Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction

Kathleen Stratton, Padma Shetty, Robert Wallace, and Stuart Bondurant, Editors, Committee to Assess the Science Base for Tobacco Harm Reduction, Board on Health Promotion and Disease Prevention

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Committee to Assess the Science Base for Tobacco Harm Reduction

Board on Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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Preface

Tobacco has been used by humans for at least a millennium, and its harmful effects have been suspected for at least 200 years. In the last 50 years, convincing and generally accepted evidence has established the fact that exposure to tobacco products is the major single cause of early human mortality and morbidity in developed nations and in many developing nations as well.

Even nonsmokers suffer morbidity and excess mortality from the toxic effects of inhalation of sidestream smoke. Both smokers and their nonsmoking associates are more likely to be injured in fires and automobile accidents. The personal and social price we pay for establishing and sustaining nicotine addiction through exposure to tobacco smoke is our greatest controllable health cost and one of our greatest social burdens.

It has been scientifically established that reduced exposure to tobacco smoke by lifelong abstinence and avoidance of smoke eliminates the added risk and harm and that cessation, even after many years of smoking, reduces risk and harm both immediately and in the long term for many tobacco-related conditions.

Several smoking cessation programs, some aimed at individuals and some at communities, have been shown to be modestly effective in assisting smokers to quit smoking. These programs have been shown to be more effective with the added use of nicotine replacement by patches for absorption through the skin, by nicotine-containing chewing gum or sprays for absorption through oral or nasal mucous membranes, or by the administration of psychotropic drugs to reduce the desire for nicotine.

However, with the most intensive application of the most effective known programs for prevention and cessation, approximately 10-15% of the adults in the United States are expected to be regular users of tobacco in 2010, and they will continue to suffer the increased incidence of harmful and lethal consequences. Among this group are many who cannot or will not stop using tobacco, and it is to this group that effective programs and products of harm reduction should be directed.

New tobacco products and nicotine replacement products are being marketed frequently and, along with products now on the market, often have associated direct or implied health claims. Some of the new products differ from traditional products in ways that appear minor, whereas others involve substantial changes in types of tobacco, in additives, or in curing, blending, or processing of the tobacco. New products may also change the composition of the aerosol the consumer inhales compared to cigarette smoke by changing the burning temperature of the tobacco by new methods of combustion, by limiting the release of smoke into the atmosphere, by dilution of the smoke with air, and/or by adding unnatural carriers for smoke particles.

Although many components of tobacco are known to be toxic, little is known of the specific dose-response relations of the individual toxins as they occur in cigarette smoke or of the interactions between the constituents of tobacco smoke. There is little direct evidence that removal of specific substances from tobacco smoke or from tobacco actually reduces risk or harm to human health. In considering the health effects of modified tobacco products it is important to remember that the health consequences of the use of any such product are determined not by the toxic agents removed from the product but by the actual exposure to the toxins that remain. Harm reduction is the net difference in harm between the products as actually used.

There is strong evidence that in the range of exposures involved in smoking, there is a quantitative relationship between the magnitude of exposure and the incidence of cancer, coronary vascular disease, pulmonary disease, and several other tobacco-related illnesses. Rarely if ever is there impartial and thorough assessment of the risk associated with new tobacco products relative to the risk of abstinence or the risk of other tobacco products prior to marketing. Unlike new tobacco products, nicotine replacement products are subject to full disclosure of content, rigorous testing, and the regulation of marketing claims by the of the Food and Drug Administration.

In addition to cigarette smoke, other forms of tobacco such as cigars, chewing tobacco, and snuff are also vectors of nicotine addiction and often have their own sets of serious toxic consequences.

The latent period between beginning exposure to tobacco and the development of most of the major adverse consequences is so long that empirical, direct evidence (assessment of immediate and long-term toxicity of individual tobacco products in humans) that one tobacco product is less harmful than another will rarely be available in time to be a basis for informing users. In the absence of direct evidence, conflicting claims of the degree of harm reduction are likely and informed usage decisions by smokers and nonsmokers will be difficult.

No one knows the dose-response relations, the specific toxins, the pathogenic mechanisms, or the interrelationship between the many components of tobacco smoke with enough precision to make scientifically reliable quantitative judgments about the risk or actual harm reduction associated with use of any tobacco product. Since we do not know which of many toxins may be the cause of specific harmful effects, we can only infer but we cannot know the health effects of the elimination of any one or several tobacco components. Further, we are just beginning to identify and understand the genetic basis and other causes of the differences in susceptibility to toxic effects among groups or individuals that largely determine the response of an individual to a toxin.

Nonetheless, it is reasonable to expect that some of the new products will reduce exposure to tobacco toxins and possibly reduce harm to some users and to others who are exposed to them. It is, therefore, urgent and important that the assessment of exposure to tobacco toxins resulting from the use of modified tobacco products or drugs be based on the best available evidence, made by the most qualified judges, and communicated to policy makers and the public completely and honestly.

There is little direct evidence available to serve as a basis for judgment as to the potential for harm reduction of specific new tobacco and pharmaceutical products. Therefore, any conclusions as to the relative harm of these products must necessarily be inferred from a base of indirect knowledge. The continuing introduction of new tobacco products with implicit or explicit claims of risk or harm reduction makes it important and urgent that the capacity for the best possible scientific assessment of these claims be put in place.

Since even the availability of harm reduction products may deter some from following the healthier course of abstinence or cessation, assessment of health claims should be based on an estimate of the effect of the product on the prevalence of smoking in the population, as well as the effect on the health risk to the individual smoker.

The most reliable scientific interpretation of necessarily incomplete indirect evidence comes when individuals who are experts in the related fields are not biased and are free of conflict of interest form a consensual

judgment. Such a judgment based on evidence of high quality should be a requirement for a conclusion that the use of a product is in fact associated with decreased exposure to toxins and that the decreased exposure is likely to be associated with less harmful outcomes.

Further, since these judgments of risk will necessarily be inferential because they are based on indirect and inconclusive evidence, some form of postmarketing surveillance of each product is important.

The charge to the committee is to address the science base for harm reduction from tobacco. The committee concluded early in its deliberations that the science base for harm reduction will evolve over time. There will inevitably be important interactions between the types of products that are developed and the science base. There will also be interactions between any regulatory process and the science base (the science base will influence regulation, and regulation will focus pertinent science) and, obviously, between regulations and products. For these reasons, the committee realized that the science base for harm reduction can be usefully considered only in the context of some sense of the types of specific products and of the consequences of regulation. Accordingly, portions of this report address both general categories of potential harm reduction products and regulatory considerations.

It is the strong sense of the committee that claims of less harm or risk associated with the use of tobacco products or drugs should be available—but only if four conditions are met: (1) There should be strong and widely available programs designed to avoid initiation and to achieve abstinence; (2) There should be premarketing evidence satisfactory to a group of disinterested experts that—as the product will actually be used by consumers—there is less exposure to toxic agents without coincidental increase in harm to the individual from other smoke components or to the population from encouraging initiation or continuation of smoking, the burden of proof of assertions of harm reduction should rest entirely with those making the assertion; (3) The public should be fully informed of the strength of the claims as assessed by an independent panel of experts; and (4) There should be an effective surveillance system in place to determine short-term behavioral and the long-term health consequences of the use of the new products.

The committee wishes to express its great appreciation to the many individuals, listed in Appendix B, who contributed generously and substantially to its deliberations. Representatives of many health agencies as well as tobacco interests responded thoughtfully and extensively to the committee's questions.

Dr. Kathleen Stratton contributed perspective, insight, meticulous attention to detail, and essential oversight to the work and report. This

report would not be possible without her substantial and important contributions.

Dr. Padma Shetty assumed responsibility for blocks of the report, and both the full report and many specific parts are testimony to her analytic, organizational, and expressive proficiency. Ann St. Claire organized the arrangements for the work of the committee with great finesse and also made useful contributions to the analytical work of the committee. Every member of the committee is deeply appreciative of the work of Dr. Stratton, Dr. Shetty, and Ms. St. Claire.

Stuart Bondurant
Chair

REVIEWERS

The report was reviewed by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments to assist the authors and the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The content of the review comments and the draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their participation in the report review process:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **David Challoner**, (review monitor) University of Florida and **Hugh Tilson**, (review coordinator) University of North Carolina. Appointed by the

National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Executive Summary

BACKGROUND

Tobacco smoke is the cause of the most deadly epidemic of modern times. Smoking causes cancer (e.g., lung, oral cavity, esophagus, larynx, pancreas, bladder, kidney), chronic obstructive pulmonary disease (COPD), myocardial infarction, and stroke. The continuing toll of tobacco use has prompted the search for means of harm reduction for those who cannot or will not stop using tobacco. Numerous products that make implied or explicit claims to reduce the burden of smoking while allowing continued nicotine consumption are now entering the market. This report is concerned with the evaluation of these products.

Nearly one-quarter of adult Americans—an estimated 47 million people—smoke cigarettes (CDC, 2000a). Although this is far lower than the 42% recorded in 1965, the decline in the rates of smoking among adults appears to have leveled off during much of the 1990s (PHS, 2000). In a recent survey, 12.8% of middle school children and 34.8% of high school students reported some form of tobacco use during the month prior to their being interviewed (CDC, 2000b). The vast majority of smokers begin tobacco use during adolescence (IOM, 1994). However, 70% of smokers say they want to quit (CDC, 1994), and 34% of smokers make an attempt to quit each year. Thus, many but not all tobacco users find it very difficult to quit and continually expose themselves to known toxic agents.

DEFINITION OF HARM REDUCTION

For the purposes of this report, a product is harm-reducing if it lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants. Many different policy strategies may contribute to harm reduction. However, this report focuses on tobacco products that may be less harmful or on pharmaceutical preparations that may be used alone or concomitantly with decreased use of conventional tobacco. The committee does not use the term "safer cigarette," in particular, in order to avoid leaving the impression that any product currently known is "safe." Every known tobacco-containing product exposes the user to toxic agents; every pharmaceutical product can have adverse effects.

HISTORY OF EFFORTS TO REDUCE HARM FROM CIGARETTES

There have been many efforts in the past to develop less harmful cigarettes, none of which has proved to be successful. One of the first innovations with the promise of harm reduction was the development of cigarettes with filters. Filters attempt to reduce the amount of toxicants that go into the smoke inhaled by the smoker. The next major modification of cigarettes with safety implications was "low-yield" cigarettes. These products emit lower tar, carbon monoxide (CO), and nicotine than other products as measured by the Federal Trade Commission (FTC) assay (the "smoking machine"). Many consumers believed, and still do, that these products pose less risk to health than other cigarettes.

However, data on the health impact of low-yield products are conflicting, in part due to a lack of systematic study early in the introduction of the products. Most current assessments of morbidity and mortality suggest that low-yield products are associated with far less health benefit, if any, than would be predicted based on estimates of reduced toxic exposure using FTC yields. In order to maintain the desired intake of nicotine, many smokers who changed to low-yield products also changed the way they smoked (e.g, compensated by inhaling more deeply than when smoking higher-yield products). Thus, their exposure to tobacco toxicants is higher than would have been predicted by standardized assays and people who have continued to use these products have not significantly reduced their disease risk by switching to them. Moreover, widespread use of these products might have increased harm to the population in the aggregate if tobacco users who might otherwise have quit did not, if former tobacco users resumed use, or if some people who would otherwise not have used tobacco did so because of perceptions that the risk with low-yield products was minimal.

TYPES OF EXPOSURE REDUCTION PRODUCTS

Tobacco and cigarette-like products have been introduced recently that, under measurement systems such as the FTC smoking machine, result in decreased emission of some toxicants compared to conventional tobacco products. Currently available products include tobacco with reportedly reduced levels of some carcinogens and cigarette-like products that deliver nicotine with less combustion than cigarettes. Two classes of pharmaceutical products approved by the Food and Drug Administration (FDA) for short-term use in smoking cessation might also be used for harm reduction. These include nicotine products, such as in patch, gum, inhaler, and nasal spray preparations, and a nonnicotine product that reduces the craving for tobacco. These cessation drugs could be used long term to maintain cessation or concomitantly with continued but decreased use of conventional tobacco products (see Table 1).

These tobacco and pharmaceutical products could *potentially* result in reduced *exposure* to toxicants. The committee uses *potentially*, because whether exposure to tobacco toxicants is reduced depends on the user's behavior, such as frequency and intensity of use. Reduced exposure, however, does not necessarily assure reduced risk to the user or reduced harm to the population. Therefore, and in order to avoid misinterpretation, the committee uses the generic phrase "potential reduced-exposure products," or PREPs, when discussing the modified tobacco products, cigarette-like products (whether tobacco containing or not), or pharmaceutical products and medical devices (whether nicotine containing or not) used for their tobacco harm reduction potential. More such products are likely to be introduced in the near future, perhaps accompanied by claims that they are less harmful than conventional products.

THE COMMITTEE CHARGE AND ASSUMPTIONS

The Institute of Medicine (IOM) convened a committee of experts to formulate scientific methods and standards by which PREPs (pharmaceutical or tobacco-related) could be assessed. Four questions were imbedded within the charge given to the committee by the Food and Drug Administration in December 1999. Where there are not yet answers, the committee was asked to outline the broad strategy by which the knowledge base might be assembled.

1. Does use of the product decrease exposure to the harmful substances in tobacco?
2. Is this decreased exposure associated with decreased harm to health?

TABLE 1 Potential Reduced-Exposure Products

Category	Descriptors	Examples
Modified tobacco	Reduced yield of selected toxicants	Advance™, low-nitrosamine tobacco cigarettes, Snus, reduced nitrosamine smokeless tobacco
Cigarette-like products	Less combustion than cigarettes	Premier™ (off market) Eclipse™ Accord™
Pharmaceutical products	Nicotine replacement	Nicotine gum, patches, inhaler, nasal spray
	Antidepressants that reduce nicotine craving	Bupropion SR, nortriptyline
	Other medications	Nicotine antagonists, clonidine

3. Are there surrogate indicators of this effect on health that could be measured in a time frame sufficient for product evaluation?
4. What are the public health implications of tobacco harm reduction products?

The first three questions deal with the adequacy of current scientific methods to determine whether and to what extent these products reduce the risk of morbidity and mortality and the nature of the advice to give to citizens, health professionals, and others. The fourth question is important because it addresses the population impact of these products. That is, although a product might be risk-reducing for an individual's health compared to conventional tobacco products, its use might not be harm-reducing for the population as a whole. The fourth question is also important because the answer lays the groundwork for educational, policy, and regulatory actions.

The committee reviewed the literature and assessed the nature and availability of the data needed to evaluate the feasibility of tobacco harm reduction. Its review encompassed the major disease categories linked by scientific evidence to tobacco consumption, including cancer, cardiovascular disease, respiratory disease, reproductive and developmental disorders, and others. The report is offered to relevant federal and state regulatory and policy bodies, Congress, scientists and health care professionals,

tobacco and pharmaceutical industries, and—most importantly—the public, who will have to decide whether or not to use these products.

The committee began with fundamental operating precepts, reiterating and reaffirming overwhelming scientific evidence and the conclusions of many scientific and policy advisory bodies:

Precept 1. Tobacco use causes serious harm to human health.

Precept 2. Nicotine is addictive.

Precept 3. The best means to protect individual and public health from tobacco harms are to achieve abstinence, prevent initiation and relapse, and eliminate environmental tobacco smoke exposure.

Precept 4. A comprehensive and authoritative national tobacco control program, with harm reduction as one component, is necessary to minimize adverse effects of tobacco.

PRINCIPAL CONCLUSIONS

The committee does not evaluate specific PREPs in this report, since the currently available tobacco-related PREPs in particular are most likely prototypes of limited life span. Under present regulatory conditions, tobacco-related PREPs can be changed with little assessment and without disclosure of their contents. Therefore, the committee considered the types of PREPs currently or likely to become available in the foreseeable future. After reviewing a large body of scientific documents and data, hearing presentations from many scientific, regulatory and industrial interests, and publicly soliciting comments on the issues at hand, the committee reaches the following principal conclusions regarding the questions posed by the charge:

Conclusion 1. *For many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible.* This conclusion is based on studies demonstrating that for many diseases, reducing tobacco smoke exposure can result in decreased disease incidence with complete abstinence providing the greatest benefit.

Conclusion 2. *PREPs have not yet been evaluated comprehensively enough (including for a sufficient time) to provide a scientific basis for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use.* One narrow exception is the use of nicotine gum in one study for maintenance of cessation, described in Chapters 8, 13, and 14. Carefully and appropriately conducted clinical and epidemiological studies could demonstrate an effect on health. However, the

impact of *PREP*s on the incidence of most tobacco-related diseases will not be directly or conclusively demonstrated for many years.

Conclusion 3. *Surrogate biological markers that are associated with tobacco-related diseases could be used to offer guidance as to whether or not PREPs are likely to be risk-reducing.* However, these markers must be validated as robust predictors of disease occurrence and should be able to predict the range of important and common conditions associated with conventional tobacco products. Furthermore, the efficacy of PREPS will likely depend on user population characteristics (e.g., those defined by gender, genetic susceptibility, ethnicity, tobacco history, and medical history).

Conclusion 4. *Currently available PREPs have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.* Many techniques exist to assess exposure reduction, but the report contains many caveats about the use of all of them, including usually an unknown predictive power for harm.

Conclusion 5. *Regulation of all tobacco products, including conventional ones as recommended in IOM, 1994, as well as all other PREPs is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected.* Regulation is needed to assure that adequate research (on everything from smoke chemistry and toxicology to long-term epidemiology) is conducted and to assure that the public has current, reliable information as to the risks and benefits of PREPs. Careful regulation of claims is needed to reduce misperception and misuse of the products. If a PREP is marketed with a claim that it reduces (or could reduce) the risk of a specific disease(s) compared to the risk of the product for which it substitutes, regulation is needed to assure that the claim is supported by scientifically sound evidence and that pertinent epidemiological data are collected to verify that claim.

Conclusion 6. *The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.* The effect on public health will depend upon the biological harm caused by these products and the individual and community behaviors with respect to their use. Regulation cannot assure that the availability of risk-reducing PREPs will lead to reduced tobacco-related harm in the population as a whole. However, a regulatory agency can assure that data are gathered that would permit the population effects to be monitored. If tobacco use increases or tobacco-related disease increases, these data would serve as a basis for developing and implementing appropriate public health interventions.

PRINCIPAL RECOMMENDATIONS

The committee believes that harm reduction is a feasible and justifiable public health policy—but only if it is implemented carefully to achieve the following objectives:

- Manufacturers have the necessary *incentive* to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease;
- Consumers are fully and accurately *informed* of all of the known, likely, and potential consequences of using these products;
- Promotion, advertising, and labeling of these products are firmly *regulated* to prevent false or misleading claims, explicit or implicit;
- Health and behavioral effects of using PREPs are *monitored* on a continuing basis;
- Basic, clinical, and epidemiological *research* is conducted to establish their potential for harm reduction for individuals and populations; and
- Harm reduction is implemented as a *component* of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

Recommendations about future research needs are based on Principal Conclusions 1-4 and can be found in the following section. They flow primarily from material presented in Section II of the report. Progress in these areas will permit the application of the principles of risk assessment to the evaluation of PREPs in the future. At present, judgement informed by incomplete science will be used to evaluate PREPs. However, immediate actions are required. Therefore, the committee makes recommendations that address Principal Conclusions 5 and 6. These conclusions and recommendations are particularly intertwined, requiring immediate attention and swift action.

The effect of PREPs could be to increase or decrease tobacco-related disease in the population. Assessing a positive public health impact will be difficult and will require extensive surveillance and research to ensure that the impact is positive. Even the strongest surveillance system could not alone provide minimal assurance of safety or protection of the public. Currently there is little public authority over tobacco products of any type. Whatever the current legal or regulatory posture with respect to these products, the committee realized that in order to obtain the best available scientific evaluation of emerging tobacco-related PREPs and to provide the best advice on use of all PREPs to the public, some national authority over these PREPs is needed. Only a comprehensive program of

regulation and assessment including extensive premarket testing and surveillance offers a reasonable possibility of net gain in health from use of PREPs instead of conventional tobacco product use.

Therefore, the committee recommends development of a surveillance system to assess the impact of promotion and use of PREPs on the health of the public. A national comprehensive surveillance system is urgently needed to collect information on a broad range of elements necessary to understand the population impact of tobacco products and PREPs, including attitudes, beliefs, product characteristics, product distribution and usage patterns, marketing messages such as harm reduction claims and advertising, the incidence of initiation and quitting, and nontobacco risk factors for tobacco-related conditions. There should be surveillance of major smoking-related diseases as well as construction of aggregate population health measures of the net impact of conventional products and PREPs.

The surveillance system should consist of mandatory, industry-furnished data on tobacco product constituents and population distribution and sales. Resources should be made available for a program of epidemiological studies that specifically address the health outcomes of PREPs and conventional tobacco products, built on a robust surveillance system and using all available basic and clinical scientific findings.

The committee further recommends strengthened federal regulation of all modified tobacco products with risk reduction or exposure reduction claims, explicit or implicit, and any other products offered to the public to promote reduction in or cessation of tobacco use. The committee outlines 11 principles to govern the regulation of PREPs. The regulation proposed by this committee is narrowly focused on assuring that the products reduce risk of disease to the user and accumulating data that would indicate whether or not the products are harm-reducing for the population in the aggregate. Other potential regulatory approaches to tobacco control are not addressed within this report.

The recommended regulatory structure builds on the foundation of existing food and drug law, with appropriate adaptations to take into account the unique history and toxicity of tobacco products. These principles envision testing and reporting for all tobacco products, approval of claims regarding reduced exposure and reduced risk regarding tobacco or cigarette-like products, and retention of current FDA regulation of pharmaceutical PREPs. Manufacturers of tobacco products and pharmaceuticals should be encouraged to develop and introduce new products that will reduce the burden of tobacco-related disease. The regulatory system proposed in this report is not to be viewed in isolation. It is

proposed as an essential component of a package of public health initiatives (including research, education, and surveillance) that this committee believes is necessary to realize whatever benefit tobacco and pharmaceutical product innovation can offer in reducing the nation's burden of tobacco-related illness and death. (See Box 1.)

Research Conclusions and Recommendations

Many fruitful research directions should be explored to strengthen the scientific basis for assessing harm reduction. In reviewing the range of scientific disciplines and disease areas, the committee specifically noted five general scientific issues: (1) description of the dose-response relationship between tobacco smoke and/or constituent exposure and health outcomes, (2) identification and development of surrogate markers for disease, (3) the utility of preclinical research, (4) utility of short-term clinical and epidemiological studies, and (5) the role of long-term epidemiological studies and surveillance. The committee has reviewed the evidence available regarding these points and has described a research agenda to facilitate evaluation of the harm reduction potential of these products. This section summarizes the committee's conclusions and recommendations for future research, which are elaborated in detail in Section II of this report.

1. *Currently available data allow estimation, albeit imprecise, of a dose-response relationship between exposure to whole tobacco smoke and major diseases that can be monitored for evaluation of harm reduction potential.*

There are more than 4,000 different chemicals in tobacco smoke; many of these are known to be toxic. Many of the mechanisms of pathogenesis attributed to tobacco use have been explicated, and in a few cases, causative tobacco constituents have been identified. In order to effectively evaluate the toxic effects of tobacco smoke and identify the primary causal agents, the toxic components of PREPs and comparison products must be identified and be disclosed. For the most part, the data are insufficient to accurately describe the relationship of tobacco use and disease formation at the level of detail that would establish all causal agents involved or the exact dose-response relationship. The characteristics of this relationship vary among diseases and are affected by differences in compensation and actual exposure and by interindividual or population differences. Consequently, the confidence with which the adverse effects or harm reduction potential of PREPs can be extrapolated, especially at low doses, is uncertain. Also, there is currently no evidence to support a threshold level of tobacco exposure below which no risk exists for any of the reviewed health outcomes.

BOX 1
Regulatory Principles

Regulatory Principle 1. Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.

Regulatory Principle 2. All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various tobacco smoke constituents should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

Regulatory Principle 3. Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models as well as appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency.

Regulatory Principle 4. Manufacturers should be permitted to market tobacco-related products with exposure-reduction or risk-reduction claims only after prior agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, as compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that measurable reduction in morbidity and/or mortality (in subsequent clinical or epidemiological studies) would be anticipated, as judged by independent scientific experts.

Regulatory Principle 5. The labeling, advertising, and promotion of all tobacco-related products with exposure-reduction or risk-reduction claims must be carefully regulated under a "not false or misleading" standard with the burden of proof on the manufacturer, not the government. The agency should have the authority and resources to conduct its own surveys of consumer perceptions relating to these claims.

Regulatory Principle 6. The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct post-marketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.

Regulatory Principle 7. In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to *increase* the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects or other adverse

continues

BOX 1 Continued

health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information.

Regulatory Principle 8. All added ingredients in tobacco products, including those already on the market, should be reported to the agency and subject to a comprehensive toxicological review.

Regulatory Principle 9. The regulatory agency should be empowered to set performance standards (e.g., maximum levels of contaminants; definitions of terms such as "low tar") for all tobacco products, whether conventional or modified, or for classes of products.

Regulatory Principle 10. The regulatory agency should have enforcement powers commensurate with its mission, including power to issue subpoenas.

Regulatory Principle 11. Exposure reduction and risk reduction claims for drugs that are supported by appropriate scientific and clinical evidence should be allowed by the FDA.

In summary, current knowledge of the dose-response relationships is sufficient to support risk reduction through exposure reduction as a goal for the individual through the use of these various products. To date, these relationships are not defined well enough in terms of specific components of smoke to serve as a predictive tool for the effect a particular product will have on most health outcomes. However, a strong quantitative relationship between maternal tobacco exposure and the incidence of spontaneous abortions and intrauterine growth retardation leading to low infant birthweight has been documented extensively. This population is one in which the actual health effects of PREPs and potential for harm reduction may be most directly evaluated. Further discussion regarding dose-response can be found in the disease-specific chapters in Section II (Chapters 12–16).

2. *Although candidate disease-specific surrogate markers are currently available, further validation of these markers is needed. In addition, other biomarkers that accurately reflect mechanisms of disease must be developed to serve as intermediate indicators of disease and disease risk.*

Biomarkers are measurements of any tobacco constituent, tobacco smoke constituent, or effect of such a compound in a body fluid (including exhaled air) or organ. Although some biomarkers currently exist, these require further validation and more must be developed that have adequate sensitivity, specificity, and limited complexity and that quantitatively link biological exposure of tobacco smoke or specific constituents to disease induction or progression prior to the advent of clinically apparent

disease. Validation and development of biomarkers will provide a stronger foundation by which to make scientific evaluations and regulatory decisions regarding PREPs.

Although no panel of markers can be utilized currently to evaluate the health effects of PREP use, potential biomarkers have been and are being developed for many of the relevant disease categories. The committee recommends further study of biomarkers for various disease categories that may potentially be determined to be intermediate indicators of disease and disease risk. For example, possible measures include markers of platelet and vascular activation, lipid peroxidation, and inflammation, which have the potential to be related to measures of cardiovascular physiology and, ultimately, reflect the risk of clinical cardiovascular disease as well as markers of inflammation in lung disease. Also, biomarkers of cancer that may indicate early carcinogenic processes and risk of cancer development include but are not limited to markers of genetic damage in blood, sputum, urine, and internal organs. Another potential marker is the measurement of bone density as a direct reflection of the severity and risk of osteoporosis.

Ideally, a set of behavioral markers is needed to monitor product use patterns, thereby enabling clinicians and researchers to measure substitution of PREP use for cessation. Although the committee realizes the difficulty of developing a set of such behavioral markers, they are needed for a comprehensive evaluation of PREPs. A further detailed research strategy regarding the development of biomarkers can be found in the disease-specific chapters (Chapters 12–16) and the chapter on exposure and biomarkers assessment (Chapter 11).

3. *The evaluation of PREPs will be facilitated by the development of appropriate animal models and in vitro assays of the pathogenesis of tobacco-attributable diseases.*

Animal models and in vitro testing can contribute to the evaluation of individual PREPs and to the development of a scientific basis for designing and evaluating harm reduction products. Such studies could include cell culture, animal studies, and molecular studies to document specific toxicants as the most likely causative agents, to better define pathogenic effects of tobacco smoke exposure, to better explain the relationship of disease risk regression and exposure regression (dose-response relationships), and to validate biomarkers of exposure and biological effect.

The new technologies of genomics and proteomics have the potential for evaluating and comparing the effects of tobacco exposure and PREP use on gene translation and expression in neoplastic and nonneoplastic disease.

The committee recommends specific applications of pre-clinical models for specific tobacco-attributable disease. For example, the committee

recommends the utilization of genomic and proteomic technologies to investigate the effect on gene translation and expression of tobacco smoke exposure and its relevance for pulmonary, cardiovascular, and neoplastic health outcomes. Also, accurate models are needed for smoke or tobacco constituent exposure (including nicotine) and exposure to PREPs and their effects on the development of COPD, cardiovascular disease, neoplasia, and in utero injury. Again, a more detailed pre-clinical research agenda can be found in the disease-specific chapters in Section II (Chapter 12–16).

4. *Short-term clinical and epidemiological studies in humans are required for the comprehensive evaluation of PREPs.*

Some effects of PREPs in humans could be evaluated by epidemiological studies, by measurement of intermediate disease markers or, in some cases, by clinical studies of smokers who are unwilling or unable to quit but are willing to use PREPs (compared to a control group of conventional tobacco product users). The committee recommends the utilization of validated intermediate biomarkers of disease effect in these studies in order to assess potential harm reduction within a practical time frame for diseases that occur only after prolonged exposure. Examples of potential measures include the use of lung function tests or inflammatory changes, evaluated through bronchoalveolar lavage, as intermediate markers for COPD in interventional studies.

A few smoking-attributable diseases develop after relatively brief exposure (weeks to months) and provide an opportunity for strong short-term clinical and epidemiological studies. These diseases include intrauterine growth retardation leading to low infant birthweight, slowed wound or ulcer healing, and perhaps acute myocardial infarction. Human studies are also required for evaluating the relationship of individual smoking history, environment, gender, race, and other factors (e.g., diet) to disease risk and susceptibility. Further discussion regarding the utilization of clinical studies can be found in Section II (Chapters 12–16).

5. *Long-term epidemiological studies of populations and/or pilot groups of users should monitor the incidence of disease or other adverse effects.*

Most tobacco-related diseases develop clinically over many years, and the only direct and definitive way to evaluate the harm reduction value of PREPs is to monitor the health outcomes of users compared to appropriate control groups over an extended period of time. Such surveillance could be an add-on to other epidemiological studies and should include ongoing reports of smoking behavior, types of products used, and health outcomes, as well as intermittent collection of biological samples for biomarker assessment in a segment of users. Further discussion can be

found in Chapter 6 and in the disease-specific chapters in Section II (Chapters 12–16).

Risk Assessment

A report published in 1983 by a committee of the National Research Council (NRC) outlined important steps and considerations in risk assessment (NRC, 1983). The "Red Book" identified important steps: hazard identification (Does the toxicant cause the adverse effect?), dose-response assessment (What is the relationship between dose and incidence in humans?), exposure assessment (What exposures are currently experienced or anticipated under difference circumstances?), and risk characterization (What is the estimated incidence of the adverse effect in a given population?). A risk characterization provides important information for risk management, which also includes public health, social, economic, and political considerations.

The committee did not do a formal risk assessment of PREPs. The knowledge base is inadequate to do so at this time. However, the "Red Book" framework has great utility in presenting the committee's work. Table 2 uses it to summarize material discussed in Chapters 1, 5, 6, 7 and 8. Even though the committee has concluded that harm reduction through the use of PREPs is not yet convincingly demonstrated, Table 2 illustrates how the committee's conclusions and recommendations are key to gathering important data. This new knowledge base will permit a more definitive evaluation of harm reduction as a strategy and of PREPs as tools for reducing tobacco-related morbidity and mortality.

Based on an extensive review of the scientific and medical literature, the committee concludes that although harm reduction is feasible, no currently available PREPs have been shown to be associated with biologically relevant exposure reduction or with decreased tobacco-related harm. One narrow exception is the use of nicotine gum in one study for maintenance of cessation, described in Chapters 8, 13, and 14. Without a comprehensive program of scientific research, surveillance, and regulation, the potential benefit of harm reduction will go unrealized. Furthermore, without such a comprehensive program PREPs could, in fact, be detrimental to both individual and public health.

TABLE 2 Use of Risk Assessment Framework in Assessing Tobacco Harm Reduction

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Information required as described in 1983 "Red Book"	Epidemiology Animal bioassay Short-term studies Comparisons of molecular structure	Epidemiology Low-dose extrapolation Animal to human extrapolation	Dose to which humans are exposed Dose of special populations Estimation of size of population potentially exposed	Estimate of the magnitude of the public health problem	A risk-assessment (qualitative or quantitative) may be one of the bases of risk management
Challenges in risk assessment of conventional tobacco products	Complex mixture Animal models are limited Constituents and additives are proprietary information	Dose changes for an individual over time Dose of individual toxicants varies over time Exposure at time of disease progression	Changes in smoking topography Complex mixture	For which disease? At which point in smoking history?	FTC regarding advertising
Additional challenges of PREP risk assessment	Tobacco-related products will change rapidly with time	Assessing effect of moving backwards on a dose-exposure curve, assuming long-time previous higher exposure	Changing exposure after long-term higher dose exposure Some toxicants could increase	Need models to consider effects on initiation, cessation, and relapse	FDA authority currently exerted only over pharmaceutical PREPs

continues

TABLE 2 Continued

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Committee charge	1. Does product decrease exposure to the **harmful substances** in or produced during use of tobacco?	2. Is decreased exposure associated with decreased harm to health? 3. Are there useful surrogate indicators of disease that could be used?	1. Does product **decrease exposure**?	4. What are the public health implications?	4. What are the public health implications?
Disease-specific summary data (Chapter 5; Section II)	3. Utility of preclinical research to judge feasibility	1. Dose-response data for conventional tobacco products 2. Validation and development of biomarkers 4. Short-term clinical and epidemiological studies	2. Validation and development of biomarkers 4. Short-term clinical and epidemiological studies	5. Long-term epidemiological studies and surveillance	
Principal conclusions	1. Risk reduction is feasible 4. Exposure reduction can be demonstrated.	3. Surrogate measures could be used to predict risk reduction	4. Exposure reduction can be demonstrated	1. Risk reduction is feasible 2. Risk reduction not yet demonstrated 6. Public health impact is unknown	5. Regulation is a necessary precondition for assuring a science base and for assuring protection of the health of the public

Elements of surveillance system	Specific tobacco constituents of both the products and the smoke they generate	Disease outcomes	Consumption of tobacco products and of PREPs Biomarkers of exposure to tobacco products Personal tobacco product use and related behavioral patterns	Disease outcomes	Tobacco product marketing, including PREPs
Regulatory principles (all refer to tobacco-related PREPS, except for 11)	1. Ingredient disclosure 3. Preclinical testing required to support health-related claims 7. Evidence for no increased risk 8. Added ingredient review 9. Performance Standards	6. Products with claims would require post-marketing surveillance and epidemiological studies	2. Yield Assessment 4. With specific claims, no increased exposure to unclaimed compounds 9. Performance Standards 11. Exposure reduction claims for pharmaceutical PREPs	5. Labeling for products with claims cannot be false or misleading	10. Enforcement power
Recommendations	3. Develop appropriate animal models and in vitro assays of pathogenesis	1. Sufficient data to allow estimation of dose–response 2. Need to develop validated biomarkers of disease	4. Clinical and epidemiological studies in human are required	Comprehensive surveillance is recommended	Regulation is recommended

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6

Surveillance for the Health and Behavioral Consequences of Exposure Reduction

The goal of surveillance systems in epidemiology and public health is to provide timely information from populations on the occurrence of diseases and conditions of interest, the presence of risk factors for those conditions, and the impact of disease control programs. Public health surveillance systems are not the only sources of information on the frequency or causes of various disease nor are they the only indicators of disease control program success or failure, but the population perspective brings focus to the entire community and the totality of the burden of suffering from various conditions.

The Centers for Disease Control and Prevention (CDC) offers the following definition of surveillance (Thacker and Berkelman, 1988):

> Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know. The final link in the surveillance chain is the application of these data to prevention and control. A surveillance system includes a capacity for data collection, analysis, and dissemination linked to public health programs.

The extent and sophistication of surveillance systems have evolved over the years (Remington and Goodman, 1998). At the turn of the 20th century, they largely involved monitoring of persons with particular infectious diseases and their personal contacts, such as surveillance of persons who came in contact with smallpox or typhus cases. By mid-century,

they evolved into monitoring a wide variety of communicable diseases for detection and control purposes. Selected chronic illnesses became the target of surveillance programs beginning in the 1970s. Later, a host of surveillance techniques were used to monitor environmental exposures such as hazardous occupations, personal injuries, and health-related individual behaviors. Tobacco use was first studied in a federal survey in 1955 (Haenszel et al, 1956). In 1996, the Council of State and Territorial Epidemiologists added the state-specific prevalence of cigarette smoking to the list of conditions designated as notifiable by states to the CDC (CDC, 1996).

Among the attributes that are used to evaluate surveillance systems are simplicity, flexibility, acceptability, sensitivity, representativeness, and timeliness (Klaucke et al., 1988). The *simplicity* of a given surveillance system is influenced both by its structure and ease of operation. A given surveillance system will ideally be as simple as possible and still meet all of its objectives. A *flexible* system can economically adapt to changing information needs or operating conditions. *Acceptability* refers to the willingness of organizations and individuals to adopt and/or participate in the surveillance system. In this instance, acceptability will be influenced by whether the system is mandated. *Sensitivity* refers to the ability of a system to detect diseases and conditions, health states, or various health behaviors or attitudes of interest. A *representative* surveillance system will accurately describe the distribution of a health event by person, place, and time. A *timely* system minimizes the delay between occurrence of an event and the initiation and completion of the process of monitoring and reporting of findings.

Another important attribute of surveillance systems is whether the detection targets are collected *actively* or *passively*. Passive surveillance generally involved the collection of spontaneously reported health events from interested health professionals or others. The current system of reporting adverse drug events to the Food and Drug Administration generally falls into this category. On the other hand, active surveillance involves expending the resources to marshal all available data collection modes to assure as complete an ascertainment as possible of the health and behavioral events of interest. Active surveillance would seem to be essential for helping to assess the impact of PREPs in population context.

This chapter reviews existing surveillance systems and activities for monitoring tobacco product exposure and their health consequences, with emphasis on the introduction and use of PREPs and the issue of harm reduction in the United States. Then proposals to enhance existing surveillance programs are offered. While surveillance data provide only one part of the information needed for scientific and regulatory judgments, it is a critical component that complements clinical, basic, and other data

collection. In general, a successful surveillance activity would determine amounts and types of tobacco products distributed in the community, population patterns of product use, and rates of smoking-related conditions. Specifically, an ideal surveillance system for evaluation of PREPs and other tobacco products would contain the following elements:

1. *Consumption of tobacco products and PREPs.* A first step to understanding changes in tobacco-attributable diseases and the impact of control programs is to monitor consumption rates for conventional tobacco products and PREPs. The federal government has monitored per capita consumption (in pounds) of tobacco products for over a century (Millmore and Conover, 1956; U.S. Department of Agriculture, 2000). National estimates of consumption use overall include sales data and are adjusted to incorporate estimates of smuggling. Information on the use of pharmaceutical aids for smoking cessation has been published recently (CDC, 2000b).
2. *Specific tobacco constituents of both the products and the smoke they generate.* Central to any surveillance system is accurate characterization of environmental exposures of interest. With respect to conventional tobacco products and PREPs, documenting the physical and chemical content of these products, including additives and structural components, is critical. It is equally important to determine the constituents of the products of tobacco product combustion and other elements otherwise delivered during human consumption.
3. *Tobacco product marketing, including PREPs.* It is similarly extremely important to understand the distribution and availability of PREPs in the community. For example, monitoring of general media advertising, free-sample distribution, and other marketing practices including mass mailings and public relations activities would seem essential to monitor any health claims, implicit or explicit, related to PREPs as well as conventional tobacco products.
4. *Biomarkers of exposure to tobacco products.* Depending fully on personal self-report of tobacco product use is important but not always sufficient. On occasion, individuals may misrepresent their tobacco exposure or may not be fully aware of it. Further, bodily exposure to tobacco constituents may not be fully ascertained from self-report due to variation in smoking behavior and use patterns (i.e., smoking topography). Biomarkers can also provide indication of the degree of exposure to environmental tobacco smoke among nontobacco users. For these and other reasons, population levels of biomarkers of exposure become extremely important.

5 *Personal tobacco product use and related behavioral patterns.* Critical to assessing the health impact of conventional tobacco products and PREPs is the determination of actual products used, including product types and brands. It is also important to understand the impact of PREPs in terms of smoking initiation, quit attempts, maintained abstinence, and personal consumption patterns (Shiffman, 1999). In general, this can only be determined from sample surveys of relevant populations. Attitudes toward tobacco usage and knowledge of actual threats to health would also be important components of such a system.

6 *Disease outcomes.* Current surveillance of tobacco-related illnesses through mechanisms such as vital records and disease registries provide important information. The development of additional types of registries, clinical record monitoring systems, and systems measuring aggregate health outcomes would add further useful information. Supplementary epidemiological studies of PREPs would enhance the ability to determine specific health outcomes. These studies would deal with use of various product lines and with potential confounders and effect modifiers of the associations. Surveillance and other long-term studies are necessary because of the duration of exposure before many chronic diseases appear. These adverse outcomes would include the health consequences that are expected based on the toxicological profile of the PREP, as well as those that are unexpected.

EXISTING TOBACCO SURVEILLANCE SYSTEMS

This section highlights existing systems of surveillance that monitor tobacco product consumption patterns, knowledge, attitudes, behaviors, and health consequences—elements that would inform the evaluation of PREP usage and impact (Giovino, 2000). The section emphasizes national and state level systems. It is possible that local or regional systems may add considerable useful information. Citations or web sites are provided for the reader who desires more detailed information.

Consumption of Tobacco Products and PREPS

The U.S. Department of Agriculture reports consumption data for the various types of tobacco products (U.S. Department of Agriculture, 2000; ERS, 2001). FTC also reports on the characteristics of cigarettes (e.g., length, filtered/non-filtered, mentholated/nonmentholated) sold in the United States (FTC, 2000a). At least one research unit (the Roswell Park Cancer Institute's Department of Cancer Prevention, Epidemiology and Biostatistics) has begun to monitor the introduction of new products.

Specific Tobacco Constituents of Both the Products and the Smoke They Generate

Currently, there is no U.S. nation-wide reporting by tobacco manufacturers of the physicochemical content of tobacco products, nor of additives or structural components. The Federal Trade Commission (FTC) reports on the results of testing of cigarette brands for tar, nicotine, and carbon monoxide (e.g., FTC, 2000a). However, as described elsewhere (Chapter 11), the usefulness of this system has been challenged (NCI, 1996).

The National Center for Environmental Health at CDC is building capacity for monitoring and research on various aspects of product design, including studies of tobacco, tobacco smoke, and biomarkers in human body fluids. Other laboratories (e.g., the American Health Foundation) have the capacity to perform tests of tobacco constituents and combustion product exposure, but they also do not conduct population surveillance.

In the Commonwealth of Massachusetts, cigarette companies (Brown and Williamson Tobacco Company, Lorillard Tobacco Company, Philip Morris USA, and R.J. Reynolds Tobacco Company) provide benchmark indicators on a sample of cigarette brands deemed representative of the U.S. market (Borgerding, 2000). The 1999 Massachusetts Benchmark Study investigated the functional relationships between standard smoke-yield parameters (e.g., "tar," nicotine, and carbon monoxide) and selected smoke constituent (e.g., acetaldehyde, 4-Aminobiphenyl, arsenic, and benzene) yields. Measures were taken on both mainstream and sidestream smoke. However, there are regional variations in tobacco product use and no national system of tobacco product distribution and consumption is in place.

Tobacco Product Marketing

No comprehensive surveillance system exists for monitoring industrial activities. The Federal Trade Commission annually collects brand-specific data but reports only aggregated national data on industry marketing expenditures (FTC, 2000b), in part obtained by subpoena. Several researchers analyze and report industry lobbying, sponsorship, and public relations activities (Glantz and Begay, 1994; Glantz et al., 1996; Siegel, 2000).

Biomarkers of Exposure to Tobacco Products

The National Health and Nutrition Examination Survey (NHANES) assesses self-reported tobacco use and serum cotinine levels annually on

nationally representative samples of children, adolescents, and adults (NCHS, 2000). Determination of serum cotinine levels, a nicotine metabolite, permits biochemical validation of active use and assessment of environmental tobacco smoke exposure in persons who don't use tobacco products. However, there is insufficient but growing ascertainment of specific tobacco product brands or detailed smoking behaviors. The National Center for Environmental Health at CDC is building capacity for monitoring and research on tobacco products, including studies of biomarkers in human body fluids.

Personal Tobacco Product Use and Related Behavioral Patterns

Since most tobacco use initiation occurs among adolescents, their knowledge, attitudes and usage patterns become an important part of tobacco and PREP assessment. Three major national surveys of adolescents exist that measure at least some tobacco-related knowledge, attitudes, and behaviors (Table 6-1). These are the National Youth Tobacco Survey (NYTS) (TIPS, 2000), the Monitoring the Future (MTF) surveys of 8th, 10th, and 12th grade students (Monitoring the Future, 2001), and the National Household Survey on Drug Abuse (NHSDA) (SAMHSA, 2000). The NYTS is a categorical survey, dedicated to measuring tobacco-related knowledge, attitudes, and behaviors in middle and high school students. The MTF and the NHSDA are primarily designed to measure illicit drug use, with more limited coverage of tobacco. NHSDA surveys persons aged 12 years old and older. The Youth Risk Behavior Survey (YRBS) (NCCDPHP, 2001b) measures health risk behaviors in high school students. Several states conduct their own versions of the YRBS (Kahn, 1998) and the Youth Tobacco Survey (U.S. DHHS, 2000). MTF includes a longitudinal component, but only for 12th grade students (Johnston et al., 2000).

Three major national surveys of adults (persons aged 18 years and older) ascertain tobacco-related knowledge, attitudes, and behaviors (Table 6-1). The National Health Interview Survey (NHIS) measures several tobacco use indicators on the core instrument every year, and assesses knowledge, attitudes, and additional behavioral measures on periodic supplements (NCHS, 2001). The NHSDA questions for adults are similar to those for adolescents. The National Cancer Institute Tobacco Use Supplement of the Current Population Survey (CPS) provides measures of tobacco-related knowledge and behaviors, as well as opinions about various tobacco control policies for all states and the District of Columbia (Gerlach et al., 1997). In addition, the Behavioral Risk Factor Surveillance System (BRFSS), a set of coordinated statewide health behavior surveys, queries self-reported tobacco use in all states and the District

TABLE 6-1 Inclusion of Key Variables Regarding Tobacco Use on Existing National Surveys

Variable	YRBS	NYTS	MTF	NHSDA	NHIS	BRFSS	CPS
Susceptibility/intentions		X	X	X			
Ever smoke cigarettes (even a puff)	X	X	X	X			
Age/grade of first try/first whole cigarette	X	X	X	X			
Ever smoke regularly/daily	X	X	X	X			X
Age/grade first smoked regularly/daily			X	X	X		X
Smoked 100+ cigarettes		X		X	X	X	X
Detailed # lifetime cigarettes		X					
Current use	X	X	X	X	X	X	X
Patterns of current use	X	X	X	X	X	X	X
Indicators of dependence		X		X			
Duration of abstinence		X		X	X	X	X
Ever tried to quit	X				X		X
# prior attempts (ever)		X			X		
Quit attempt in previous year		X			X		X
# attempts (previous year)							X
Duration of previous quit attempt (most recent)		X					
Stage of change					X		X
Motivation to quit		X					
MD discuss tobacco		X			X		
MD advise quitting							X
Dentist discuss tobacco		X					
Dentist advise quitting							X
Method(s) used to quit		X			X		
Ever use other tobacco products		X		X	X	X	
Current use of other tobacco products	X	X	X	X	X	X	X
Self-esteem			X				
Stress			X				
Depressive symptoms/other mental health indicators				X			
Perception of youth smoking prevalence			X				
Family/peer use of tobacco		X		X			
Parental relationship quality			X				
Parental monitoring			X				
Anti-tobacco socialization by parents		X					
Home bans							X
Home exposure to ETS					X		
Worksite indoor air policy					X		X

continues

TABLE 6-1 Continued

Variable	YRBS	NYTS	MTF	NHSDA	NHIS	BRFSS	CPS
Outcome of last purchase attempt		X		X			
Source(s) of cigarettes		X	X				
Price paid for tobacco		X		X			
Usual brand		X	X	X			
Promotional items (own/would use or wear)		X					
Perceived risks of smoking		X	X	X	X		
Harm reduction mindset		X			X		
Risk orientation			X	X			
Functional utility		X					
Approval/disapproval				X			
Social environment			X	X			
School performance		X	X				
Religiosity		X	X				
Receptivity to marketing		X					

NOTES: YRBS=Youth Risk Behavior Survey—high school students (items listed are on the national YRBS).
NYTS=National Youth Tobacco Survey—middle and high school students.
MTF=Monitoring the Future Surveys—8th, 10th, and 12th grade students (only two tobacco questions are on the core questionnaire: one deals with lifetime use and the other deals with current patterns of use. All others are on subsets of the full sample, meaning that they provide less precise estimates) (Monitoring the Future, 2001).
NHSDA=National Household Survey on Drug Abuse—ages 12 years and older (2000 questionnaire).
NHIS=National Health Interview Survey—ages 18 years and older (NHIS 2000 Cancer Supplements).
BRFSS=Behavioral Risk Factor Surveillance Survey—ages 18 years and older; state-specific estimates.
CPS=Current Population Survey—ages 15 years and older; state-specific estimates (note that CPS uses proxy estimates for some selected sample persons; proxy reports of smoking for teenagers are more likely to lead to under estimates of prevalence than self-reports).

of Columbia (NCCDPHP, 2001a). BRFSS is developing the capacity to provide small area estimates. As noted above, the NHANES assesses adult use and serum cotinine values to biochemically validate active use and assess exposure to environmental tobacco smoke.

Two ongoing surveys provide information on tobacco and reproductive health issues. The National Survey of Family Growth surveys women 15-44 years of age to assess factors affecting pregnancy and women's health (National Vital Statistics System, 2001). The Pregnancy Risk Assessment Monitoring System (PRAMS) provides representative data from

23 states on maternal attitudes, behaviors, and experiences in order to reduce adverse outcomes of pregnancy (NCCDPHP, 1999).

Disease Outcomes

Since tobacco product use has been linked to so many different diseases and conditions, reviewed elsewhere in this report, national determination of tobacco-related morbidity assessment would be a daunting task. For example, not all states have comprehensive cancer surveillance, the most complete of which is sponsored by the registries of the U.S. National Cancer Institute (NCI, 2001) and the CDC cancer surveillance program (CDC, 1999). In addition, birth certificates for such issues as low birthweight (NVSS, 2000) and data from surveys of hospital discharges (Agency for Healthcare Research and Quality, 2000) and medical expenditures (MEPS, 2001) could be used. There is no ongoing national surveillance of incident heart disease and stroke, chronic lung disease, osteoporotic fractures, or most other tobacco-related health outcomes. However, the NHIS and the NHANES do assess self-reported conditions on a regular basis, sometimes supplemented with physiological measurements.

The National Vital Statistics System coordinates data from state operated registration systems (NVSS, 2000). Many states assess tobacco use on the death certificate and other vital records. The universal vital record system in the United States can be extremely useful for tobacco-related outcomes that often lead to death, but leaves the remaining important outcomes unassessed. Further, tobacco usage histories on vital record documents has not been fully validated, and linking mortality to tobacco product use generally requires special studies.

Other Surveillance Activities: The Social and Legislative Environment

Current systems monitor state and local legislation and programmatic activities (CDC, 2001; Robert Wood Johnson Foundation, 2001; Stillman et al. 1999); exposure to pro-health messages (Robert Wood Johnson Foundation, 2001); and tobacco placement in stores, promotions, and prices (Robert Wood Johnson Foundation, 2001). NCI's ASSIST project monitors newspaper stories and editorials, permitting assessment of the print media's coverage of and policy on tobacco control activities (Stillman et al., 1999).

PROPOSED SURVEILLANCE SYSTEM ENHANCEMENTS

The overriding goal of a surveillance system on PREPs should be to maximize the ability to assess the public health impact of the introduction of these products, with the explicit goal of maximizing the health of the

public. As derived from the elements of an ideal surveillance system noted in the introduction to this chapter, and existing surveillance activities noted above, the following are suggestions for new or enhanced components to these existing activities.

Consumption of Tobacco Products and PREPs

State and regional information on the consumption of various products would provide useful information, especially if reported on a monthly or quarterly basis. In addition, future reporting systems that include PREPs may also need to be based on milligrams of nicotine consumed per product, as pounds of tobacco may become a less complete marker of consumption.

Specific Tobacco Constituents of Both the Products and the Smoke They Generate

At the time of PREP and other new product release, there should be detailed, manufacturer-derived information on important and major physical and chemical constituents of all tobacco products, including additives and the structural components of the products, such as filters, fibers, and fragments of fibers. Some independent postmarketing monitoring of product constituents may be necessary to ensure that changes are known to the public and the scientific community. For example, a recent letter from the Commissioner of the Massachusetts Department of Public Health to the Chairman of the Federal Trade Commission (Koh, 2000) highlighted the need for such monitoring. Koh points out that R.J. Reynolds' Eclipse product produced higher concentrations of toxic chemicals in 2000 than in 1996, suggesting that consumers would need to be informed of the added dangers from the 2000 version of the product. More details and specific recommendations can be found in Chapter 7, Implementation of a Science-Based Policy of Harm Reduction.

Product constituents can be influenced by agricultural and manufacturing practices. There is currently no systematic surveillance of agricultural practices or curing processes that can influence levels of undesirable constituents (e.g., tobacco-specific nitrosamines), as well as new breeds or hybrids (including genetically-altered) of tobacco that may have implications for human health. Hence, there should be enhanced monitoring of tobacco agricultural practices. General data on the types and amounts of tobacco harvested, as well as curing and processing practices would assist in identifying new and existing potentially undesirable constituents (e.g., tobacco-specific nitrosamines), as well as new breeds or hybrids (including those genetically altered) of tobacco that may have implications for

human health. There should be similar information on imported tobacco products. Additionally, surveillance of manufacturing practices, especially those involving ingredients, should be instituted.

Tobacco Product Marketing

The monitoring of tobacco product marketing and public relations strategies will provide policy makers with data upon which to base decisions about the accuracy of information presented to the public and health professionals. The FTC (or another agency) could release brand-specific marketing data, if permitted to do so by legislation. Systematic media and other marketing practice monitoring would allow the assessment of messages conveyed on television, the Internet and in movies, newspapers, magazines, and mass mailings. Some monitoring of the industrially produced technical information may be of value. Another important question is whether industry marketing and public relations strategies undermine explicit public policies, laws, and regulations relevant to tobacco control.

While a research topic for further evaluation, routine message evaluation before release could provide early warnings of future problems. For example, Shiffman (1999) described two methods of testing messages. In the first, people from groups of concern (e.g., adolescents) are exposed to test stimuli and assessed for changes in attitudes, beliefs, and intentions. This system is generally conservative, as laboratory testing situations do not replicate the real world in terms of the number of repetitions of the test message or the number of different messages an individual receives on the same topic from numerous channels. Thus, any indications of future problems should be seriously considered, while false negatives may be common. In the second, expert qualitative analysis is employed to assess likely message impact.

Biomarkers of Exposure to Tobacco Products

Studies of biological fluids should be continued within the context of NHANES, which serves as a robust national sample survey that acquires serum and urine specimens. The specific biomarkers to be determined would evolve over time with scientific advancements and would be aimed at biomarker-based determination of exposure to tobacco products in general, including environmental tobacco smoke, and to specific constituents that might allow determination of specific tobacco product usage or that have predictive value for tobacco-related diseases and conditions. Additional relevant biomarkers are suggested in Section II of this volume. In addition, special studies should be conducted to assess relevant

biomarkers in special groups who may not be well-represented in representative national surveys, such as living in a test market area or pregnant women.

Personal Tobacco Product Use and Related Behavioral Patterns

Key predictors of tobacco product usage that are relevant to important changes in population morbidity and mortality, such as changes in prevalence of use, initiation occurrence rates, product quitting behavior rates, and patterns of relapse, should be carefully monitored. Detailed measures of lifetime product use patterns are also needed. Studies of product usage in special populations, such as pregnant women, should be considered as a matter of routine, as well the use of nicotine replacement therapy. Finally, exposure to environmental tobacco smoke should be also be monitored at a level that can estimate the magnitude of population exposure. Whether through basic surveillance or special, it will be important to have estimates, for each product, not only of lifetime exposure, but age-at-initiation, quantitative "person-years" assessments of exposure, including the ages at which these exposures occurred, and age-at-permanent-quitting. Quantitative exposure determinations will be central to understanding whether disease outcomes may have been altered by PREP use.

Tobacco product use, and specifically PREP use, should also be measured in an ongoing and systematic manner. One central question about the net population impact of PREP introduction is whether these products influence patterns of quitting. A comprehensive surveillance system should be able to characterize factors that influence quitting. For example, measuring stages-of-change, motivation to quit, dependence, personal relevance of possible harm from tobacco use, favorable and unfavorable attitudes toward smoking, misperceptions of both tobacco use and PREPs, and reasons for relapse among those who do would be particularly important. Relevant populations of interest include tobacco users who adopt PREPs, tobacco users who don't adopt PREPs, and ex-users at risk for relapse (Shiffman, 1999).

Ancillary prospective studies of representative populations could further inform PREP impact. These studies would ideally be set up prior to the introduction of these products. Baseline data on a number of relevant variables would provide researchers with information that may explain, at least in part, why some tobacco users adopt PREPs, others do not, and others simply quit. This study would need to measure and statistically control for other environmental factors (e.g., prices of tobacco products, policy changes, treatment options, and emerging medical information), thus making it difficult to clearly detect an independent effect for a PREP

or set of PREPs. An additional limitation is that these studies would provide information after an undesirable event (e.g., reduced quitting), requiring regulators to attempt to ameliorate the harm already done (Shiffman, 1999). Nevertheless, detection of change in behavioral studies is more rapid than in studies of some of the health outcomes (e.g., lung cancer or emphysema).

Another central question is whether the introduction of PREPs influences the attractiveness of tobacco use among those who have never regularly used PREPs or other tobacco products, particularly adolescents. Only population surveillance of tobacco-naïve populations could address this issue. Again, studies ancillary to the regular surveillance system can provide important and relevant information. For example, Pierce and colleagues (1996) have demonstrated among adolescents the predictive validity of a measure of susceptibility to smoke, which combines the domains of intention to smoke and perceived ability to resist the offer of a cigarette by a best friend. Susceptibility to smoke could be used as an early indicator of future changes in initiation. Another important part of behavioral surveillance is to determine misperceptions about risks from use of tobacco and PREPs as well as attitudes about their use and about persons who use them. Monitoring of these indicators and incorporation of new measures as they develop will optimally assess changes in this construct.

The population-based surveys currently providing data to the public health community are generally released from 7 to 24 months after data collection. In addition, questionnaire content is often inflexible. Prevention programming would be better served if smaller, but more frequent (e.g., monthly) tracking surveys were conducted to assess reactions to new products and campaigns (Giovino, 2000).

Disease Outcomes

As noted above, there is no systematic, ongoing, national morbidity surveillance system for the major illnesses and conditions related to tobacco products, although elements of this information are available from representative federal sample surveys of Americans, regional disease registries, and vital records. National morbidity data could in itself provide important insights into tobacco product and PREP outcomes, but could also be used for other analytical studies. For example, ecological comparisons of lung cancer mortality rates (from the National Vital Statistics System) with historical patterns of cigarette smoking (from the National Health Interview Survey)(e.g., Mannino et al., 2001; Shopland, 1995) are consistent with the interpretation that historical smoking patterns strongly influence rates of lung cancer. Similar analyses to assess the influence of

PREPs, would be more problematic and would thus require a variety of specific epidemiological studies that would not be part of routine surveillance, in part because of the duration between exposure and disease outcomes, and the complexity of multiple product exposure. For lung cancer and chronic obstructive lung disease, mortality data could serve as useful proxies of disease incidence.

As part of a comprehensive scientific program to determine the relation of PREPs to disease outcomes, analytical epidemiological studies would provide most robust and direct findings. As an example, cross-sectional surveys of tobacco product utilization could be turned into population-referent cohorts for determining health outcomes according to types of tobacco or PREP consumed, with over-sampling of persons who use new products. Surveys could also provide the data for case-control studies. A related case-control approach would be to append specific smoking histories to cancer and other disease surveillance systems, with suitable control populations.

For many policy and regulatory purposes, it may be sufficient to know whether PREPs have clinically and epidemiologically important and significant effects on occurrence and mortality for important individual chronic illnesses such as lung cancer, heart attack and chronic obstructive lung disease. However, there are several reasons why addressing these outcomes alone may be an insufficient approach to determining harm reduction potential: this approach does not document symptom patterns, various organ system dysfunctions, and the quality-of-life prior to the occurrence of a major chronic illness. As noted elsewhere in this volume, current tobacco products cause many other important health conditions as well as dysfunction and disability; and the effects of new tobacco products may be in opposite directions, causing lesser incidence of some but greater incidence of other outcomes.

Thus, in addition to specific major disease outcomes, more summary and inclusive measures of health status and outcomes should be used in assessing PREP effects. Those selected should be based on conceptual models of health status (Steinwachs, 1989) as well as the questions to be addressed and methodological considerations and impediments (McHorney, 1999). Some general approaches to these outcomes are suggested:

- Determining the occurrence of other important smoking-related conditions, such as osteoporotic fracture, low birthweight, and cataract can inform the general nature of PREP outcomes.
- Surveying for the occurrence of various symptoms and syndromes related to smoking. Such chronic or persistent conditions such as cough, sputum production, back pain due to osteoporosis, skin

lesions or discoloration, and healing time for surgical wounds and peptic ulcers may be important to individuals and to optimal function. Some of these outcome measures (e.g., cough, sputum production) also have the advantage of requiring a relatively short amount of time to develop.

- Assessing various types of biological function can summarize the net biological and clinical impact of environmental exposures across several organ systems and anatomic sites. For example, common physical functions such as the ability to jog or carry groceries are dependent in part on cardiac, pulmonary, musculo-skeletal and neurological function.
- Various measures of mortality can be of use in addition to cause-specific death rates. The overall mortality rate is increased among cigarette smokers and effect of PREPs should be evaluated in this regard. A mortality assessment approach that combines age-specific mortality rates with general social functioning, such as in the "Years of Potential Life Lost," (Lai and Hardy, 1999) which has been used for several specific causes of death, might be considered. Mortality outcomes may also have an impact on other summary measures of health outcome and the quality-of-life (CDC, 2000a).
- Self-reported health status can be an important summary measure of both general physical health, as well as mental and social functional problems (Cott et al., 1999). A variation that has proven useful occurs when individuals are allowed to assess changes in their health status, such as might occur after a clinical intervention (Fischer et al., 1999).
- There are a number of multivariate approaches to determining general health status, going under the general term "health-related quality-of-life," reflecting symptoms, conditions, dysfunctions, behaviors, and biological markers. These measures have found application in both the clinical and public health settings (Hennessy et al., 1994; Tsevat et al, 1994). Some measures combine a large number of diverse health domains, such as the "SF-36" (Ware and Sherbourne, 1992), and others combine measures of function with mortality (Tsuchiya, 2000).

Other measures exist that can't be summarized here. However, it seems important to define aggregate health measures that are sufficiently comprehensive and sensitive to the changing constituents of new tobacco products, in order to define health problems in global as well as specific terms.

Surveillance systems can also be used to assess the prevalence of non-tobacco risk factors that influence tobacco-induced illnesses (e.g., alcohol use in head and neck cancers). The committee also sees this system as an opportunity to monitor behavioral patterns such as diet and elicit drug use. Although the committee recognizes that available data do not support the hypothesis that illicit drug use increases as tobacco use decreases (Chaloupka et al., 1999; Frosch et al., 2000; Lê et al., 2000; Taylor et al., 2000), the committee notes the ease with which such data could be obtained and recommends surveillance of this undesirable outcome.

ISSUES AND LIMITATIONS REGARDING SURVEILLANCE SYSTEMS FOR ASSESSING TOBACCO-RELATED HEALTH OUTCOMES

One important issue is who would conduct surveillance on conventional tobacco products and PREPs. The types of data recommended above would almost preclude all surveillance being conducted by one organization or agency. It is likely that the elements of surveillance will come from many sources, and a coordinated effort will be needed to plan, assimilate, and interpret information for reasons of efficiency and standardization. As noted elsewhere in this volume, it will be important to include all conventional tobacco products, since they become one critical reference for health outcome studies, and to monitor changes in these products themselves. A part of the surveillance system would be to validate manufacturer claims of product distribution, content and biological and clinical effects.

Another issue is the collection of ancillary information necessary to conduct credible epidemiological studies with disease outcomes, as suggested above. For example, understanding lung cancer causation and changing frequency may require ascertainment of other risk factors such as radon or occupational exposures. Monitoring coronary disease outcomes requires determination of major risk factors other than tobacco exposure, such as those noted in Chapter 13. It may not be the burden of the surveillance system to furnish all relevant risk factors for smoking-related conditions, but where possible, this would be helpful.

There are several limitations and issues with respect to applying surveillance systems to the assessment of tobacco product usage and health. As noted above, there are many tobacco-related health outcomes for which no comprehensive, geographic surveillance system exists, and a great limitation is that such surveillance systems are costly, especially for national ascertainment of tobacco and PREP-related illnesses. However, these are the most common and important preventable conditions and the

investment seems justified. Decreasing the sample sizes in national population surveys or limiting population coverage may cause compromises in data quality or generalizability. A related issue is that it might take very large population surveys to adequately cover important demographic subgroups of interest, such as pregnant women or certain minority groups. Thus, it may be more efficient to have separate surveys or surveillance surveys of special populations than only one large population survey. A comprehensive surveillance system, as described in this chapter, could also be critical for other disease control activities that are not tobacco-related, and conceivably the cost of the system could be shared.

Another important limitation is that many aspects of population surveillance depend largely on self-report, which can be subject to error. In some instances, tobacco product usage can be validated by external means, but not in all circumstances. There are also limitations to predicting behaviors based on self-reported personal knowledge and attitudes, although both are important. Here, too, there are mechanisms to improve the validity of these reports.

There may not be suitable or logistically feasible biomarkers of exposures for the range of important tobacco products and toxicants to which users are exposed. Some of the biomarkers of exposure used in the past, such as cotinine, may still have utility for assessing conventional tobacco product exposure, but as new PREPs come to the marketplace, these markers may no longer be fully suitable because they won't necessarily serve as adequate surrogate markers for the range of major tobacco constituents.

Some elements of a comprehensive surveillance system, such as mandating tobacco manufacturers to report product characteristics, ingredients, additives, and brand-specific sales and distribution data might require a legislative or regulatory approach to enforce. Without this information, a comprehensive surveillance program would be much weaker.

Finally, it should be noted that it is not the burden of surveillance systems *per se* to relate PREPs or other tobacco product exposure to specific health outcomes or altered levels of those outcomes. That is usually the function of targeted epidemiological studies such as cohort studies of persons using PREPs to monitor for long-term health effects, with suitable contrast groups. Well-designed case-control studies may also be appropriate vehicles for exploring certain tobacco-disease associations, although the retrospective recall of the past product usage may not always be credible. As always, epidemiological studies should be accompanied by the best basic science and clinical research to guide the study design, apply the most modern markers of exposure and disease, and optimally interpret the findings.

SUMMARY AND RECOMMENDATIONS

The goal of the proposed surveillance system and accompanying epidemiologic studies is to provide much of the data need to determine the ongoing contribution of tobacco products and PREPs to the public's health status and to inform policy initiatives and regulatory judgments. Thus, the system will need to estimate relative changes in the prevalence of tobacco use, as well as changes in the relative harm to users of PREPs. Strong data accumulated over many years are necessary to judge if PREPs (or classes of PREPs) contribute to maximizing the health of the public. Public health officials will need to determine if the prevalence of tobacco use drops to a level at or near what it would have in the absence of PREPs and if the health benefits (if any) caused by switching to PREPs compensate for any decrement in prevalence reduction that they cause. This will be a challenging process, but one that will only be possible if optimal data collection systems are swiftly put in place. Until surveillance mechanisms that would enable prospective assessment of the public health impact are in place, it might be prudent to take an especially risk averse position regarding communications and claims (see Chapter 7). Given this approach, **the committee makes the following recommendations:**

1. There is an urgent need for a national comprehensive surveillance system that collects information on a broad range of elements necessary to understand the population impact of tobacco products and PREPs, including attitudes, beliefs, product characteristics, product distribution and usage patterns, marketing messages such as harm reduction claims and advertising, the incidence of initiation and quitting and nontobacco risk factors for tobacco-related conditions. There should be surveillance of major smoking-related diseases as well as construction of aggregate population health measures of the net impact of conventional product and PREPs.
2. The surveillance system should consist of mandatory, industry-furnished data on tobacco product constituents, additives, and population distribution and sales.
3. Resources should be made available for a program of epidemiological studies that specifically address the health outcomes of PREPs and conventional tobacco products, built on a robust surveillance system and using all available basic and clinical scientific findings.

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