

**Section 1. INTRODUCTION,  
SUMMARY, AND  
RESEARCH  
RECOMMENDATIONS**

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## **Research Recommendations From the Working Meeting "Research Needs on Low-Yield Cigarettes"**

## Introduction

Great changes have taken place in the cigarette product in recent decades. In 1954, the average "tar" yield of the sales-weighted average cigarette was 37 mg and average nicotine yield was 2 mg. In 1980, the comparable figures are expected to be less than 14 mg of "tar" and less than 1 mg of nicotine. No cigarette marketed in the United States in 1979 yielded more than 30 mg of "tar."<sup>1</sup>

Smokers have turned to these new products because of health concerns. In the 1950s, cigarette manufacturers introduced cigarette filters as "health protection" and advertised them widely. The 1964 Report of the Surgeon General's Advisory Committee on Smoking and Health did not discuss cigarette smoke filtration, but in 1966 the Public Health Service reviewed the issue of smoke constituents. That report stated, "The preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the less harmful would be the effect." Thereafter, Government and tobacco industry scientists conducted studies of cigarette engineering and tobacco cultivation that could lead to lower "tar" and nicotine yields. Later, when new products appeared, cigarette manufacturers aggressively promoted them through advertising.

The request by Congress for an assessment of the "relative health risks associated with smoking cigarettes of varying levels of 'tar,' nicotine, and carbon monoxide," and "the health risks associated with smoking cigarettes containing any substances commonly added to commercially manufactured cigarettes" has come at an appropriate time. In the 2 years since Congress called for the present study, manufacturers have marketed cigarettes that yield as little as 0.01 mg of "tar" when measured by present Federal Trade Commission technology.

The technology of producing lower "tar" cigarettes has progressed well beyond a simple reduction in the amount of tobacco in the cigarette or the removal of a portion of the "tar" by filtration. Present technology has achieved "tar" reduction by alterations in plant genetics, changes in the cultivation and processing of the tobacco leaf, and changes in cigarette paper and filtration of the cigarette.

The methods used in testing cigarettes by machine may not correspond to the way persons actually smoke. There is evidence to suggest that the cigarette yields measured by machine are very different from the yields that the consumer actually obtains by smoking the cigarette, due in part to the difference in patterns of smoking between testing machines and individual smokers. Therefore, "tar" measurements of current cigarettes may not reflect the same

<sup>1</sup>"Tar" is the term given to the particulate matter of cigarette smoke that is retained by a Cambridge filter pad after extraction of nicotine and water. In this Report, the term "tar" is placed in quotation marks to emphasize that "tar" is not a single constituent but consists of many different chemical constituents and classes of constituents.

estimate of risk provided by the "tar" measurement of cigarettes manufactured at the time of the 1966 Public Health Service Review.

Another closely related concern about lower "tar" and nicotine cigarettes is the use of flavorings and other chemical additives. In order to enhance consumer acceptability, flavoring substances are added to cigarettes; it may be that the lower the "tar" yield, the more flavoring additives are used. It is impossible to make an assessment of the risks of these additives, as cigarette manufacturers are not required to reveal what additives they use. No agency of the Federal Government currently exercises oversight or regulatory authority in the manufacture of cigarette products. Further, no agency is empowered to require public or confidential disclosure of the additives actually in use by the cigarette manufacturers.

At the same time that changes have occurred in the cigarette, marked changes have occurred in the smoking patterns of the U.S. population that may have substantially altered the risk of smoking lower "tar" cigarettes. Over recent years, smokers have been taking up regular smoking at younger ages, and the number of women who smoke currently far exceeds the number from several decades previously. The multiplicative risks of smoking and oral contraceptive use is an example of how changes in the population of smokers can make both quantitative and qualitative changes in the nature of the risk. The proportion of the population that smokes has declined, but the average number of cigarettes smoked by each smoker appears to have increased over several decades. Changes have occurred in the environment, dietary habits, and behavioral patterns of the population, which may alter the interaction between cigarette smoking and other risk factors for disease. Thus, we have a continually changing population of smokers who smoke a continually changing cigarette in a continually changing manner.

### **Dose-Response Relationship**

A clear dose-response relationship has been established between cigarette smoking and a number of disease states; this constitutes a major part of the evidence suggesting that lower "tar" cigarettes may be less hazardous. It is important to understand this dose-response relationship and the limits of the data.

The major prospective studies on smoking and disease show that the risk of coronary heart disease and lung cancer increases in a roughly linear manner with increasing numbers of cigarettes smoked per day. There is also a marked increase in the risk of death from chronic lung disease with the number of cigarettes smoked per day, but problems in classification of this disease make it unclear whether the relationship is linear. There is no clear evidence of a threshold effect in any of these studies. The relationship between number of cigarettes and disease is strengthened by showing that the risk increases with longer duration

of the smoking habit and with younger age at initiation of regular smoking. Risk is thus closely related to smoke dose as measured by number of cigarettes consumed. The relationship may result from the effect either of repetitive doses or of cumulative smoke dosage. The effect on risk of the time interval between cigarettes has not been thoroughly examined, but there is evidence to suggest that risk is related to the total dose of smoke delivered to the smoker, regardless of the time pattern of exposure. Overall, disease risk clearly increases with increasing depth of cigarette smoke inhalation. Pipe and cigar smokers who do not inhale have a lower risk of tobacco-related diseases. Thus, it is logical to hypothesize that a reduction in the actual dose of cigarette smoke to the smoker would be accompanied by a reduction in the risk of developing heart and lung disease.

“Tar” is a major portion of the total particulate matter of cigarette smoke. To the extent that the machine measurements of “tar” yield of cigarettes reflect the actual smoke exposure resulting from use of that cigarette, a lower “tar” cigarette should be less hazardous. In order for the measured “tar” yield of a cigarette to reflect smoke exposure, a number of conditions would have to be met.

First, changing the “tar” yield should not change the pattern, or style, of cigarette use. If the smoker compensates for reduced yield by increasing the number of cigarettes, the depth of inhalation, or the volume or frequency of puffs, a reduction in “tar” might not result in a reduced smoke exposure. The possible increase in the average number of cigarettes smoked by each smoker and the possibility that the depth of inhalation and puff volume may also have increased as the average “tar” yield of the cigarette has declined raise a real concern that the shift to the use of lower “tar” cigarettes may not have resulted in a proportionate drop in smoker exposure.

A second assumption in equating lower “tar” yield per cigarette with lower smoke exposure, and therefore lower risks of disease, is that the reduction in “tar” is accompanied by a similar reduction in all of the constituents of smoke, or at least all of those constituents related to disease. As long as the lowering of the “tar” yield was largely secondary to a reduced amount of tobacco in the cigarette or a filtration of the smoke, a reduced “tar” yield could be assumed to represent a lower smoke exposure. Prior to 1971, the reduction in “tar” yield was very similar to the reduction in weight of tobacco per cigarette (see Figure 8, Section 8), but since that time the reduction in “tar” has been proportionately somewhat greater than the reduction in weight of tobacco per cigarette, and this difference appears to have increased since 1975. As discussed in this Report, the recent reductions in “tar” yield have been accomplished by altering tobacco growth and processing and by changes in cigarette manufacture. These changes may have produced a “tar” with a different composition from that of

old higher "tar" cigarettes, and may have changed the concentrations of some of the constituents contained in the gas phase of the smoke.

An additional concern is that the production of cigarettes with lower "tar" and nicotine yields may involve the increasing use of additives for tobacco processing or flavoring. Some additives available for use are either known or suspect carcinogens or give rise to carcinogenic substances when burned. The use of these additives may negate beneficial effects of the reduction of "tar" yield, or might pose increased or new and different disease risks. Therefore, the "tar" yield of cigarettes currently being manufactured probably cannot be used as a precise measure of current smoke exposure risk, nor be compared quantitatively with the smoke exposure risk of the older higher "tar" cigarettes. The major prospective studies that provide the data for our assessment of smoking-related health risks examined persons who smoked these older, higher "tar" cigarettes.

A third assumption in equating "tar" yield with smoke exposure is that the "tar" yield of a machine-smoked cigarette be equal to or at least proportional to the yield of the same cigarette when it is consumed by the smoker. Later sections of this Report clearly establish that the "tar" yield of the current cigarette may vary markedly with style of smoking, with much higher yields being produced by higher puff volumes or occlusion of the perforations in the cigarette wrapper. Thus, the manufacturing changes that have resulted in low "tar" yield measurements may not have resulted in a comparable reduction in the exposure of the individual cigarette smoker.

#### **Relative Risks of Lower "Tar" Cigarettes for Specific Diseases**

Having examined the nature of the dose-response relationship and some of the limitations of using "tar" measurements as the measure of dosage, we can now examine the evidence available that assesses the relative risk of lower "tar" cigarettes for specific disease processes. An understanding that the different health consequences of smoking may be caused by different smoke constituents is pivotal to these assessments of relative risk. Our understanding of the specific etiologic mechanisms by which cigarette smoke constituents cause different diseases remains incomplete at this time.

The individual sections of this Report review in detail evidence on the relative health hazards of lower "tar" and nicotine cigarettes. Assessment of the relative risk of these cigarettes requires the integration of this information; final assessment of the overall relative health hazard of these cigarettes has not been reached. The major issue is the potential and actual health impact of the introduction of these cigarettes into the marketplace. Assessment of this requires understanding of the changes that have taken place in the cigarette product, the effects of those changes on smoking initiation, cessation, and patterns of cigarette use, and the probable health effects of the net

change in cigarette smoke dose. It also requires an understanding of the changes in risk that occur secondary to switching to lower "tar" cigarettes distinct from the risks of lifelong use of these products.

Lung cancer is the disease process in which the relative risk of lower "tar" and nicotine cigarettes has been most clearly evaluated. Approximately 85 percent of the incidence of lung cancer can be directly attributed to cigarette smoking; there are relatively few problems with changing criteria for classification of cause of death, and there is a clear, linear dose-response relationship. Moreover, the "tar" portion of the smoke probably contains most of the carcinogenic activity of the whole smoke. If the reduction in machine-measured "tar" yield is accompanied by an actual reduction in smoker exposure dose, then there should be a relatively proportionate reduction in lung cancer risk.

Lower "tar" cigarettes are associated with a reduction in the risk of developing lung cancer, although the proportionate reduction in risk is substantially less than that of "tar" yield.

A smaller percent reduction in lung cancer risk versus that of measured cigarette "tar" yield could result from several factors, including compensation (such as an increased depth of inhalation or a greater number of cigarettes smoked per day), or from a lack of comparable reductions in other carcinogens.

For several reasons, it is difficult to extrapolate these risk reduction data to the current very low "tar" cigarettes. Because the lower "tar" yield of the cigarettes evaluated in the published studies probably was accomplished predominantly by reducing the weight of tobacco in the cigarette and by removing "tar" through filtration, use of these cigarettes might reasonably be expected to result in a lower smoke exposure if compensation did not occur. It is not clear, however, that the alterations in the techniques of tobacco processing and cigarette manufacture that have produced the very low machine-measured "tar" yields can be expected to result in similar reductions in actual smoker exposure to toxic smoke constituents. In addition, the potential carcinogenic effect of the substances added to these cigarettes has not been evaluated. The demonstrated reduction in mouse skin tumorigenicity of "tar" has not, however, been accompanied by a reduction in the incidence of or mortality rates due to lung cancer among humans.

Cigarette smoking is an independent risk factor for coronary heart disease, one that interacts synergistically with other risk factors such as hypertension and hypercholesterolemia. The effect of cigarette smoking in coronary heart disease risk is clearly dose related, and cessation of smoking reduces the risk. Estimation of the impact of varying cigarettes on coronary heart disease risk is difficult, because the exact etiologic agent(s) have not been identified. A number of agents have been suggested to be active in the development of coronary heart disease, including nicotine and carbon monoxide. Any change in risk that might occur because of switching to lower "tar"

and nicotine cigarettes might be expected to become evident more rapidly for coronary heart disease risk than for cancer risk, due to the acute effects of cigarette smoke in causing adverse coronary heart disease events such as sudden death.

As in the case of cancer, the expectation that a risk reduction for coronary heart disease would accompany the use of lower "tar" and nicotine cigarettes is based on the premise that the use of lower "tar" cigarettes results in a reduction of exposure to the responsible smoke constituents. This assumption is reasonable if nicotine is a major etiologic agent, because there is a close relationship between the "tar" and nicotine yields for individual cigarettes. That is, among the cigarettes currently available in the United States, a lower "tar" cigarette is also a lower nicotine cigarette.

The variations of the other constituents in the particulate phase of the smoke in relation to "tar" yield is largely unknown, especially in those cigarettes specially formulated to produce very low machine measurements of "tar" yields.

Carbon monoxide is one gas in cigarette smoke that may be closely associated with coronary heart disease risk, perhaps through interference with myocardial oxygenation, enhancement of platelet adhesiveness, or promotion of atherosclerosis. The relationship between carbon monoxide yield and "tar" yield, however, has not been as thoroughly examined as that between "tar" and nicotine. The factors that influence the carbon monoxide yield are closely related to the manufacturing process (e.g., porosity of the paper, filter ventilation, etc.), and therefore may vary somewhat independently of "tar" yield. In addition, the absorption of carbon monoxide is more dependent on depth of inhalation than is the absorption of nicotine and, if the use of lower "tar" products results in a compensatory increase in depth of inhalation, smoker exposure to carbon monoxide may remain unchanged or actually increase. The reality of this concern is borne out by those studies that show no lowering of carboxyhemoglobin levels in smokers who switch to lower "tar" cigarettes. If carbon monoxide is an active etiologic agent for cigarette-related coronary heart disease, and if significant compensatory changes in the style of smoking occur with use of lower "tar" cigarettes, then the risk of coronary heart disease with lower "tar" cigarettes may be similar to, or possibly greater than, the risk of smoking higher "tar" cigarettes.

Some other agents in the gas phase of cigarette smoke have also been suggested as possible contributors to the development of coronary heart disease. Little is known about the relationship between the yield of the gas phase of the smoke and the "tar" yield. The change in formulation that allows the reduction in "tar" yield of the new lower "tar" cigarettes has not been examined for its effect on the yield of individual gas phase constituents. The potential for creating new substances and for increasing the yields of existing gas phase



constituents by changes in formulation cannot be assessed from existing data, but may well impact on the risk of coronary heart disease produced by smoking lower "tar" cigarettes.

It is not surprising that the studies looking at the relative risk of lower "tar" cigarettes reviewed in the cardiovascular section have not produced a clear estimate of relative risk, given the difficulty in relating a difference in "tar" yield to a difference in coronary heart disease risk and the existence of gaps in our understanding of the etiologic agents in smoke that cause coronary heart disease. Thus, the impact of a reduction in the "tar" yield of cigarettes on the coronary heart disease risk produced by smoking cannot be estimated at this time.

Approximately 70 percent of chronic obstructive lung disease deaths are attributable to cigarette smoking. The number of deaths attributed to chronic obstructive lung disease is much smaller than the number of lung cancer deaths. This fact, and the relatively long interval of time between the onset of symptomatic chronic airflow limitation and death from respiratory failure, reduce the usefulness of mortality data from chronic lung disease in assessing the relative risks of lower "tar" cigarettes. Therefore, attention has focused on the level of symptoms and measured reductions in air flow for evaluating relative risk of chronic obstructive lung disease.

As reviewed in the section on chronic obstructive lung disease, there are three major aspects of cigarette-induced lung injury: chronic mucous hypersecretion, airway inflammation and narrowing, and alveolar septal destruction. The causal agents for each type of lung injury may be different, and therefore each type may be affected quite differently by a reduction in the "tar" yield of the cigarette.

The mucous hypersecretion and cough are a response of the lung to the chronic irritant effects of cigarette smoke. To the extent that a reduction in "tar" yield reflects a reduction in smoke exposure, smoking lower "tar" cigarettes should result in reduced cough and sputum production. In the studies that have looked at this question, the expected decrease in cough and sputum production has indeed accompanied the use of lower "tar" cigarettes.

Airflow limitation is not produced by mucous hypersecretion *per se* but rather by airway narrowing and loss of parenchymal lung units. The same studies that showed a reduction in symptoms with the use of lower "tar" cigarettes failed to show a similarly reduced effect on air flow limitation. This finding may indicate that tests of air flow limitation are not sufficiently sensitive to measure the differences in extent of disease. It could also result from a failure to produce lower exposure to the causative agent(s) with the use of lower "tar" cigarettes, either due to a lack of reduction in concentration of the agent(s) or to compensatory changes in smoking behavior.

The loss of parenchymal lung units that is the hallmark of emphysema is extremely difficult to measure during life, but there has been substantial progress toward an understanding of how this disease is produced by cigarette smoking. This work is reviewed in detail in the section on chronic obstructive lung disease; it is suggested that alveolar walls are destroyed by excess proteolytic activity. Cigarette smoke may promote this excess activity through a combination of an increased cellular release of proteolytic enzymes and the oxidative inactivation of the inhibitor of these proteolytic enzymes. Since the airways filter out most of the particulate matter in the smoke, it is felt that the gas phase may be the component of smoke responsible for the changes in enzymatic activity. The gas phase contains a number of agents capable of oxidative inhibition of the enzyme inhibitor alpha-antitrypsin. Therefore, the risk of developing emphysema may not be related to the "tar" yield of the cigarette smoked. Even if the reduction in "tar" yield results in a reduction in smoker exposure to "tar," a pattern of compensation that produces a deeper inhalation may deliver a greater dose of the gas phase of that smoke to the alveoli where it produces a pathologic effect. In addition, the techniques used in formulation of the newer very low "tar" cigarettes may result in an increase in the concentrations of etiologic agents in the smoke. Therefore, the relative risk for lower "tar" cigarette usage in the development of chronic obstructive lung disease is highly problematical. The lower "tar" and nicotine cigarettes may well produce less of the symptomatic component of this disease, but even if they do result in a reduction of total smoke exposure, the pattern of that smoke exposure may negate any reduction in risk.

The relative risks for both the mother and the fetus of smoking lower "tar" and nicotine cigarettes during pregnancy are of great concern, both because of the numbers of young women who smoke and because of younger women's more frequent use of lower "tar" cigarettes. The increased use of cigarettes with lower "tar" yields has not been investigated for its effect on changes in risk of adverse effects of smoking on pregnancy. Accordingly, no reduction in risk relative to higher "tar" and nicotine cigarettes has been demonstrated.

Of particular concern is the potential teratogenic effect of additives and their combustion products. Thus, it is not possible to assume that switching to a lower "tar" cigarette would have an effect in reducing risk during or after pregnancy. It is clear that the only recommendation that can be made to reduce risk in the smoking mother is for her to quit smoking.

The ultimate assessment of risk is, of course, overall mortality. One study examined the effect of smoking lower "tar" and nicotine cigarettes on overall mortality. Persons smoking cigarettes with lower "tar" and nicotine yield exhibited a decline in mortality rate from any cause of approximately 15 percent in comparison with that of smokers

of higher "tar" cigarettes. Direct extrapolation of these overall mortality results to current smoking exposure is not possible. The lowest "tar" categories in that study included cigarettes that would be considered higher "tar" products today; the mechanisms by which subsequent reductions have been achieved may differ from earlier techniques. There was no evidence available on the duration of use of lower "tar" products in this population.

### **Methodologies for Assessing Relative Risk**

The task of monitoring the relative risks of lower "tar" cigarettes is complex, but it is not impossible. Four approaches can be used: constituent toxicology, bioassay systems, observational epidemiology, and the study of fundamental mechanisms of disease production. Each approach makes a unique contribution to our understanding of relative risk. Each approach also has significant limitations to its contribution to a complete assessment of risk. It is necessary to combine the information gathered by each of these methods in order to understand the risk. The final assessment of relative risk requires data from each of these four methodologies. To the extent that information from any one area is lacking, the estimation of relative risk is incomplete.

The first approach is that of constituent toxicology. A tremendous amount of time and effort has been spent to characterize cigarette smoke and to identify disease-producing smoke constituents. Several thousand individual constituents have been identified. Much has been learned about the effects of cigarette reformulation on the pyrolytic process. Studies have led to a better understanding of human absorption of these substances and how this is influenced by differing patterns of puffing and inhalation. The identification of carcinogens, oxidants, and ciliotoxic compounds represents an important advance in understanding the risks of cigarette smoking. The fundamental strength of this approach is that it might ultimately allow risk to be measured by examining the chemical composition of the smoke and its absorption. Thus, assessment of risk might be made prior to allowing human exposure to the smoke. It could lead to the selective removal of toxic substances from smoke.

The major limitation of this approach is the sheer magnitude of the task. It would be necessary to identify each of the several thousand substances, the site and amount of absorption with different patterns of smoking, and the toxicity for each organ system. It would also be necessary to address the more complicated question of the potential interactions between smoke constituents, environmental and occupational exposures, and other exposures, such as medications. The monumental nature of this task does not mean that constituent toxicology is unable to contribute to our assessment of relative risk. It simply means that it alone cannot solve the problem. The choice of what substances to measure in order to assess risk must be guided by

an understanding of the basic mechanisms of disease production and must be correlated with changes in disease occurrence in human populations. In this way the search can be, and is being, focused on those areas and substances that may provide the best measure of risk.

A second method of assessing risk is through the use of bioassay systems. The term "bioassay" is used broadly to include animal models as well as cellular or organ responses. This approach can also rapidly provide information on risk without human exposure and has the additional advantage that whole smoke or major fractions of smoke can be tested rather than individual constituents. The limitation of this method is that the estimate of risk is only as good as the bioassay system. Unless the system truly approximates the disease process of concern, changes in that system may not reflect risk of disease. A number of bioassay systems exist for the study of cigarette risk. Unfortunately, none of them can be said to exactly duplicate human disease. At the present time, estimates derived from these systems cannot stand alone, but must be interpreted in the light of information derived from other methods.

The ultimate "bioassay" is, of course, human exposure. The occurrence of disease in human populations would provide the most accurate estimate of the relative risk of lower "tar" cigarette smoking. An important drawback to this approach is that it permits the development of that disease in the population prior to measuring risk and taking appropriate public health action. An additional limitation of the observational epidemiology is that the risk being measured is caused by a product and a pattern of use that occurred in the past. Because of the long time lag between regular exposure to smoke and the development of most cigarette-related diseases, and the time lag between development of disease and diagnosis of that disease, the relative risk determined by observational epidemiologic methods may lag many years behind the current risk. It may take 20 to 30 years before smoking-related disease is observed. With a rapidly changing cigarette product, it is necessary to estimate the risks of current exposures rather than those of past exposures. This assessment is complicated by the difficulty of defining and measuring any differences in individual smoker exposure resulting from changes or individual variations in styles of smoking. Nonetheless, despite these difficulties, the epidemiologic method remains the major tool in assessing the relative health risks of differing cigarettes.

Some of the limitations of the observational epidemiologic method can be overcome by incorporating information from the other approaches to risk assessment. Information on the toxicology of cigarette smoke might allow epidemiologists to sharpen their measurement of actual smoker dosage, and might identify earlier tests of toxicity than the traditional end points of disease occurrence or death. Information on the basic mechanisms of disease production could improve the

estimation of relative risk by directed measurement of the basic pathophysiologic processes or their biochemical or metabolic sequelae. An excellent example of this kind of potential interaction is the testing of populations of smokers for the byproducts of elastin degradation suggested in the section on chronic obstructive lung disease.

The fourth method of assessing relative risk is the definition of the fundamental mechanisms of disease production. An obvious attraction of this approach is its potential to provide information that would permit the prevention or cure of the disease process.

The difficulty with this method of risk assessment is our limited understanding of these fundamental mechanisms. It is important to incorporate what understanding we do have into the risk assessment produced by other methods, and equally important to incorporate information from other methods into the search for disease mechanisms. As an example, it would be fruitless to examine the effect of a given substance on the cell function in alveoli if it has been learned from absorption studies that the substance is absorbed in the upper airway and never reaches the alveoli.

Once the mechanism of disease is understood, however, an estimate of relative risk might be made, not only by measuring the dose of etiologic agents in smoke, but also those determinants of the disease process pre-existing in a given individual.

## **Conclusion**

In summary, the final estimation of the relative risk of smoking lower "tar" and nicotine cigarettes must be based on a synthesis of the information derived from several methodologies. Despite the lack of comprehensive and conclusive evidence currently available, the Public Health Service policy on lower "tar" and nicotine cigarettes must remain unchanged. The health risks of cigarette smoking can only be eliminated by quitting. For those who continue to smoke, some risk reduction may result from a switch to lower "tar" and nicotine cigarettes, provided that no compensatory changes in style of smoking occur.

This Report of the relative risks of lower yields of "tar," nicotine, and carbon monoxide has defined the following more clearly: the conclusions warranted by present evidence; the difficulties and importance of defining and monitoring changes in cigarette yields and actual smoker exposure; and the major questions remaining unanswered, which constitute the major areas for future research efforts.

Summaries of the available data on the relative risks of cigarette-related diseases among smokers of differing cigarettes follow. They are grouped by topic.

Following these summaries are the research recommendations from the Working Meeting, "Research Needs on Low-Yield Cigarettes."

These recommendations are combined, reflecting the common underlying concerns among disciplines.

## **Summaries**

### **Pharmacology and Toxicology**

1. Several thousand constituents have been identified in tobacco and tobacco smoke. Of these, nicotine appears to be the most important acute-acting pharmacologic agent. Nicotine's physiologic effects include increased heart rate and blood pressure. Nicotine also can permit the formation of tobacco-specific nitrosamines, which are potent carcinogens, and nicotine itself may be a significant cocarcinogen. The carcinogenic potency of cigarette smoke condensates appears to depend on the nicotine content of the "tar." This relationship may be due in part to the conversion of nicotine to tobacco-specific nitrosamines or to the coexistence of nicotine and some other unidentified carcinogen. Whether the carcinogenic effects of nicotine as determined in animal studies are directly applicable to humans is not known at present.
2. In an important study to predict the carcinogenic activity of cigarette smoke condensate, the amount of available nicotine delivered to the mice was found to be a factor in every term but one of the predictive model.
3. Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are two prominent classes of tumor initiators found in the smoke condensates of commercial cigarettes. Of the polycyclic aromatic hydrocarbons formed during combustion, benzo[a]pyrene (BaP) may be the most important and has been studied the most extensively. A correlation has been found between benzo[a]pyrene levels and the carcinogenic activity of smoke condensates from several types of cigarettes, but other studies have failed to show that carcinogenic potential is significantly dependent on benzo[a]pyrene content. However, the interaction of BaP with nicotine does appear important in carcinogenesis.
4. The tobacco-specific nitrosamines (TSNA) are formed during curing and fermentation of tobacco leaves and combustion of cigarettes. TSNAs induce cancer in the lungs and trachea of hamsters and may be of particular importance in the induction of human laryngeal cancer. They may be active as contact carcinogens, or their metabolism at distant sites may produce carcinogens that are then transported to a target site.
5. It is not known whether the unidentified mutagens in cigarette smoke are an important cause of lung cancer in humans, but

added exposure to any tumor initiators probably carries an increased risk of cancer.

6. Cigarette smoke contains oxidants that have been shown to reduce the activity of alpha<sub>1</sub>-antitrypsin in animals and man. This inhibitory function is distinct from the effect whole smoke has on increasing levels of elastolytic enzymes released by neutrophils and macrophages.
7. The great variety of tobacco types makes it possible to manipulate the plant genetically to change the content of the constituents of the leaf. The chemical content of the leaf is also affected by agricultural practices and curing methods. The nicotine content of tobacco, for example, is related to the amount of nitrate fertilizer used in cultivation. Modification of tobacco as reconstituted sheet incorporates substantial amounts of tobacco stems that contain less nicotine than the leaf. The physical nature of reconstituted sheets can be controlled to change their burning characteristics and smoke composition.
8. Vapor-phase constituents of cigarette smoke inhibit ciliary motility and mucous flow in experimental animals.
9. Cigarette smokers metabolize several compounds more rapidly than do nonsmokers. This effect is believed to be caused by the induction of microsomal oxidases, which include aryl hydrocarbon hydroxylase (AHH). Induction of AHH activity appears to be caused by systemic exposure to the smoke compounds themselves or to the metabolites of those compounds. The AHH system may be involved in the metabolic formation of ultimate carcinogens from procarcinogen precursors.
10. In recent years, a number of flavoring additives or cellulose-based tobacco substitutes may have been included in manufactured cigarettes. The nature and amounts of such additives as actually used are not known, nor is it known what influence these additives may have on the chemical composition or subsequent biological activity of cigarette smoke.
11. Cigarette design has a major effect on smoke composition. The filter is the design characteristic that has the most impact on "tar" yield; it can also selectively remove nitrosamines and semivolatile phenols from smoke. The porosity of cigarette paper and the presence of holes in the mouthpiece influence smoke composition because ventilation reduces the quantity of "tar" and dilutes the gas phase of smoke.
12. Because of the complexity of cigarette smoke, the total impact of any cigarette modification on smoke composition will probably never be fully known.
13. Many laboratory studies of the effects of smoke constituents have been carried out using smoking machines that control puff volume, frequency and duration, butt length, and other factors

according to standardized parameters. However, the most widely used parameters were established in 1967, and the type of cigarettes generally smoked today are substantially different with respect to length, paper porosity, "tar" and nicotine content, and concentration of gas phase constituents. Evaluation of the toxicological and pharmacological properties of smoke from new types of cigarettes requires detailed knowledge of the manner in which those cigarettes are smoked, as well as of how smoking patterns affect smoke composition.

### **Cancer**

1. Today's filter-tipped, lower "tar" and nicotine cigarettes produce lower rates of lung cancer than do their higher "tar" and nicotine predecessors. Nonetheless, smokers of lower "tar" and nicotine cigarettes have much higher lung cancer incidence and mortality than do nonsmokers.
2. Smokers of lower "tar" and nicotine cigarettes may tend to smoke larger numbers of cigarettes, to inhale more deeply, to have relatively higher amounts of carboxyhemoglobin than predicted from machine measurements of carbon monoxide yield, and to have higher than predicted carbon monoxide in exhaled air.
3. In attempting to develop a "less hazardous" cigarette, singular emphasis has been placed on reducing the "tar" yield of cigarette smoke because of the early demonstration of a causal relationship between "tar" and lung cancer. Comparable data on changes in yield of constituents in the gas phase of smoke are not publicly available.
4. The occurrence of laryngeal cancer has been reported to be reduced among smokers who use filtered cigarettes, compared with those who use nonfiltered cigarettes.
5. There is no epidemiologic evidence to prove or to disprove a decreased occurrence of cancers of other sites in humans who smoke lower "tar" and nicotine cigarettes.
6. In evaluating the effect of smoking lower "tar" and nicotine cigarettes on histologic changes in the bronchial epithelium, it was determined in one autopsy study that male smokers who died between 1970 and 1977 had fewer histological changes than those smokers who died between 1950 and 1955.
7. Even among those who do not develop cancer, histologic changes in the tracheobronchial tree are more advanced at autopsy in smokers of cigarettes with higher "tar" and nicotine than among smokers of cigarettes with lower yields.
8. The "tar" content of smoke condensate of today's cigarettes is less tumorigenic to mouse skin than that of cigarettes of 30 years ago. Levels of the known carcinogen benzo[a]pyrene are lower in



the smoke of today's cigarettes than in that of cigarettes of 30 years ago. Flavor additives used in lower "tar" and nicotine cigarettes produce traces of mutagenic compounds.

9. Although studies point to polycyclic aromatic hydrocarbons in the "tar" of inhaled cigarette smoke as potential carcinogens for humans, additional work is needed to determine whether nicotine plays a major role as a carcinogen. Definition of the role of nicotine in carcinogenesis is necessary prior to advocacy of cigarettes yielding less "tar" but more nicotine.
10. Animal studies have shown that a significant reduction of "tar" and a selective reduction of tumor initiators and cocarcinogens can markedly reduce the tumorigenic potency of cigarette smoke.

#### **Cardiovascular Diseases**

1. Epidemiological studies show that the incidence of coronary heart disease (CHD) increases as the daily number of cigarettes smoked increases and that the incidence of CHD decreases among those who quit smoking. These dose-related effects suggest that lower "tar" and nicotine cigarettes might be associated with lower risks of CHD. However, the overall changes in the composition of cigarettes that have occurred during the last 10 to 15 years have not produced a clearly demonstrated effect on cardiovascular disease, and some studies suggest that a decreased risk of CHD may not have occurred.
2. Of the several thousand substances found in cigarette smoke, only a few have been implicated in cardiovascular risk. A number of substances have not yet been adequately assessed. Further, the changes in smoke constituents that have resulted from changes in the cigarette product have not been documented.
3. Linking cigarette smoke yields to cardiovascular disease is complicated by the evidence that smokers of lower "tar" and nicotine cigarettes may smoke more "intensively," although they may not smoke a substantially greater number of cigarettes daily than do smokers of higher "tar" and nicotine cigarettes. The net result could be to decrease the actual intake of "tar," nicotine, and carbon monoxide less than that expected on the basis of machine measurements.
4. Nicotine stimulates the sympathetic nervous system, producing a rise in catecholamines that in turn increases heart rate, elevates systolic blood pressure, constricts cutaneous blood vessels, and increases levels of free fatty acids. The nicotine-stimulated release of catecholamines has been suggested as the cause of increased platelet stickiness and aggregation, pointing to a potential role in coronary disease. There is some evidence that these physiological effects may be dose related and somewhat diminished with lower nicotine varieties of cigarettes.

5. Carbon monoxide has a negative inotropic effect on the myocardium of patients with angina pectoris. When combined with hemoglobin in the form of carboxyhemoglobin, carbon monoxide may increase the permeability of the blood vessel walls to lipids, thereby promoting atherosclerosis.
6. Cigarettes with unperforated filters yield lower "tar" and nicotine levels than unfiltered cigarettes, but they yield more carbon monoxide than do unfiltered cigarettes at the same "tar" yield. Carbon monoxide yields are lower in cigarettes with perforated filters, but as the composition of cigarettes has changed, carbon monoxide yields have decreased much less in proportion to the decrease in "tar" and nicotine yields.
7. In studies of patients with angina pectoris, increased carboxyhemoglobin levels significantly shorten exercise time until the onset of angina pectoris.
8. Myocardial ultrastructural changes have been found in rabbits exposed to carbon monoxide.
9. Most cardiovascular studies have focused on nicotine and carbon monoxide rather than on "tar," which has not been shown to have a major acute role in cardiovascular disease. Even less is known about other constituents of cigarette smoke.
10. Not all cigarettes that produce a lower yield of one substance necessarily provide a lower yield of other substances.
11. Evidence on the association between CHD and filter cigarettes is somewhat conflicting. One major study showed a reduction of 10 to 20 percent in coronary deaths among persons smoking lower "tar" and nicotine cigarettes as compared with those who smoked higher yield cigarettes, but other surveys have shown a slightly increased risk of coronary mortality in people who smoked filter cigarettes relative to those who smoked nonfiltered cigarettes. Recent unpublished data from the Framingham Study do not show a lower CHD risk among smokers of filter cigarettes.

#### **Chronic Obstructive Lung Disease**

1. The relationship between cigarette smoking and chronic obstructive lung disease (COLD) is well documented. The constituents of cigarette smoke that are responsible are currently not known. Whether a difference in risk of COLD has occurred with lower "tar" and nicotine cigarettes as compared with higher "tar" and nicotine cigarettes is currently unknown.
2. Cigarette smoking is associated with the release by alveolar macrophages of an increased amount of the elastolytic enzymes, which degrade alveolar tissue, and with reduced activity of alpha<sub>1</sub>-antitrypsin, the primary elastase inhibitor. This mechanism has not yet been directly related to the development of human emphysema. To date there are no published studies that

compare the effects of higher versus lower “tar” and nicotine cigarettes on elastolytic enzymes and inhibitor activity.

3. Cigarette smoke also contains relatively high levels of oxides of nitrogen. The nitrogen oxides produce lung damage in animals that is similar to that induced in humans by cigarette smoke. The oxides of nitrogen may be responsible for the early lesions of human emphysema.
4. An individual’s smoking pattern is one of the most important determinants of the relative concentration of smoke constituents that reach the lungs and of the subsequent response of the airways to smoke inhalation. Holding smoke in the mouth before inhaling it into the lungs produces less response of the airways than direct inhalation, which causes spirometric changes indicative of bronchoconstriction. This effect is independent of the “tar” content of the cigarette.
5. Pulmonary mucous hypersecretion and symptoms of cough and phlegm appear to be affected by the “tar” content of cigarette smoke. The development of airway obstruction is closely related to the number of cigarettes smoked. Smokers of lower “tar” and nicotine cigarettes who compensate by smoking more or inhaling more deeply might thereby increase their risk of developing obstructive airway disease.
6. Population studies that have examined the rate of decline of lung function in relation to the number of cigarettes smoked have shown variable results, and most of the available data do not relate lung function to cigarette yield. Overall, the mean difference between the rate of decline of FEV<sub>1</sub> in asymptomatic smokers and nonsmokers is very small, but there is a subgroup of the smoking population that shows more rapid decline and is apparently more likely to develop significant pulmonary disease.

### **Pregnancy and Infant Health**

1. Cigarette smoking during pregnancy has been shown to have adverse effects on the mother, the fetus, the placenta, the newborn infant, and the child in later years. There is no evidence available that lower “tar” and nicotine cigarettes decrease or increase these health risks, relative to those posed by higher “tar” and nicotine cigarettes.
2. Problems that have been linked to smoking during pregnancy include placenta previa, abruptio placentae, vaginal bleeding, and reduced average birthweight of newborn infants.
3. Smoking by pregnant women increases the risk of spontaneous abortion, premature delivery, fetal death, and perinatal death. Parental smoking is associated with the sudden infant death syndrome.

4. The fetuses of smoking mothers have higher blood carboxyhemoglobin levels and lower fetal arterial oxygen levels than do the mothers.
5. Children of smoking mothers appear to show a greater susceptibility to some adverse health effects, such as bronchitis, pneumonia, and respiratory disease, during early childhood. Slight differences in physical growth and other forms of behavioral and intellectual development may be found in children as old as 11 years of age.
6. Although "tar," nicotine, carbon monoxide, and some other constituents of cigarette smoke produce deleterious effects, the specific etiologic agents and their mechanisms of action for adverse effects on pregnancy are not clearly determined. Thus, the relative importance of "tar" and nicotine, or carbon monoxide and other constituents of tobacco smoke in the etiology of adverse gestational and fetal events is not known.

### **Behavioral Aspects**

1. Nicotine appears to be the primary pharmacological reinforcer in tobacco, but other pharmacological and psychosocial factors may also contribute a reinforcing effect.
2. It appears that some smokers make compensatory adjustments in their smoking behavior with cigarettes of different yields that might increase the amounts of harmful substances entering the body. The frequency and amount of spontaneous compensatory changes in smoking style with different cigarettes require further investigation.
3. Additional information is needed on the role of lower "tar" and nicotine cigarettes in the initiation, maintenance, and cessation of smoking.
4. Rigorous comparative behavioral studies involving animals are needed to provide comprehensive, experimentally valid results on behavioral aspects of smoking.
5. Laboratory techniques developed for study of opioids and alcohol should be adapted for studies of tolerance and dependence on nicotine.
6. Improved laboratory facilities are necessary for more tightly controlled behavioral research. A particular need exists for clinically acceptable cigarettes with standardized ingredients.
7. Smoking-machine measurements that more closely simulate the practices of human smokers must be developed.

### **Lower "Tar" and Nicotine Cigarettes: Product Choice and Use**

1. Public awareness of the dangers of smoking has steadily increased since 1965. In 1978, more than 90 percent of all Americans believed cigarette smoking to be hazardous to health.

2. Cigarette product choice has shifted dramatically since the 1950s. In 1979, 91.7 percent of U.S. smokers used filter-tipped cigarettes, compared with 1.4 percent in the early 1950s.
3. Lower "tar" cigarettes conventionally have been defined as yielding 15 mg of "tar" or less per cigarette. The proportion of all cigarettes consumed in the United States that are lower "tar" has increased from 3.6 percent in 1970 to almost 50 percent in 1979. In 1979, 58.5 percent of all cigarette brands marketed in the United States yielded 15 or fewer mg of "tar."
4. Since 1968, the "tar" content of the "average cigarette" in the United States has declined by 32.2 percent, and nicotine content has fallen by 25.6 percent. These declines may be partially accounted for by lower tobacco weight per cigarette—down 23.8 percent from 1968 to 1978—and by the greater length of the filter and overwrap of the average cigarette, which could result in a declining number of machine puffs per cigarette.
5. The prevalence of smoking in the U.S. adult and adolescent populations has continued to decline. In 1979, 32.5 percent of the adult population smoked cigarettes (36.1 percent of men and 29.4 percent of women). However, evidence suggests that the average daily number of cigarettes consumed by those adults who continue to smoke has increased over several decades. The availability and use of lower "tar" cigarettes have increased over recent years.
6. In 1979, 33.3 percent of adult regular smokers used cigarettes yielding 15 mg "tar" or less. Studies show that women smokers are more likely to use lower yield cigarettes than men are, and white smokers use lower yield cigarettes in greater proportions than do blacks. Smokers of higher income and education also select lower yield cigarettes in a higher percent of cases.
7. A large national survey found that smokers in older aged cohorts choose both the lowest and highest yield cigarettes in higher proportions than do younger cohorts.
8. Although black smokers choose cigarettes of higher "tar" and nicotine in greater proportions than do whites, the lower daily number of cigarettes smoked by blacks suggests that their average daily intake of "tar" and nicotine may be lower than that of white smokers.
9. In 1979, 33.5 percent of adolescent smokers (age 12 to 18) used lower "tar" cigarettes, compared with 6.7 percent in 1974. Boys and girls smoke cigarettes of about the same level of "tar" content.
10. Adult smokers started smoking regularly at the average age of 18 years. One survey showed that the higher the "tar" level of the cigarette currently smoked, the younger the reported age of beginning smoking.

11. Evidence from a large national survey does not support a correlation between a greater mean number of cigarettes smoked per day by users of lower "tar" and nicotine cigarettes than by higher "tar" users.
12. In a national survey, smokers of lower "tar" and nicotine cigarettes more frequently reported having attempted to quit at least once, and among these smokers, a higher proportion report having attempted unsuccessfully to quit multiple times. The applicability of these data to defining the role of "tar" or nicotine yields of cigarettes in quitting behavior is not clear in the absence of more detailed longitudinal data.
13. Although a greater proportion of unsuccessful quitters reported smoking the lowest "tar" and nicotine products than did recent successful quitters in one large survey, interpretation of these data is made difficult by the noncomparability of brand reported (i.e., unsuccessful quitters reported the brand smoked after an attempt, successful quitters reported the brand smoked prior to the attempt).
14. In a large national survey, the mean duration of the latest unsuccessful attempt to quit shows no clear relationship to "tar" or nicotine yields.

#### **Research Recommendations From the Working Meeting "Research Needs on Low-Yield Cigarettes"**

The following list is an overview of research recommendations submitted as a result of the working group reports from the June 1980 conference "Working Meeting: Research Needs on Low-Yield Cigarettes." No attempt has been made to place them in order of priority.

- It must be determined whether lower "tar" and nicotine cigarettes change smoking behavior. For instance, compensatory adjustment, such as deeper, longer, and more frequent puffs, may turn a nominally lower yield cigarette into a higher yield cigarette. Studies are needed to determine whether adjustments made by smokers of lower "tar" and nicotine cigarettes may inadvertently increase their exposure to "tar" and carbon monoxide beyond that expected from a less intensively smoked higher yield cigarette.
- Because of changes in cigarette composition, further retrospective and prospective epidemiologic studies are needed to assess the health effects of these changes. A primary need is to establish whether there are measurable differences in morbidity between smokers of higher "tar" and nicotine cigarettes and smokers of lower "tar" and nicotine cigarettes. Efforts should include ongoing long-term studies that are adaptable to such epidemiologic inquiry.

- The increased use of nonhuman primate models might permit comparison of the effects of lower “tar” and nicotine cigarettes with those of higher “tar” and nicotine cigarettes under controlled conditions.
- More indepth studies on the mechanisms of cardiovascular and pulmonary disease are needed to assess new brands of lower “tar” and nicotine cigarettes. With improved noninvasive techniques, scientists will be better able to determine how a particular cigarette affects cardiac function and other physiological activities. Genetic markers should be explored as a possible method of identifying high-risk groups who are more likely to develop tobacco-related diseases if they smoke.
- Additional emphasis should be given to both human and animal research models for the developmental mechanism of chronic obstructive pulmonary disease and its possible alteration by lower “tar” and nicotine cigarettes. The elastase-inhibitor imbalance hypothesis of emphysema pathogenesis needs confirmation for human disease. Recently developed tests that measure lung elastin degradation products in plasma and urine need rapid clinical evaluation.
- Emphasis should be placed on studies that determine the character and magnitude of the health hazards that lower “tar” and nicotine cigarettes pose for pregnant women and their offspring. Specifically, the smoking habits of pregnant women should be analyzed in prospective epidemiologic studies to determine the effect of varying cigarettes on the course and outcome of pregnancy. Careful laboratory measurements of various physical capacities and functions of newborn infants and pregnant women should be performed in case-control and prospective studies to determine the influence of smoking on pregnancy outcome. Clinical and experimental studies using animals should be conducted to evaluate the effect of individual constituents of cigarette smoke on tissues and physical responses. Direct intervention strategies should be aimed at pregnant adolescents who smoke.
- Another research need is routine, frequent surveillance of current and future lower “tar” and nicotine cigarettes for specific chemical constituents and biological activity. In addition to “tar,” nicotine, and carbon monoxide yield, new types of cigarettes should be monitored regularly for delivery of other potentially harmful constituents, such as benzo[a]pyrene, phenols, catechols, nitrosamines, nitrogen oxides, volatile aldehydes, and radionuclides. More frequently updated ratings of “tar,” nicotine, and carbon monoxide content would permit more accurate studies on the potential impact of cigarette components on health.