöber (1984), based primarily on studies by Hiller et al. (1982), Mitchell (1962), and Polydorova (1961). These results suggest that as much as 80% of the MS particulates are deposited in the lung (i.e., $f_{NP} + f_{TB} + f_P = 0.8$), while 10% to 20% of the ETS particulates are deposited. The value for ETS is consistent with the predictions of total lung deposition from an age-dependent model by Crawford (1982, 1983), which yields values of 1%, 4%, and 10% for f_{NP}, f_{TB}, and f_P, respectively, for a MMAD of 0.15μ.

The very high value of total deposition in active smokers appears to arise from several factors. The first is hygroscopic growth, which may be expected to double the size of particulate MS from 0.7μ to 1.4μ (Ishizu et al., 1980). The second factor is breath-holding, in which cigarette smoke is held in the lungs for several seconds prior to exhalation. If the model of Crawford (1982, 1983) is used with a breath-holding period of 3 seconds, particle diameters of 1.4μ are predicted to yield values of 1%, 15%, and 60% for f_{NP}, f_{TB}, and f_P, respectively. Since these sum to approximately the 80 percent reported in experiments, these values will be assumed here. Hygroscopic growth of ETS particles will not be assumed, since the inhaled and exhaled particles appear to be of the same diameter (Hiller et al., 1982).

As described previously, the total intake of RSP is assumed to be 240 mg in an active smoker and 3 mg in a passive smoker in our example. Using these values in conjunction with the estimates of f_{NP}, f_{TB}, and f_P from Equations 5 through 7, the calculated daily uptakes in mg by lung region are 12 mg, 36 mg and 144 mg for the NP, TB and P regions of the active smoker; 0.03 mg, 0.12 mg and 0.3 mg for the NP, TB and P regions of the passive smoker.

C.5. INTEGRAL ORGAN BURDENS FOR THE LUNG

C.5.1. Integral Organ Burden from RSP

Due to the very low assumed deposition fractions in the NP region, the focus of this discussion will be on the TB and P regions.

Translocation of the particles is on the mucus layer, which is driven forward towards the esophagus by the cilia. The velocity of this mucus blanket decreases dramatically in the deeper sections of the TB region. As a result, the length of time a particle resides in the lung depends critically on the site of deposition. Data on the removal of radiolabeled particles, however, show that removal from the TB region generally may be characterized by two phases. The first is a rapidly cleared phase, dominated by particles deposited on the mucus of the upper passageways. The second is dominated by particles deposited on the slowly moving mucus of distal passageways. Both phases are controlled primarily by the movement of the mucus and the site of deposition of the particles rather than on the chemical nature of the particles. It is possible, therefore, to use the results of the radiolabeled aerosol studies to estimate the retention of particulate ETS in the TB region.

Crawford and Eckerman (1983) have used the deposition model of Crawford (1982) and a model of mucus movement, in conjunction with measurements of retention of radiolabeled aerosol particles in healthy (non-smoking) human lungs, to develop predictive equations of retention. These retention functions contain two exponentials, corresponding to the two removal phases described above. The parameters in these equations depend upon the aerosol diameter and breathing characteristics. The general form of the equation is:

$$R(t) = (1 - b)e^{-0.693t/C_1} + b\ e^{-0.693t/C_2}$$

where t is the time since uptake into the TB region (in minutes). The parameter b is a function of median aerosol diameter, age, the GSD of the particle distribution and breathing characteristics. This parameter value equals the fraction of deposited particles found in the slowly removed component. The parameters C_1 and C_2 are the removal half-times for the rapid and slow components, respectively.

As described earlier, the MMAD for ETS particles is 0.15μ, with a GSD of 1.5. Applying the results of Crawford and Eckerman (1983) to ETS, yields values for b, C_1, and C_2 of 0.98, 450, and 710 minutes, respectively. For a MMAD of 1.4μ and a GSD of 1.5, the values of b, C_1, and C_2 are 0.82, 280, and 700 minutes, respectively. The flow of mucus in the TB region of active smokers, however, is reduced by a factor of 2 (Albert et al., 1975; Wanner et al., 1973). If the parameter values for 1.4μ in normal (non-smoking) lungs are changed to reflect the condition of slowed mucus, the half-times in the retention function would be doubled. For active smokers, therefore, C_1 and C_2 would be 560 minutes and 1400 minutes, respectively. The value of b should be unchanged.

The daily integral organ burden to the TB region from RSP may be obtained from Equation 15 by setting K equal to unity, f equal to f_{TB}, C × V equal to the daily intake of RSP, and T equal to 1440 minutes (24 hours). Using these values, the daily RSP integral organ burden to the TB region is 64,873 and 122 mg-minutes for the active and passive smokers in our example, respectively.

Solubilization and engulfment by macrophages generally dominate removal from the P region of the lung. Unfortunately, few data are available on the removal of RSP from the deep lung. It is known, however that the constituent chemical nicotine deposited in active smokers is highly soluble in lung fluid (Janoff et al., 1987). Black and Pritchard (1984) have found an alveolar retention half-time of 17 hours for RSP in active smokers, which will be used in our example. Similar measurements in passive smokers are not available. At this time, we use the same half-time for both passive and active smokers. Additional research is needed to accurately quantify removal of RSP in passive smokers. As a first approximation, a half-time of 17 hours for RSP removal will be assumed for both active and passive smokers (Wells, 1988). The retention function for the P region is

$$R(t) = e^{-0.693t/1020},$$

where t is in minutes since deposition. From Equation 15 for f_P and the daily intakes of RSP described earlier, the daily integral organ burden to the P region is 1.9×10^5 mg-minutes in active smokers and 390 mg-minutes in passive smokers.

C.5.2 Lung Integral Organ Burden from Particulate Chemicals

Chemicals should solubilize from the RSP at different rates, thereby affecting dose rate to the lung. Data to differentiate between chemical dose rates, however, are not available. The retention half-times used earlier will, therefore, be used here for other chemicals contained in particles. The ratio of integral organ burdens from chemical components, relative to RSP values, may be obtained from the ratio of intakes of those chemicals in the particulate phase shown in Table C-3. Daily integral organ burden to the lung by chemicals in the particulate phase have been calculated for the active and passive smoker of our example and are displayed in Table C-5.

C.6. CALCULATIONS FOR NICOTINE AND COTININE

The intake of nicotine by the active and passive smoker in the example described come from the particulate and vapor phases, respectively (Eudy, 1986). Leaderer (1988) gives the percentage of nicotine in the vapor phase of ETS as 95+, while Pritchard (1990) gives it as 70%.

TABLE C-5. DAILY INTEGRAL ORGAN BURDENS* FOR PARTICULATE PHASE CHEMICALS AS CALCULATED IN THIS REPORT
All Doses Are in mg-Minutes

Constituent	IB_P^{TB}	IB_P^P	IB_A^{TB}	IB_A^P
RSP	122	390	6.5×10^4	1.9×10^5
Nicotine	0	0	3.9×10^3	1.1×10^4
2-Naphthylamine	2×10^{-4}	6.2×10^{-3}	5.4×10^{-3}	0.016
4-Aminobiphenyl	5.6×10^{-4}	1.7×10^{-3}	1.4×10^{-2}	0.04
Benz(a)anthracene	5.2×10^{-4}	1.5×10^{-3}	0.14	0.4
Benzo(a)pyrene	3.2×10^{-4}	9.3×10^{-4}	0.08	0.24
λ-Butyrolactone	2×10^{-4}	5.8×10^{-4}	0.04	0.12
N-nitrosonornicotine	1.1×10^{-2}	3.1×10^{-2}	0.004	0.012
N-nitrosodiethanolamine	2×10^{-4}	5.8×10^{-4}	0.14	0.4
Nickel	3.8×10^{-3}	1.1×10^{-2}	0.14	0.4

* Superscript on IB indicates lung region (TB for tracheobronchial and P for pulmonary), and the subscript indicates passive (P) or active (A) smoker.

Our calculations, which presume that nicotine is entirely in the particulate phase for active smokers and entirely in the vapor phase for passive smokers, have been given in Table C-3. Nicotine concentrations have been measured in body fluids of active and passive smokers following known experimental exposure, providing information that can be applied to dosimetry calculations. Jarvis et al. (1984) have reported the results of nicotine measurements, which are summarized in Table 8-3 of the NRC report (1986). The nicotine/cotinine in the body fluids of passive smokers tends to be about 1% of the levels in active smokers.

As measured by Jarvis et al. (1988), Sepkovic et al. (1986), Kyerematen et al. (1982), and Benowitz et al. (1983), the clearance half-time for cotinine from the systemic body organs is on the order of 15 hours in active smokers. Sepkovic et al. (1986) suggest that this value for passive smokers is close to 45 hours. Their published data, however, indicate a half-time closer to 25 hours, a conclusion agreed upon by Jarvis et al. (1988). The half-time of 25 hours is more consistent with the measurements of urine excretion (Jarvis et al., 1988), where the half-time in passive smokers was 33 hours and in active smokers was 22 hours. This suggests that the passive-to-active ratio of half-times for removal of cotinine is about 1.5. For this ratio of excretion half-times, the data on body fluids (Jarvis et al., 1984) suggest that passive smokers take nicotine into their blood at a rate of 0.01/1.5 times the rate in active smokers, i.e., about 0.7% of the rate in active smokers. If it is assumed further that nicotine requires the same length of time to traverse the alveolar cells in passive and active smokers, a topic on which no data are available, then the ratio (active:passive) of integral organ burden for blood will equal approximately the ratio of rates into the bloodstream. This conclusion requires the assumption that the GI tract does not contribute significantly to the nicotine in the bloodstream. Data on nicotine absorption are not available at present. Since the nicotine dose to the P region is 11,000 mg-minutes for active smokers (see Table C-5), the integral organ burden to the lungs of passive smokers from vapor phase nicotine to this region will be approximately 80 mg-minutes

(or 11,400 × 0.007). For the TB region, the integral organ burden to the lungs will be 3900 × 0.007 or 27 mg-minutes. Neither the TB nor P region integral organ burdens are affected if the fraction of nicotine in the vapor phase is set equal to 70% instead of 100%. This invariance is due to the reliance on measured blood uptake for the calculation of integral organ burdens.

There is little available information on the uptake of chemicals to the bloodstream from which to calculate systemic organ doses. Again, nicotine/cotinine is an exception since measurements of body fluid concentrations and clearance half-times are available. As described above, nicotine is highly soluble in lung tissue, which implies that $f_{P,b}$ and $f_{TB,b}$ in Equation 19 are approximately 1. Thus, the uptake of nicotine to the bloodstream then equals the uptake into the P and TB regions of the lung. Once in the bloodstream, nicotine is converted to cotinine, as described by Jacob et al. (1988). This metabolic model is shown in Figure C-3, from which it may be seen that 70% of the nicotine is converted to cotinine, 9% goes directly to the urine, and 4% is metabolized to nicotine n-oxide. The remaining 17% is unaccounted for at present.

Nicotine is removed from the blood with a half-time of 2 hours in smokers (Jacob et al., 1988; Benowitz et al., 1982). As described above, the ratio of removal half-times for cotinine in passive and active smokers is 1.5. If this same ratio applies to the conversion of nicotine, passive smokers would display a removal half-time of 3 hours. If this ratio does not apply, both groups would possess a half-time of 2 hours. The retention function for nicotine then is either

$$R(t) = e^{-0.693t/2}$$

or

$$R(t) = e^{-0.693t/3},$$

depending on whether the removal half-time is 2 or 3 hours, respectively; t is in hours. Applying Equation 23, the daily integral organ burden from nicotine to the systemic organs of active

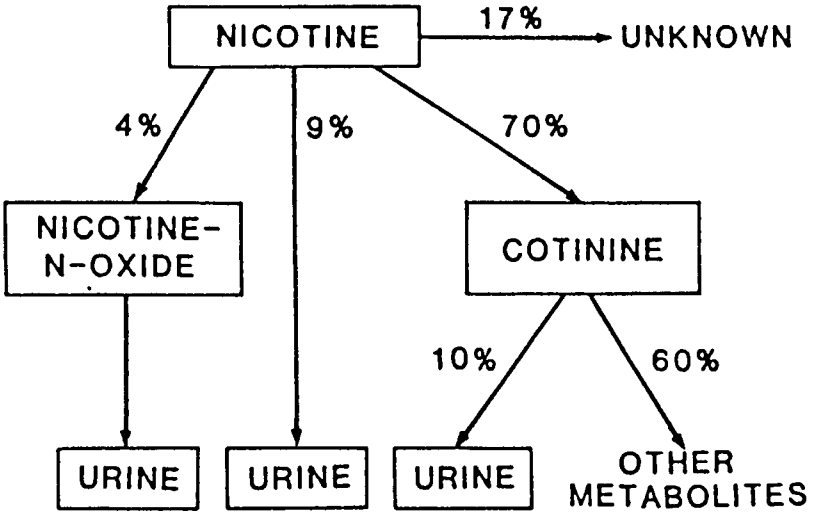

FIGURE C-3. A METABOLIC MODEL FOR THE CONVERSION OF NICOTINE AND THE EXCRETION

smokers is 2000 mg-minutes. The daily dose from nicotine to the systemic organs of passive smokers, using 0.7% of the value in active smokers, as discussed above, is approximately 16 mg-minutes if the half-time is 2 hours, and 27 mg-minutes if the half-time is 3 hours. Since the data of Kyerematen et al. (1982) and Lee et al. (1987) suggest that the rate of metabolism of nicotine is higher in active smokers, the latter value of 27 mg-minutes appears to be the best estimate.

The calculation of systemic organ doses from cotinine is more complicated than Equation 15, since cotinine is a metabolic product. The burden of nicotine in the blood at any time, t, after an uptake U_n is

$$B_n(t) = U_n e^{-0.693t/T},$$

where T is the removal half-time for nicotine (either 2 or 3 hours). The differential equation describing the rate of change of the burden of cotinine, $B_c(t)$, in blood then is:

$$\frac{dB_c(t)}{dt} = 0.693B_n(t)/T_c - 0.693B_c(t)/T_e, \tag{26}$$

where T_c is the conversion half-time from nicotine to cotinine and T_e is the elimination half-time for cotinine from the body (15 hours in smokers and 25 hours in passive smokers). The burden of cotinine is obtained by solving Equation 26 to yield

$$B_c(t) = \frac{\lambda_c U_n (e^{-\lambda t} - e^{-\lambda_e t})}{(\lambda_e - \lambda)} \tag{27}$$

where

$$\lambda_c = 0.693/T_c$$
$$\lambda_e = 0.693/T_c$$
$$\lambda = 0.693/T$$

and U_n is 10.6 mg in the active smoker and 0.08 mg in the passive smoker. The dose from cotinine then is obtained from Equations 12 and 13. The value of T_c is equal to T/0.7, where 0.7 is the fraction of nicotine converted to cotinine. The daily integral organ burden to the systemic organs of the active smoker then is 7660 mg-minutes. The daily integral organ burden to the passive smoker is approximately 145 mg-minutes if T is three hours and 140 mg-minutes if T is two hours. The measures calculated for nicotine and cotinine, and their ratios in MS to ETS, are included in Table C-6 and C-7.

TABLE C-6. SUMMARY OF DOSE MEASURES CALCULATED IN THIS REPORT (FOR OTHER PARTICULATE PHASE DOSES, SEE TABLE C-5)

Constituent	Measure	Value
1. Total RSP	Intake	P* = 3 mg A* = 240 mg
	Uptake	
	a. NP region	P = 0.03 mg A = 12 mg
	b. TB region	P = 0.12 mg A = 36 mg
	c. P region	P = 0.3 mg A = 144 mg
	Integral Organ Burden	
	a. NP region	P = na**
	b. TB region	P = 122 mg-min. A = 64,873 mg-min.
	c. P region	P = 390 mg-min. A = 1.9×10^5 mg-min.
2. Nicotine (particulate)	Intake	P = 0 mg A = 14 mg
	Uptake	
	a. NP region	P = 0 mg A = 0.72 mg
	b. TB region	P = 0 mg A = 2.2 mg
	c. P region	P = 0 mg A = 8.6 mg

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TABLE C-6. (continued)

Constituent	Measure	Value
	Integral Organ Burden	
	a. NP region	P = 0 mg A = na
	b. TB region	P = 0 mg A = 3800 mg-min.
	c. P region	P = 0 mg A = 11,000 mg-min.
	d. Systemic organs	P = 0 A = 2000 mg-min.
3. Cotinine (particulate)	Integral Organ Burden to systemic organs	P = 0 A = 7600 mg-min.
4. Nicotine (vapor)	Intake	P = 0.37 mg A = 0 mg
	Uptake	
	a. NP region	P = na A = 0 mg
	b. TB region	P = na A = 0 mg
	c. P region	P = 0.06 mg A = 0 mg
	Integral Organ Burden	
	a. NP region	P = na A = 0 mg
	b. TB region	P = 27 mg-min. A = 0 mg-min.
	c. P region	P = 80 mg-min. A = 0 mg-min.

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TABLE C-6. (continued)

Constituent	Measure	Value
	d. Systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 16 mg-min. A = 0 mg-min.
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 27 mg-min. A = 0 mg-min.
5. Cotinine (vapor)	Integral Organ Burden to systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 140 mg-min. A = 0 mg-min.
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 145 mg-min. A = 0 mg-min.
6. Nicotine (total)	Intake	P = 0.37 mg A = 14 mg
	Uptake	
	a. NP region	P = na A = 0.72 mg
	b. TB region	P = na A = 2.2 mg
	c. P region	P = 0.06 mg A = 8.6 mg
	Integral Organ Burden	
	a. NP region	P = na A = na
	b. TB region	P = 27 mg-min. A = 3800 mg-min.
	c. P region	P = 80 mg-min. A = 11,000 mg-min.

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TABLE C-6. (continued)

Constituent	Measure	Value
	d. Systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 16 mg-min. A = 2000 mg-min.
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 27 mg-min. A = 2000 mg-min.
7. Cotinine (total)	Integral Organ Burden to systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 140 mg-min. A = 7660 mg-min.
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 145 mg-min. A = 7660 mg-min.
8. Benzene	Intake	
	i. Using fresh SS	P = 21 μg A = 300 μg
	ii. Using aged SS	P = 65 μg*** A = 300 μg
9. Hydrazine	Intake	
	i. Using fresh SS	P = 8 ng A = 300 ng
	ii. Using aged SS	P = 8 ng*** A = 300 ng
10. N-nitroso-dimethylamine	Intake	
	i. Using fresh SS	P = 160 ng A = 300 ng
	ii. Using aged SS	P = 80 ng*** A = 300 ng

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TABLE C-6. (continued)

Constituent	Measure	Value
11. N-nitroso-diethylamine	Intake	
	i. Using fresh SS	P = 48 ng A = 200 ng
	ii. Using aged SS	P = 48 ng*** A = 200 ng
12. N-nitroso-pyrrolidine	Intake	
	i. Using fresh SS	P = 32 ng A = 200 ng
	ii. Using aged SS	P = 32 ng*** A = 200 ng

* P ≡ Passive, A ≡ Active.

** na = not available for calculation due to insufficient information.

*** Obtained by multiplying the passive smoking intake for fresh SS by R, where R is the ratio of the concentration of the chemical relative to nicotine in aged SS to the concentration of the chemical relative to nicotine in fresh SS.

TABLE C-7. SUMMARY OF RATIO OF MEASURES (ETS/MS) CALCULATED IN THIS REPORT

Measure of Dose	Ratio
1. Intake of Total RSP	0.013
2. Uptake of Total RSP	
a. NP region	0.0025
b. TB region	0.003
c. P region	0.002
3. Integral Organ Burden of Total RSP	
a. NP region	na*
b. TB region	0.002
c. P region	0.002
4. Intake of Particulate Nicotine	0
5. Uptake of Particulate Nicotine	
a. NP region	0
b. TB region	0
c. P region	0
6. Integral Organ Burden of Particulate Nicotine	
a. NP region	0
b. TB region	0
c. P region	0
d. Systemic organs	0
7. Integral Organ Burden of Cotinine (from particulate nicotine)	
a. Systemic organs	0
8. Intake of Vapor Nicotine	Very large†
9. Uptake of Vapor Nicotine	Very large
10. Integral Organ Burden of Vapor Nicotine	
a. NP region	Very large
b. TB region	Very large
c. P region	Very large
d. Systemic organs	Very large

(continued on following page)

TABLE C-7. (continued)

Measure of Dose	Ratio
11. Integral Organ Burden of Cotinine (from vapor nicotine)	
a. Systemic organs	Very large
12. Total Intake of Nicotine	0.03
13. Total Integral Organ Burden of Nicotine	
a. NP region	na
b. TB region	0.01
c. P region	0.01
d. Systemic organs	
i. Passive smoking Conversion $T_{½}$ = 2 hours	0.01
ii. Passive smoking Conversion $T_{½}$ = 3 hours	0.015
14. Total Integral Organ Burden of Cotinine (Systemic organs)	
i. Passive smoking Conversion $T_{½}$ = 2 hours	0.02
ii. Passive smoking Conversion $T_{½}$ = 3 hours	0.02
15. Intake of Benzene	
a. Using fresh SS	0.07
b. Using aged SS	0.2
16. Intake of Hydrazine	
a. Using fresh SS	0.03
b. Using aged SS	0.03
17. Intake of N-nitrosodimethylamine	
a. Using fresh SS	0.5
b. Using aged SS	0.3
18. Intake of N-nitrosodiethylamine	
a. Using fresh SS	0.2
b. Using aged SS	0.2
19. Intake of N-nitrosopyrrolidine	
a. Using fresh SS	0.15
b. Using aged SS	0.15

*na ≡ not applicable due to lack of data.
†Very large occurs when the value for active smokers is zero.

APPENDIX D

ALTERNATIVE APPROACHES FOR ESTIMATING THE YEARLY NUMBER OF LUNG CANCER DEATHS IN NON-SMOKERS DUE TO ETS BASED ON DOSE-RESPONSE MODELING

D.1. INTRODUCTION

In Chapter 4 the annual number of lung cancer deaths attributable to ETS was estimated from epidemiological case-control and cohort studies. This appendix investigates alternative methods based on dose-response modeling techniques.

In order to use dose-response modeling approaches to directly estimate the number of lung cancer deaths in nonsmokers attributable to ETS, three elements are required:

1. the distribution of the time-weighted exposure of ETS in the nonsmoking population,
2. the age distribution of the nonsmoking population, and
3. a mathematical dose-response model describing the relationship between the age-specific lung cancer rate and the independent variables age, sex, race, and ETS exposure.

The U.S. EPA has already collected sufficient information so that elements 1 and 2 can be approximated with reasonable accuracy in a straightforward manner. A discussion of potential methods for the derivation of the dose-response model, element (3), is the subject of this appendix.

Three independent approaches are identified for estimating the dose-response relationship between age-specific lung cancer death rates and ETS. Each of these methods has its advantages and disadvantages in estimating ETS cancer risk. Presently, none of them is developed in full detail. The purpose of presenting these preliminary approaches is to invite comment on their relative merit, solicit advice on other potential approaches that might be investigated, and to help prioritize further research efforts in this area. Much of the material

considered here is based on ongoing research that is not fully documented at this time, and it is presented as an illustration of the type of approach that could be taken.

The three proposed general approaches for deriving ETS dose-response models are:

1. Establish a dose-equivalent relationship between ETS and a positive control such as inhaled benzo[a]pyrene (B[a]P) which has an animal-based inhalation cancer dose-response model associated with it. Heavy use would be made of animal carcinogen test results in this approach. This approach will be subsequently referred to as the **Relative Potency Approach** (RPA).

2. Establish an equivalency relationship between the number of cigarettes smoked per day and ETS exposure levels in mg/m^3 inhaled air. This relationship would then be used to estimate risk based on a direct state-of-the-art cigarette smoking dose-response model obtained from multiple sources of epidemiological data. This will be referred to as the **Cigarette-equivalent Approach** (CEA).

3. Use ETS epidemiological studies where a dose-dependent increase in the risk of nonsmoking women is associated with ETS. This will be referred to as the **Direct Approach** (DA).

Details concerning these approaches, examples of information that may be used in their conduct, and an evaluation of their strengths and weaknesses are presented in the following sections.

D.2. RELATIVE POTENCY APPROACH

D.2.1. Overview

The products of incomplete combustion from hydrocarbons (e.g., tobacco products) contain very complex mixtures of agents including thousands of polycyclic aromatic hydrocarbons (PAHs), many of which are known or suspected to be carcinogenic. The direct evidence for the carcinogenicity of hydrocarbon combustion products comes mainly from three types of information:

1. animal carcinogenicity tests of pure PAHs such as benzo[a]pyrene (B[a]P), etc., that are known to be formed as part of the combustion products of hydrocarbons,

2. animal carcinogenicity tests of condensates and various fractions of the condensates from hydrocarbon combustion products (e.g., coal flue gas, gasoline engine exhaust, diesel engine exhaust, coke oven emissions, etc.), and

3. human epidemiological studies (e.g., cigarette smoking, roofing tar fumes, coke oven emissions, etc.).

The EPA has historically used this type of information to help establish air quality criteria for emissions of complex mixtures of PAHs. In one situation a criterion for coke oven emissions was set based directly on epidemiological evidence of a dose-dependent increase in lung cancer (U.S. EPA, 1984). This evidence was gained from a long-term follow-up of black male workers who were working in close proximity to the coking operations in steel mills (Redmond et al., 1972). However, in most situations, direct evidence of the combined carcinogenic potency of the complex products of an emission source is not available. What often is available is information concerning the relative potency of complex PAH mixtures compared to a standard (such as B[a]P) obtained in experimental animal test systems (e.g., skin painting, lung implant, etc.). Data of this nature are not directly extrapolatable to humans due to our inability to establish equivalent exposure units for the experimental animal and anticipated human exposure routes. As a result, Albert et al. (1982) devised indirect methods for using relative potency information to estimate the risk due to inhalation of complex PAH mixtures. The general approach is to establish the relative potency of the complex PAH mixture compared to a standard agent that has a known inhalation dose-response model associated with it. Given the relative potency value, the exposure to the PAH mixture is converted into standard agent equivalent exposure units by taking the product of the PAH mixture exposure level and the relative potency. These standard equivalent exposure units are then substituted into the standard inhalation dose-response model to obtain cancer risk estimates that could be attributed to the complex PAH mixture. This general approach has been the guiding principal behind much of the PAH risk assessment research conducted by the EPA in recent years.

One view of ETS is that it is simply another complex mixture of agents containing multiple carcinogenic PAHs. Although ETS contains many carcinogens other than PAHs, recent research

(Grimmer et al., 1988) strongly suggests that the majority of ETS lung carcinogenic potency is due to the greater than 3-ring PAHs. This suggests that the same approaches for estimating lung cancer risk for complex PAH mixtures could also be employed to good advantage for estimating ETS lung cancer risk. Some of the information that could be useful in obtaining a cancer dose-response model for ETS using the general approach for PAHs is displayed in Table D-1.

D.2.2. Estimating ETS Relative Potency

The first step in obtaining an ETS dose-response model is to establish the relative carcinogenic potency of ETS compared to an appropriate standard (e.g., B[a]P, coke oven emissions, diesel engine exhaust). All of the available experimental information should be reviewed and evaluated for its quality and relevance in obtaining ETS relative potency estimates. One experiment that is a likely candidate for use in obtaining ETS versus B[a]P relative potency estimates is the lifetime rat lung implant study conducted by Grimmer et al. (1988). Due to its potential importance the protocol of that experiment is explained briefly. Three-month-old inbred Osborne-Mendel female rats were used. Various amounts of B[a]P or ETS fractions were dissolved in residue-free acetone, warmed to 50 degrees C, and a 1:1 mixture of beeswax and Trioctanoin was added. The acetone was removed by rotary evaporation under reduced pressure. This material was then warmed to 60 degrees C and introduced by injection into the left lobe of the lung of Nembutol-anesthetized animals following thoracotomy. Following its injection, the implant hardened into a pellet from which the test material diffused into the surrounding lung tissue. Following the test material injection, the thoracotomy aperture was sutured and the skin incision clipped. No further post-operative treatment was needed; operative and post-operative mortality was less than 5%. After surgery, rats were observed until

TABLE D-1. SELECTED SOURCES OF INFORMATION POTENTIALLY USEFUL FOR DERIVING A DOSE-RESPONSE RELATIONSHIP FOR ETS

Agent	Route of exposure in animal experiments			Human risk models based on epidemiological data where exposure is inhalation
	Skin painting	Lung implants	Inhalation	
Benzo[a]Pyrene (B[a]P)	X	X	X	
3-Methylcholanthrene (MCA)	X	X		
Artificial Complex PAH Mixture			X	
Coal Flue Gas Condensate	X	X		
Gas Engine Condensate	X	X		
Diesel Engine Exhaust	X	X	X	Under development
Sidestream Cigarette Smoke (ETS)		X	X no tumors induced	Possible to develop
Mainstream Cigarette Smoke	X	X	X	State-of-the-art model required
Coke Oven Emissions	X			Model available U.S. EPA (1984)
Aluminum Smelter Emissions	X			Upper bound under development
Roofing Tar Fumes	X			Out of date
Indoor Coal	X			Under development
Wood Combustion	X			Under development

their natural deaths which was as long as 32 months post exposure. Moribund animals were killed and when all animals were dead, complete autopsies were performed. The carcinogenic data obtained in the experiment are displayed in Table D-2. The historical control data for Osborne-Mendel rats are given in Table D-3, which are useful for obtaining stable non-zero estimates of the population background cancer rates.

The advantages of the Grimmer et al. (1988) study are:

- the cancer response is at the anticipated target site for ETS (i.e., the lung),
- the animals were observed for their full lifespan,
- the exposure was a continuous, lifelong leaching of the test material out of the beeswax/Trioctanoin pellet,
- multiple dose levels of the B[a]P positive control were employed,
- the average survival time for the experimental groups are given, which allows appropriate age adjustments to be made,
- the experiment is one of a series of six on complex PAH mixtures conducted by the same investigators that allows various hypotheses to be evaluated (e.g., dose additivity, irritation effects, etc.), and
- the experiments, quality control, and the investigators' reputations are of the highest order.

The disadvantages of the experiment are:

- exposure levels were most likely exponentially decreasing over time,
- the entire ETS condensate was not evaluated as one total exposure, and as a result, dose additivity of the ETS fractions must be assumed to obtain a relative potency estimate for the entire sample,
- the ETS condensate was not as aged as much as the ETS to which humans are expected to be exposed,
- multiple exposures were not given for the ETS fractions,

TABLE D-2. DATA THAT CAN BE USED TO OBTAIN RELATIVE POTENCY ESTIMATES FOR ETS CONSTITUENTS

Material	Dose mg x	Median survival t	Animals with epidermoid carcinomas/ Total animals
PAH-free material and PAH 2,3 rings	16.00	102	1/35
PAH 4 and more rings	1.06	105	5/35
Semivolatives (gaseous phase)	11.80	104	0/35
Benzo[a]Pyrene	0.03	93	3/35
	0.10	98	11/35
	0.30	75	27/35
Controls	Historical*	104	1/1945
	Vehicle	102	0/35
	Untreated	105	0/35

Source: Grimmer et al. (1988) and *Goodman et al. (1980)

TABLE D-3. HISTORICAL LUNG TUMOR CONTROL DATA FOR OSBORNE-MENDEL RATS

Lung tumors	Male	Female	Combined
Epidermoid Carcinomas	1/975	0/970	1/1945*
Alveolar/Bronchiolar Adenoma	4/975	2/970	6/1945
Alveolar Bronchiolar Carcinoma	3/975	3/970	6/1945

Source: Goodman et al. 1980
*Value used in ETS fraction relative potency estimation.

- the ETS mixture contains only the SS component and not the exhaled MS components of ETS, and
- the tumors were epidermoid carcinomas at the implant site rather than the alveolar-bronchiolar carcinomas usually associated with cigarette smoke.

The relative potency estimates of the ETS fractions and the theoretical estimates of the total emission based on the assumption of dose additivity are displayed in Table D-4. The dose additivity assumption has been shown to be consistent with information obtained in the same animal model system employing diesel or gas engine exhaust condensate. It is estimated that more than 70% of the total carcinogenic potency of the ETS is due to the 4 or more ringed PAHs (i.e. [.03673 x .05833]/.00302 = .7098). The relative potency estimates incorporate a special case of a two-stage mathematical model where the first stage preneoplastic clone has no selective advantage over normal tissue in the rat lung. The U.S. EPA is developing this model to estimate the relative potencies of other complex PAH mixtures whose carcinogenicity has been evaluated by the lung implant experimental system (Thorslund 1990).

TABLE D-4. RELATIVE POTENCY ESTIMATES OF ETS CONSTITUENTS*

Constituents	j	Dose mg. (x_j)	Fraction sample (f_j)	Maximum likelihood relative potency estimates (ρ_j)	% of total carcinogenicity attributable to constituent
PAH-free PAH 2,3 rings	1	16.00	0.55440	0.00158	29.02
PAH 4 and more rings	2	1.06	0.03673	0.05833	70.98
Semivolatiles (gaseous phase)	3	11.80	0.40887	0.00000	0.00
Weighted Total		28.86	1.00000	0.00302 $= \rho_T$	100.00

*Source of data: Grimmer et al. (1988)

Refinements in the estimate and a more complete documentation of the techniques employed in the analysis are required. Also, results from other experimental systems should be used to estimate relative potencies if possible. The discussion given here should be regarded only as an illustration of the type of analysis that can be conducted with some of the available information.

D.2.3. Inhalation Dose-Response Models for PAHs

Once the relative potency of ETS to the standard agent (e.g., B[a]P) has been estimated, the result is used to estimate the standard equivalent exposure units which are substituted into the standard inhalation dose-response model to obtain cancer risk estimates. As indicated in Table D-1, a number of alternatives exist upon which a standard inhalation dose-response model could be based. We shall evaluate three potential choices in this section.

D.2.3.1. Hamster Inhalation B[a]P Dose-Response--The only animal pure PAH inhalation experiment presently available that contains sufficient information to establish a dose-response relationship was conducted by Thyssen et al. (1981). In that study Syrian golden hamsters were exposed over their entire lifespan to pure B[a]P via an NaCl aerosol. The tumors most closely associated with B[a]P exposure were malignant and found in the larynx and pharynx. Summarized results of the study are displayed in Table D-5. Thorslund (1990) demonstrated that a two-stage model with exponential growth of preneoplastic targets can adequately describe the experiment. The advantages of using the Thyssen et al. (1981) study are:

- the exposure was well monitored over the entire length of the experiment,
- the average lifetime exposure and age at death was available for each animal in the experiment,

TABLE D-5. EXAMPLE OF ANIMAL INHALATION DOSE-RESPONSE MODEL SYRIAN GOLDEN HAMSTERS EXPOSED TO B[a]P VIA NaCl AEROSOL
(Thyssen et al. 1981)

Lifetime average exposure (mg/m^3 B[a]P) x	**Average survival (weeks) t**	**Animals examined**	**# of hamsters with one or more malignant laryngeal or pharyngeal tumors**	
			Observed	**Predicted (sum of individual data)**
Historical Controls	80.0	226	1	0.642
Matched Controls	105.0	22	0	0.179
Total Controls	-----	248	1	0.821
Low Exposure Chamber (2 mg/m^3) 0.250 mg/m^3	100.5	24	0	1.23
Middle Exposure Chamber (10 mg/m^3) 1.016 mg/m^3	102.5	23	11	8.55
High Exposure Chamber (50 mg/m^3) 4.292 mg/m^3	.70.7	23	17	17.98

Model*

$$P(x,t) = 1 - \exp - H(x,t)$$

$$H(x,t) = \frac{A}{G^2}(1+Sx)^2\{[\exp(Gt) - 1 - Gt]\}$$

$$A = 3.865 \times 10^{-7},\ S = 6.843,\ G = 0.0263$$

*Thorslund (1990)

- the animals were followed for their entire natural lifespan, and
- careful histopathological examinations were conducted on each animal.

The disadvantages of this study are:

- the hamsters are not humans,
- the tumors did not develop at the site anticipated in humans (i.e., lung),
- the hamsters are resistant to lung tumor formation, and
- the bioavailability of the B[a]P/NaCl aerosol may be different from the bioavailability of the PAH-matrix to which humans are exposed.

When confronted with inhalation exposures of complex PAH mixtures, the approach used by the EPA program offices has usually been to assume that the entire PAH mixture is as potent as B[a]P and to substitute the total exposure units into an earlier version of the B[a]P dose-response model derived from the Thyssen et al. (1981) data. This approach is recognized as having numerous uncertainties and as being conservative.

D.2.3.2. Rat Inhalation Diesel Engine Exhaust Dose-Response--The diesel engine exhaust rat inhalation study of Mauderly et al. (1987) offers another possibility for establishing an inhalation dose-response model. The advantages of this study are:

- the tumors appeared in the lung,
- the PAH-matrix is reasonably similar to the type one might expect with human exposures, and
- the lung burden exposure measurements are available.

The disadvantages of this study are:

- the rats are not humans,
- the lung tumors were for the most part not malignant, and
- the relative potency estimates compared to B[a]P for the exact diesel engine emissions used in the experiment are not available.

The authors of the diesel engine exhaust paper obtained a dose-response model from their experiment results. However, their derived model would not be consistent with the usual regulatory assumption of low dose linearity. The same type of model employed for B[a]P could also be used for diesel engine exhaust. As a result, it would be desirable to acquire the individual animal data and fit the two-stage model to it to maintain a consistent approach throughout.

To use this study an estimate of the relative potency of ETS compared to diesel engine exhaust is required. Several options for obtaining such estimates exist. Perhaps the most direct approach would be to pool the data obtained in the Grimmer et al. (1987, 1988) papers on ETS and diesel engine exhaust which both employed the lung implant experimental system.

D.2.3.3. Human Inhalation Coke Oven Dose-Response--As noted previously, a dose-response model for coke oven emissions has been used by the U.S. EPA (1984). This model is based on a simple linear absolute risk model where the age-specific lung cancer risk is proportional to a lag-time adjusted cumulative exposure. The advantages of using this model are:

- it is based on human occupational epidemiological data,
- the coke oven exposure in inhaled air is comparable to how humans are exposed to ETS, and
- human coke oven inhalation data have been used by EPA to support regulatory decisions.

The disadvantages are:

- the model should be updated with regard to presently available mortality and exposure information, which would require considerable effort and resources,
- the cigarette smoking rates of the cohort members are unknown and thus are not adjusted for and could be an important confounding variable, and

- two different bioassay systems are required to obtain coke oven equivalent exposure units for ETS (i.e., ETS compared to B[a]P lung implant and coke oven emissions compared to B[a]P skin painting).

Re-evaluating the coke oven data using the same two-stage model approach employed for the other PAH data sets and the updated mortality experience appear to be a more scientifically sound path to follow, but would require substantial resources.

D.3. CIGARETTE-EQUIVALENT APPROACH

D.3.1. Overview

The most obvious approach for obtaining an inhalation dose-response model for ETS is to use direct cigarette smoking. The cigarette-equivalent approach (CEA) may be viewed as a special case of the RPA with an added complication. An adjustment is required to equate the lung deposition of carcinogens achieved by forced deep puffing on cigarettes with that resulting from normal inhalation of ETS in the surrounding air. In chapter 4 several approaches were discussed for making such adjustments that were felt to be inadequate. In this section an alternative general approach based on specific biological markers is suggested.

The three necessary elements required to develop a credible ETS dose-response model are:

- a state-of-the-art human mainstream smoke (MS) dose-response model,
- a relative potency estimate of ETS compared to MS, and
- a deposition rate equivalency for an appropriate biological marker (e.g., B[a]P-DNA adduct) between ETS and MS.

Each of these elements are discussed in the following sections.

D.3.2. State-of-the-Art Mainstream Cigarette Dose-Response Model

The ideal study for establishing a dose-response model for mainstream smoking would be based on a large cohort where many of the members had died of lung cancer, and the following information on each member of the cohort would be obtainable.

1. detailed smoking history
    a. age at start of smoking
    b. way of smoking
        i. inhalation patterns
        ii. average puffs per cigarette
        iii. length to which cigarette is smoked
    c. smoking intensity (i.e., number of cigarettes smoked per day)
    d. changing pattern of cigarette use over time
2. age at the start and end of the observation period and vital status at the end of the observation period.
3. most detailed pathology information available
4. demographic information
    a. race
    b. sex
    c. population density of domicile
    d. job status
5. workplace exposure to other known lung carcinogens

While the information contained in any actual conducted study will not even come close to conforming to the ideal, the list still is a convenient yard stick to measure potential studies for possible inclusion in our dose-response development. Different limited studies may be useful in contributing information concerning as little as one parameter in the eventual dose-response model.

D.3.2.1. Sources of Epidemiological Information Useful for Constructing a Dose-Response Model--A number of epidemiological studies may be viewed as primary sources of information concerning the dose-response relationship between mainstream cigarette smoke and lung cancer. These studies are briefly described below.

D.3.2.1.1. U.S. American war veterans (AWV). A cohort of about 300,000 American male war veterans was assembled in 1954 by Dorn and their mortality experience subsequently reported on by Kahn (1966), Rogot (1974), Whittemore (1988), and Freedman and Navidi (1989). This study includes information of age at start of smoking and number of cigarettes smoked per day. It also included ex-smokers. The study has the distinct advantage of having a total of 1266 lung cancer deaths available for analysis, and some details on individual cohort members are potentially obtainable from National Cancer Institute (NCI) data tapes. The study's disadvantages are that exposure information was only obtained at the beginning of the observation period so that changes in smoking patterns, except for stopping, cannot be taken into account. Also, there are no women in the cohort.

D.3.2.1.2. American Cancer Society (ACS) volunteers. The ACS enlisted the help of a large number of volunteer workers to help define and follow a cohort of about 440,000 male and 570,000 female predominantly middle to upper class white Americans. This study was reported by Hammond (1966) with additional information available from ACS personnel. The study is particularly useful in that it contains extensive information on women and nonsmokers not available from other sources. Additional advantages of the study are the large number of lung cancer deaths in the cohort, 1542 for male smokers and 164 for the females, and information on age when smoking started and length of follow-up is available for each cohort member. The

main disadvantages of the study are: (1) it took place over a relatively narrow time frame of 8.5 years which increases the potential for a calendar year bias, and (2) the lower social economic classes are under-represented which may introduce a bias due to the difference in type and way cigarettes are smoked.

D.3.2.1.3. British male physicians. Doll and Peto (1978) published the data shown in Table D-6 based on the information obtained by following the survival of a cohort of approximately 34,000 British male physicians. The smoking histories of each individual in the cohort were obtained by questionnaires at three different points in time. Table D-6 is a subset of the total cohort consisting of subjects who smoked at a nearly constant rate over their smoking lifetime. Due to the quality of the smoking information and pathology confirmation of most of the cases, this study is generally acknowledged to be the most informative available for establishing dose-response relationships. The disadvantages are that the number of observed lung cancer deaths are relatively small (i.e., 215), no women are included in the sample, and information on ex-smokers was never published in a form suitable for analysis. Also, a sample of physicians has a high potential for a sociological bias to be built into it. Ten years of additional observation is available on the cohort that has not yet been published and could be of considerable importance in the establishment of a dose-response model.

TABLE D-6. NUMBER OF LUNG CANCER DEATHS AND PERSON-YEARS OF OBSERVATION FOR BRITISH MALE PHYSICIANS

Mid-point age interval (years)		Average exposure (cigarettes per day)								
		0.0	2.7	6.6	11.3	16.0	20.4	25.4	30.2	38.0
42.5	observed lung cancer deaths	0.0	0.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
	person-years	17,846.5	1,216.0	2,041.5	3,795.5	4,824.0	7,046.0	2,523.0	1,715.5	892.5
47.5	observed lung cancer deaths	0.0	0.0	0.0	1.0	1.0	1.0	2.0	2.0	0.0
	person-years	15,832.5	1,000.5	1,745.0	3,205.0	3,995.0	6,460.5	2,565.5	2,123.0	1,150.0
52.5	observed lung cancer deaths	0.0	0.0	0.0	2.0	4.0	6.0	3.0	3.0	3.0
	person-years	12,226.0	853.5	1,562.5	2,727.0	3,278.5	5,583.0	2,620.0	2,226.5	1,281.0
57.5	observed lung cancer deaths	2.0	1.0	0.0	1.0	0.0	8.0	5.0	6.0	4.0
	person-years	8,905.5	625.0	1,355.0	2,288.0	2,466.5	4,357.5	2,108.5	1,923.0	1,063.0
62.5	observed lung cancer deaths	0.0	1.0	1.0	1.0	2.0	13.0	4.0	11.0	7.0
	person-years	6,248.0	509.5	1,068.0	1,714.0	1,829.5	2,863.5	1,508.5	1,362.0	826.0
67.5	observed lung cancer deaths	0.0	0.0	1.0	2.0	2.0	12.0	5.0	9.0	9.0
	person-years	4,351.0	392.5	843.5	1,214.0	1,237.0	1,930.0	974.5	763.5	515.0
72.5	observed lung cancer deaths	1.0	1.0	2.0	4.0	4.0	10.0	7.0	2.0	5.0
	person-years	2,723.5	242.0	696.5	862.0	683.5	1,055.0	527.0	317.5	233.0
77.5	observed lung cancer deaths	2.0	0.0	0.0	4.0	5.0	7.0	4.0	2.0	2.0
	person-years	1,772.0	208.5	517.5	547.0	370.5	512.0	209.5	130.0	88.5

Source: Doll and Peto (1978)

D.3.2.1.4. Other data sources. Other sources of information that could prove useful in obtaining information on a dose-response model are Best (1966), Canadian smokers; Bross et al. (1968), individuals who switched to filter cigarettes; Cederlof et al. (1975), a national probability sample of Swedish subjects; Graham and Levin (1971), individuals who stopped smoking; Hirayama (1977), Japanese smokers; Stevens and Moolgavkar (1984), British males; Lubin et al. (1984), individuals who changed smoking habits; Wald et al. (1988), U.K. smoking statistics; the IARC monograph on the evaluation of the carcinogenic risk of tobacco smoking to humans IARC (1986), general information; and the U.S. Public Health Service, Smoking and Health Report series for various types of smoking related information.

D.3.2.2. Modeling Approach for Cigarette Smoking Data--Various investigators, such as Doll and Peto (1978), Thorslund and Charnley (1987), Brown and Chu (1987), Gaffney and Altshuler (1988), Darby and Pike (1988), Freedman and Navidi (1989), and Moolgavkar et al. (1989), were successful in fitting various forms of multi-stage type models to the British physicians data. Modeling attempts using the AWV and ACS data have been less successful. Freedman and Navidi (1989) could not obtain adequate fits using standard multi-stage models to the AWV and ACS data sets when information on ex-smokers was included. The reasons for this inability could be either deficiencies in the multi-stage model (hypothesis put forth by the authors) or some unknown bias in the data that distorts the true dose-response relationship. To clarify the situation other modeling approaches should be attempted.

Probably the most successful approach for mathematically modeling cigarette smoking data was put forth by Moolgavkar et al. (1989). This is the only attempt to date to incorporate a promotional component of cigarette smoke into a dose-response model. Using Moolgavkar's basic model and the additional simplifying robust assumptions that:

- the number of stem (target) cells are constant over time,
- the ratio S of unit exposure induced to background cell transition rates are equal for the two cellular transitions (i.e., normal stem to preneoplastic and preneoplastic to neoplastic), and
- the growth rate of preneoplastic cells is a function, G(x), of the number of cigarettes smoked per day,

the age-specific lung cancer rate of an individual at age t who has smoked x cigarettes per day since age t_0 can be expressed as:

$$h(x,t) = \frac{A}{G(x)}(1+Sx)^2\{\exp[G(x)(t-t_0)]-1\}+\frac{A}{G(0)}(1+Sx)\exp[G(x)(t-t_0)]\{\exp[G(0)t_0]-1\}$$

where A is the product of the background transition rates, $G(x)=G(0)[1+(R-1)M(x)]$ with $R=G(\infty)/G(0)$ being the maximum relative growth rate increase that can be induced by cigarettes and M(x) is a still to be specified function that defines the fraction of the maximum growth rate increase that is induced with x cigarettes per day. In the model employed by Moolgavkar, the simplifying assumption $G(x)=G(0)+\Delta x$ was made. While this assumed relationship may be appropriate at low doses, it very likely results in a distortion of the effect for heavy smokers.

It is proposed that the Moolgavkar (i.e., two-stage) model parameter estimates be obtained by simultaneously using multiple epidemiological-smoking-lung cancer data sets and the following modifications and extensions of the above basic model:

- Moolgavkar assumed that the time from the development of a neoplastic cell until death due to a lung cancer was a constant 3.5 years for each of the lung cancer deaths. As an alternative this length of time will be estimated by maximum likelihood methods assuming:

  1. it is a constant unknown value for all lung cancer deaths, and
  2. it is a random variable with an integer gamma probability distribution.

- Alternative specific forms for G(x) will be specified based on various assumptions of how binding of smoking product agents with preneoplastic cells induce promotion.

- An adjustment will be made for the difference between British and American cigarettes and British and American smoking habits.
- An investigation will be made of the hypothesis that G(0) may be different pre- and post-exposure to accommodate the observation of rapidly falling age-specific rates post cessation of smoking.

The largest information data base possible will be used in fitting the different variations of the model. An illustration of how one of the parameters in the model, G(0), could be estimated is given below.

Hammond (1966) pooled the ACS lung cancer mortality data for men and women nonsmokers and obtained age-specific death rates for five-year age intervals. This information is displayed in Table D-7. The justification given by Hammond (1966) for pooling the data was the inability to reject the hypothesis of equal rates for the sexes on the basis of a statistical test. Under the assumption of no cigarette smoking, $x=0$, so the previously described age-specific rates for the two-stage model has the reduced form:

$$h(0,t) = \frac{A}{G(0)}\{\exp[G(0)t]-1\}$$

Assuming that the number of lung cancer cases out of the number of person years of observation was an independent binomial random variable for each age class, maximum likelihood estimates were obtained for the unknown parameters A and G(0) in the above model. The adequate fit of the model is displayed in Table D-7 and Figure D-1.

It is reasonable to assume that the parameter G(0) is human population independent and, perhaps, even species independent taken on a lifetime equivalent time scale. However, the value A would most likely be dependent on the environmental conditions an individual is living under. Therefore, different values for U.S. and British populations should be estimated.

TABLE D-7. LUNG CANCER DEATH RATES PER 100,000 PERSON-YEARS AND OBSERVED AND PREDICTED NUMBER OF LUNG CANCER DEATHS AMONG MEN AND WOMEN WHO NEVER SMOKED REGULARLY

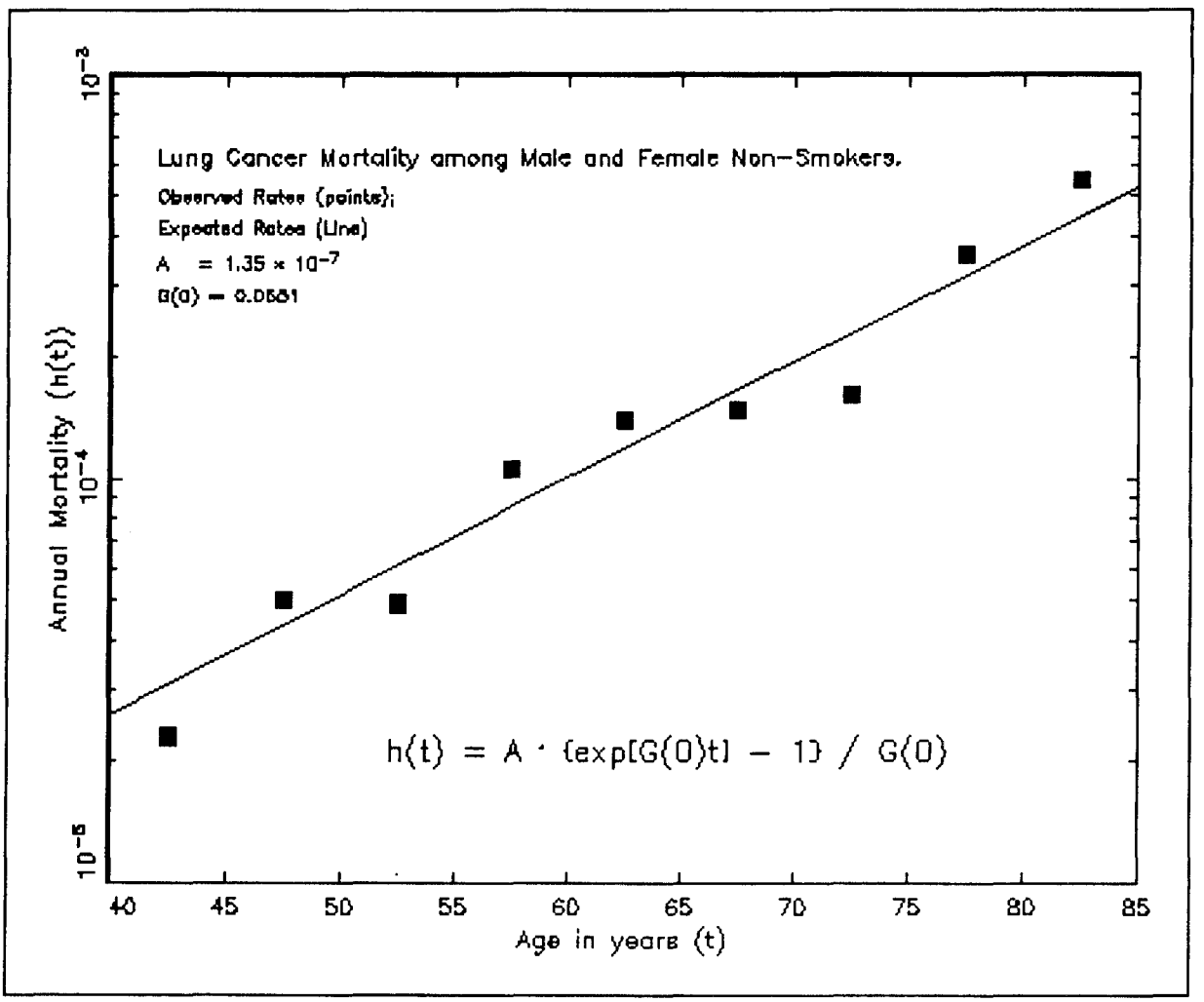
Age group L to L+5	Combined men and women			Population size N (person-years)
	Number of lung cancer deaths n		Death rate dr	
	Observed	Predicted		
40-44	4	5.40	2.3	173,913
45-49	16	14.01	5.0	320,000
50-54	16	20.05	4.9	326,531
55-59	30	24.52	10.5	285,714
60-64	32	27.53	13.9	230,216
65-69	26	29.43	14.7	176,871
70-74	18	25.84	16.1	111,801
75-79	21	18.82	35.8	58,659
80-84	14	11.41	54.6	25,641
Total	177	----		

Source: Hammond (1966)/ACS Study

* $N = \frac{nx10^5}{dr}$

calculated from data $\chi^2_7 = 7.036$ $p = 0.425$

FIGURE D-1.
GOODNESS-OF-FIT OF TWO-STAGE MODEL TO NON-SMOKERS
AGE-DEPENDENT LUNG CANCER DATA



Source of data: Hammond et al. (1966).

The obvious advantage of the proposed CEA is that it is based on the most extensive body of information concerning the dose-dependent effects of an environmental agent on a human cancer response that exists. The main disadvantages are the complexity of the analysis and the possibility of not establishing a credible ETS equivalency relationship. The latter factor is discussed in the next sections.

D.3.3. Estimation of the Relative Potency of ETS Compared to MS

Previous approaches for establishing ETS/cigarette equivalency (e.g., Darby and Pike, 1988) have made the implicit assumption that the ratio of the potency of emissions to some surrogate measure of internal exposure (e.g., nicotine, cotinine, etc.) is the same for ETS and MS. The large variability in relative potency estimates of complex-PAH mixtures that are displayed in Table D-8 suggests that the implicit assumption of equal potency is suspect.

Several methods can be used to estimate the ETS compared to MS relative potency. The inhalation studies in Syrian golden hamsters where laryngeal carcinomas were elicited from MS (Dontenwill et al., 1973; 1977) and from B[a]P (Thyssen, 1981) can be used to obtain a MS-to-B[a]P relative potency estimate. Dividing this obtained potency value into the ETS-to-B[a]P, the relative potency obtained from the lung implant studies discussed in Section D.1.3.1 would give a relatively potent estimate of ETS to MS. Stanton et al. (1972) conducted a lung implant study using cigarette smoke condensate (CSC). Unfortunately for our present purposes, 3-methylcholanthrene (MCA) was used as the positive control in the experiment so direct comparison with ETS is not possible. However, Grimmer and his colleagues for the most part closely adopted Stanton's experimental protocol for conducting lung implant studies. Thus, a direct pooling of the data in the Stanton and Grimmer experiments could logically be used to obtain a potency estimate. As an alternative, the two-step approach of estimating the potency of

TABLE D-8. RELATIVE POTENCY ESTIMATES OF COMPLEX MIXTURES OF INCOMPLETE COMBUSTION PRODUCTS OF HYDROCARBONS COMPARED TO B[a]P

Complex PAH exposure	Direct bioassay estimate[+] of relative potency
Coal Flue Gas Condensate	0.05444
Gas Engine Condensate	0.02190
Diesel Engine Exhaust	0.00230
Sidestream Cigarette Smoke	0.00302
Coke Oven Emissions	0.03180[*]

[+]Lung implant studies
[*]Skin painting

CSC compared to MCA from the Stanton experiment and then establishing the relative potency of MCA compared to B[a]P in another assay system (e.g., subcutaneous injection, skin painting, etc.) could be employed. A final alternative might be to compare the weighted relative potency estimates of the known constituents in the MS and ETS samples that have stable established estimates of their carcinogenic potency compared to B[a]P. One potential list of stable relative potency estimates developed by Thorslund (1990) is shown in Table D-9.

The last piece of information required to obtain an ETS risk model based upon the CEA is a deposition ratio estimate between MS via active smoking and ETS under normal inhalation conditions. One promising approach of using B[a]P-DNA-adducts and other endpoints as biomarkers is discussed in the next section.

D.3.4. Deposition Differences of Chemicals from Cigarette Smoke in Smokers and Nonsmokers

To obtain an equivalency relationship between MS and ETS, both potency and deliverable dose conversion factors are needed in order to use the MS-lung cancer data as a surrogate for lung cancer induced by ETS.

TABLE D-9. RELATIVE POTENCY ESTIMATES OF AGENTS COMPARED TO B[a]P

Agent	Relative potency	Source of estimate
Anthracene	0.00000	IARC adequately studied; no indication of carcinogenic effect category
Fluoranthene	0.00000	
Pyrene	0.00000	
Benzo[b]fluoranthene	0.12277	Deutsch-Wenzel et al. (1983) (Grimmer's group) lung implant data Thorslund (1990) estimates
Benzo[k]fluoranthene	0.05322	
Benzo[j]fluoranthene	0.05232	
Benzo[e]pyrene	0.00704	
Benzo[a]pyrene	1.00000	
Indeno Pyrene	0.27800	
Benzo[ghi]perylene	0.02124	
Anthanthrene	0.31598	

Under the assumption that the PAHs possess most of the carcinogenic potency in MS and ETS, the deliverable target dose can be estimated by directly measuring the number of DNA adducts formed in people smoking different numbers of cigarettes per day and in people who are nonsmokers in the presence of smokers with different frequencies of smoking.

Specific adducts, such as the DNA 7,8-diol-9,10-epoxide of B[a]P which is present in both MS and ETS, can be detected using sensitive immunoassays or postlabelling DNA techniques (Shamsuddin et al., 1985; Randerath et al., 1986). Differences in adduct formation between smokers and nonsmokers varied depending on the experiment but was as high as 400-fold when DNA from oral mucosa was analyzed using the postlabelling technique. Hemoglobin adducts as markers of genotoxicity have been analyzed in smokers and nonsmokers where smokers had about a 7-fold greater number of adducts than nonsmokers.

Indirect measures of dose between smokers and nonsmokers may also be available in which gene mutations can be measured in peripheral leukocytes at the Hypoxanthine phosphoribosyl transferase locus as well as other loci. In fact, such a test could conceivably be used directly to obtain a cigarette equivalence estimate without making potency difference adjustments. Other genetic damage tests, such as chromosomal aberrations and sister chromatid exchanges, may also be useful in determining deliverable target dose information for smokers and nonsmokers exposed to ETS.

To obtain an equivalency relationship of deliverable dose between smokers and nonsmokers, a thorough review of the literature for articles that show dose-response relationships between MS/ETS and DNA adducts, protein adducts, and gene mutations should be conducted and the most appropriate endpoints selected for use in the equivalency estimate. The main advantage of the approach is the high suspected correlation of the endpoint with the cancer response. The main disadvantage is the discounting of potential agents that act exclusively as promoters.

D.4. DIRECT APPROACH

The most straightforward approach for estimating ETS lung cancer risk is to estimate ETS exposure in a suitable cohort and follow the resulting mortality pattern over time. As of yet, no directly measured ETS exposure data exist on a cohort. The ideal in this regard would be personal monitoring data obtained from nonsmokers for an agent such as cotinine which is closely and uniquely associated with cigarette smoke. In this application, the use of cotinine is appropriate as long as it is linearly related to total ETS air levels. In lieu of such information, investigators have attempted to obtain surrogate measures of ETS. One such measure is the number of cigarettes smoked per day by the spouses of nonsmoking individuals. The quality of such a surrogate measurement depends upon: (1) the extent that nonsmokers are exposed to

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smokers other than their spouses, (2) the consistency within the cohort of the husbands' and wives' spatial and time closeness, and (3) the consistency within the cohort of the fraction of the total cigarettes that are smoked by the spouse in the home. Due to sociological factors regarding a woman's place in Japan, the homogeneity of the Japanese society, and the small, close living arrangements of Japanese couples, probably the best surrogate measure of ETS exposure available is the number of cigarettes smoked per day by the husbands of Japanese women. The person-years of observation and the number of lung cancer deaths for Japanese women classified in regard to their husband's age and smoking habits obtained in the prospective study conducted by Hirayama (1984) is displayed in Table D-10. Under the assumption that all the excess lung cancer risk in Japanese women was due to husband-produced ETS exposure in the home, crude risk models can be generated from the information supplied in Table D-10. Better estimates could be obtained if information such as the length of marriage, wife's age, age husband started smoking, and smoking habits of wife's parents were available for individual cohort members. A fair amount of such information has been generated by Hirayama (1984) but presently is not reported in the open literature. Gaining access to the data could prove valuable.

TABLE D-10. LUNG CANCER MORTALITY IN JAPANESE WOMEN BY HUSBAND'S AGE GROUP AND SMOKING HABITS (PATIENT HERSELF A NON-SMOKER)*

Husband's age group	Husband's smoking habit											
	Non-smoker		Ex-smoker		1-14/day		15-19/day		20+/day		Total	
40-49	4	6,229	1	1,255	8	8,621	6	5,158	16	10,764	35	32,027
50-59	10	7,791	3	1,922	20	9,668	8	4,052	24	9,820	65	33,253
60-69	18	7,120	11	2,687	28	7,243	9	2,513	23	4,651	89	24,214
70-79	5	755	2	348	2	612	1	105	1	226	11	2,046
Total	37	21,895	17	6,212	58	26,144	24	11,828	64	25,461	200	91,540

*Number of lung cancer deaths out of number of wives in the same cross classification cell.
Source: Hirayama (1984).

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