Reducing tobacco harm: Research challenges and issues

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Review

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The emergence of potential reduced-exposure tobacco and cigarette-like products and the reduction of smoking as a treatment approach, have recently been forcing the debate and discussion about the science that is necessary to inform policies, regulation, and programs. To deal effectively with the issues evolving around tobacco harm reduction, a comprehensive and strategic research agenda must be forged, and a multidisciplinary, collaborative approach must be taken. The goal of this article is to describe research challenges and issues related to tobacco exposure and harm reduction. Scientists from multiple disciplines and individuals from government agencies, nonprofit organizations, and tobacco control advocacy groups as well as the pharmaceutical and tobacco industries attended a two-day meeting that focused on addressing the current knowledge regarding tobacco harm reduction, identifying gaps in knowledge, and recommending research directions. Workgroups, comprising a subset of attendees, met after the conference to synthesize, discuss, and prioritize the important research frontiers. The resulting document provides guidance for scientists, grant funding agencies, industry and policy makers by identifying areas in which to invest research effort and funds to develop a science base to ensure the future health of this nation and world.

In early 2001, the Institute of Medicine (Stratton, Shetty, Wallace, & Bondurant, 2001) issued an FDA-commissioned report, Clearing the Smoke: The Science Base for Tobacco Harm Reduction. One of the priority recommendations of this report was the call for research that would inform policies and programs related to methods and products purported to reduce exposure to tobacco-related toxins and potential harm. In May of 2001, a conference was held, Reducing Tobacco Harm, with the primary goal of identifying key issues related to reducing the harms or tobacco toxin exposure associated with tobacco use and critical research areas that need to be addressed. This conference was a collaborative effort sponsored by the National Cancer Institute, National Institute on Drug Abuse, Centers for Disease Control and Prevention, American Legacy Foundation, and the Robert Wood Johnson Foundation.

Three topic areas were addressed at this conference: (a) products and methods for reduction in tobacco toxin exposure; (b) exposure and toxicity assessment; and (c) measures to ensure public health. The first topic involved a discussion of what the Institute of Medicine report described as potential reduced-exposure products (PREPs). The products included various tobacco or cigarette-like delivery devices designed to reduce tobacco toxin exposure: low tar and nicotine cigarettes; tobacco products processed, modified, or sprayed with chemicals to reduce carcinogens; cigarette-like devices that produce less combustion than traditional cigarettes; and non-combusted tobacco products, conventional and novel. In addition, methods to reduce cigarette con-
sumption and thereby reduce tobacco toxin exposure were described. These methods included the use of pharmaceutical products (e.g., medicinal nicotine), behavioral techniques (e.g., increasing the interval between cigarettes), and policies (e.g., increased taxes and smoking bans). Finally, although not fully described in the Institute of Medicine report, chemoprevention, that is, treatments to reduce the probability of manifesting a smoking-related disease, was discussed. The exposure and toxicity assessment topic included presentations on assaying the health-relevant chemicals that are contained in the tobacco products, surrogate in vivo biomarkers that are currently available to measure health effects, and the biomarkers that have been used in prior clinical trials. Presenters for the third topic discussed measures that need to be taken to ensure public health. These measures covered risk communication, surveillance, marketing, and regulatory and policy interventions on state, national, and global levels. The format was structured so that presenters, discussants, and audience participants would be able to identify gaps in the scientific literature related to these topics.

Immediately after the end of the conference, workgroups for each of the three topic areas were convened to discuss the proceedings of the conference, summarize, and then develop a list of research needs within their assigned area. Workgroup members were composed of expert scientists and academics, representatives of governmental agencies, and members of advocacy organizations and were selected by the planning committee for the conference. (See Appendix for Workgroup members and their affiliations.)

This paper describes the deliberations of each workgroup. Overlapping themes emerged across workgroups and were merged to avoid duplication. The intent of this article is to inform researchers as well as public and nonprofit funding agencies of areas for investments of time, talent, and funding to prepare for the rapidly changing landscape of tobacco products and their use. No efforts were made to prioritize these research challenges because of the complexity and evolving nature of this area. Researchers and the public health community, however, must be prepared for PREPs to ensure both that appropriate research can assess their health effects and that policy decisions regarding those products can be based on science.

Products and methods for reduced tobacco toxin exposure and harm reduction

This workgroup strongly believed that the primary focus of research should be directed toward examining the products and strategies, including policies that are likely to result in the greatest net benefit. They expressed skepticism that modifications of combusted tobacco products would have a significant positive impact on public health. This is because combustion produces many of the pyrolysis products associated with disease (Stratton et al., 2001). However, this group also acknowledged that, should regulation be enacted, federal agencies are going to be required to have a solid science base by which to judge the extent of tobacco toxin exposure of these products. It was also recognized that the development and use of tobacco products that are proven to reduce tobacco toxin exposure rather than the products that deliver higher levels of toxins should be encouraged. Furthermore, standards should be set for procedures and methods to measure the constituents and extent of exposure, as well as for disclosure, as described in the Institute of Medicine report (Stratton et al., 2001). The following were the important research issues considered by this workgroup.

1. Examine methods to reduce tobacco toxin exposure

*Develop or examine effective methods and products that could lead to sustained reduced smoking or significantly reduce tobacco toxin exposure*

Few studies exist that specifically address whether reduced smoking is a feasible and viable approach to harm reduction. Although pharmacological products and behavioral methods have been shown to produce a reduction in smoking rate (Stratton et al., 2001), whether this reduction is sustained, is meaningful, or can be improved upon is poorly understood. In addition, the public scientific community has exerted too little effort to examine, improve, and develop products that produce less toxicity than currently available nicotine-containing devices. The following studies and research questions are examples of areas that need to be addressed:

a. Studies on the feasibility of tobacco use reduction as an approach to harm reduction. For example, to what extent can smoking be reduced, and is this level sufficient to produce meaningful health benefits? Can this reduction be sustained? Will reduced smoking facilitate or deter abstinence? Are there potential negative behavioral side effects from reduced smoking? For example, will reduced tobacco use lead to use of tobacco products with higher nicotine content or increase the use of other addictive agents?

b. Research to determine the feasibility and effects of long-term medicinal nicotine use. Although the use of currently available medicinal nicotine is almost certain to result in reduced harm compared with use of smokeless tobacco or cigarette-like nicotine delivery devices, there are still gaps in our knowledge about the long-term safety and outcome of using medicinal nicotine. Research on the safety and toxicity of nicotine per se on the cardiovascular system and pregnancy is necessary.

c. Studies of nicotine addiction and toxicity as a function of the route and rate of dosing. For
example, are there some nicotine preparations that are able to replicate the reinforcing qualities and thus replace cigarette smoking? If so, what is the toxicity profile of such preparations compared with standard preparations such as transdermal nicotine or nicotine gum?

d. Development of novel pharmaceutical products to substitute for tobacco products that would more likely lead to a greater net health benefit (e.g., nicotine analogues with minimal cardiovascular and fetal effects) and to greater probability of use or consumer appeal.

Much debate has been directed toward determining the nicotine and tar amounts and ratio that will result in the least harm for the individual and the population. Lowering the nicotine and tar of cigarettes may render them less reinforcing, thereby reducing the initiation and maintenance of cigarettes (Benowitz & Henningfield, 1994; Henningfield, Benowitz, Slade, Houston, & Davis, 1998). However, if nicotine levels were not sufficiently low, compensatory smoking might occur that would negate any beneficial effects of low-nicotine-containing cigarettes. On the other hand, high nicotine but low tar cigarettes, while not focused on the prevention of initiation or on cessation, may lead to reduced smoking since adequate nicotine may be achieved with fewer cigarettes. However, this ratio may contribute to sustained use and increased initiation. The following are examples of research questions directed toward finding optimal nicotine and tar amounts.

a. Studies on the effect of tar amounts in tobacco products. For example, can net public health benefit be achieved by reducing tar exposure in smokers? If so, how much tar exposure needs to be reduced before benefit is achieved?

b. Studies on the effects of low nicotine tobacco products. For example, at what level will nicotine no longer be reinforcing to the majority of the population of smokers? Can individuals adapt to lower nicotine intake levels over time? Will lowering the nicotine to this level reduce initiation of smoking and facilitate quitting? Will this lower level of nicotine also minimize compensatory smoking behavior? What unorthodox methods might consumers employ to override this strategy (e.g., use of nicotine spray to introduce more satisfying levels of nicotine into the product)? Is a national strategy that gradually reduces the nicotine levels of cigarettes feasible, and what plan of action or modifications in cigarettes besides lowering the nicotine can be made to enhance its feasibility?

c. Studies on the effects of high-nicotine tobacco products. Will high nicotine but low tar cigarettes produce a reduction in smoking among those who switch from conventional cigarettes; and will it reduce the number of cigarettes per day compared to conventional cigarettes among those who initiate smoking? Will smokers who use these high-nicotine products maintain a low rate of smoking, or will the smoking of cigarettes increase over time? Will these high-nicotine products result in an increase in smoking uptake?

Develop and examine the effects of chemopreventive agents across disease states

Chemoprevention involves the use of agents to prevent or minimize the occurrence of disease progression. Whereas chemotherapy is the treatment of cancer with toxic agents, chemoprevention involves treatment with nontoxic agents to prevent cancer (Alberts, Colvin, Conney, et al. 1999). Chemoprevention potentially can be coupled with smoking cessation and may be a practical approach for reduction of disease in smokers as well as ex-smokers. To date, the most promising studies have been primarily conducted in the area of tobacco-related cancer. For example, epidemiologic studies indicate that vegetable consumption is protective against lung cancer, suggesting that there are naturally occurring chemopreventive agents in vegetables (World Cancer Research Fund/American Institute for Cancer Research, 1997). Indeed, three recent epidemiologic studies demonstrate protection against lung cancer through consumption of vegetables containing isothiocyanates (London et al., 2000; Spitz et al., 2000; Zhao, Seow, Lee, Poh, Teh, Eng, Wang, Tan, Yu, & Lee, 2001), a class of compounds which have shown chemopreventive efficacy in laboratory animals (Hecht, 2000). The following research areas were raised:

a. Studies on chemoprevention agents for not only tobacco-related cancer but also cardiovascular disease and chronic obstructive pulmonary disease.

b. Methodological studies that determine appropriate biomarkers to examine the efficacy of these agents and the best animal and human models to use for the development of chemopreventive agents.

c. Identification of individuals who are most susceptible to diseases and therefore most appropriate for chemoprevention.

d. Examination of the effects of the availability and promotion of chemopreventive strategies on quitting attempts.

2. Explore the basic processes that are associated with nicotine addiction and sustained tobacco use

The workgroup identified a need to better understand the basic processes that underlie addiction to nicotine and sustained tobacco use, as well as the use of nicotine for purposes of self-medication. This knowledge will facilitate the development of novel and more effective methods and products for reducing exposure to tobacco toxins, and hence potential harm reduction, as well as facilitate the development of novel and effective methods for cessation.
Examine the biological, behavioral, learning, sensory, and environmental basis for nicotine addiction or sustained tobacco use

According to the 1988 Surgeon General’s report (U.S. Department of Health and Human Services, 1988), nicotine is an addictive drug. Although some of the basic biobehavioral mechanisms causing this addiction were described in 1988, it is apparent that we are only at the beginning stages of understanding these processes. Since the 1988 report, several of the nicotinic cholinergic receptor subtypes (e.g., α4β2, α7) have been identified and their potential functions in maintaining addiction to nicotine explored (Watkins, Koob, & Markou, 2000). Studies are evolving that examine genotypes as well as phenotypes of tobacco-dependent smokers. The areas that have been investigated include how the extent of nicotine metabolism (Tyndale, Pianezza, & Sellers, 1999) and individual differences in dopamine receptor subtypes (e.g., Lerman, Caporaso, Audrain, Main, Bowman, Lockshin, Boyd, & Shields, 1999) might contribute to the dependence process as well as provide insight into ways to individualize treatments. To date, although a strong knowledge base is being developed on nicotine’s effect on brain neurochemistry, information on the contributions of these effects to the development and various aspects of nicotine addiction (reinforcement, tolerance, or neuroadaptation, withdrawal) is limited. Furthermore, although the important role of some of the sensory aspects of tobacco use in the maintenance of tobacco use has been realized, few nonindustry researchers have dissected the product characteristics that may contribute to the sensory aspects, which may sustain the use of tobacco. Finally, few research studies have developed new behavioral and learning models for understanding the addictive processes. The workgroup proposed the following research agenda to increase our understanding of why people continue to smoke when the risks of smoking are so well known.

Studies on the biological, behavioral, and sociocultural basis for the development and maintenance of sustained tobacco use or nicotine addiction. For example, what are the contributions of specific transporters and different neurotransmitters, receptor subtypes, and hormones separately and jointly in the addiction process and varying aspects of addiction? What are the critical behavioral, sensory, and cognitive or learning processes and the biological basis for these processes that contribute to tobacco use and nicotine addiction? What are the specific benefits derived from tobacco use that are associated with tobacco or nicotine-seeking behavior? What are the sociocultural norms, messages, and beliefs that contribute to the development of tobacco and nicotine addiction? How do these biological, behavioral, learning, and sociocultural processes interact with each other? How do genetics and individual differences contribute to and interact with these various effects of nicotine?

Examine the basis for the relationship between smoking and mental illness

About 40% of the individuals who are experiencing past-month mental illness (including substance abuse) currently smoke (Lasser, Boyd, Woolhandler, Himmelstein, McCormick, & Bor, 2000). Due to the high smoking rate among this population, more research is necessary to understand the underlying basis for the link between psychiatric disorders and use of nicotine-containing products. Examination of this area is important because harm reduction approaches may be particularly appealing to this population of smokers. Smokers who seek treatment for harm reduction vs. cessation tend to be more highly dependent and experience higher rates of psychiatric problems including alcohol and illicit drug use (Lemmonds, Mooney, Reich, & Hatsukami, in press). A better elucidation of the beneficial effects from nicotine may lead to more efficacious treatments targeted toward this population of smokers. Examples of research topics include the following:

a. Studies on the impact of mental illness on the development or maintenance of nicotine addiction. For example, what are the underlying biobehavioral bases for smoking among those who are diagnosed with major depressive disorder, schizophrenia, anxiety disorders, attention deficit, conduct disorders, or substance abuse disorders? How do these various psychiatric disorders affect the responses to nicotine, including tobacco use patterns?

b. Conversely, studies on the effects of nicotine on mental illness. What is the role of nicotine and other components derived from cigarette smoking or tobacco use in the development or manifestations of these disorders? What changes occur in the brain in response to nicotine that may impact these disorders? How are moods, cognitive processes, the valence of other reinforcers, affected by nicotine among smokers experiencing these various disorders? How do the changes in the brain interact with changes in mood, cognitive processes, or behavior? Could nicotine play a role in lessening the adverse consequences of these disorders? Are there medications that can substitute for the functions served by tobacco-derived nicotine or other components of tobacco smoke?

c. Studies on whether psychotropic agents used to treat psychiatric disorders produce cognitive and affective states that smokers try to offset or modulate with nicotine.

Further examine the role of nicotine in maintaining specific levels of smoking

The occurrence of compensatory smoking when smokers switch to lower nicotine cigarettes or smoke fewer cigarettes has been observed and presents a concern. The supposed beneficial effects derived from low tar/low nicotine ‘light’ or ‘mild’ cigarettes are reduced due to the
increased smoking that occurs in efforts to achieve a higher level of nicotine (National Cancer Institute, 2001). Studies examining methods for reduced smoking also show some compensatory smoking, even when nicotine replacement agents are prescribed. A better understanding of the ‘titration’ theory of smoking, that is, when smokers adjust their smoking behavior to attain a certain level of nicotine, is needed. While nicotine has been considered to be the primary reason for compensatory smoking, other variables such as cigarette pressure drop, ‘tar yields,’ and sensory stimulation may also play important roles (Scherer, 1999) and require consideration. The workgroup recommended studies that address the following topics:

a. The extent to which tobacco users try to maintain certain levels of nicotine (peak, trough, or both), the variability of these levels across smokers and the factors that contribute to this variation.

b. Examination of whether these levels can be altered and how they can be altered.

c. Examination of whether there are other aspects of tobacco use that tobacco users are striving to achieve (e.g., certain degree of sensory stimulation, effects from other constituents of tobacco), how modification of other aspects of tobacco use influence tobacco use behavior, and whether these behavioral changes can be sustained.

d. Studies on the relationships among yield, intake, and exposure for different tobacco products.

3. Promote research that analyzes existing or proposed policies relevant to harm reduction

The workgroup believed that epidemiology and surveillance research should be conducted to provide greater understanding of how different policies and regulations across different states in the United States and internationally would affect product use and smoking behavior. States differ in their tobacco control policies ranging from very comprehensive (e.g., Massachusetts, California, and Arizona) to minimal (e.g., Kentucky). Policies such as increased taxation of tobacco products, home and workplace smoking restrictions, and comprehensive tobacco policies (Stratton et al., 2001) have led to reduced prevalence of smoking and number of cigarettes smoked. In addition, the Massachusetts Department of Public Health has a proposal involving disclosure of ingredients in tobacco products. If this regulation is endorsed, then it would provide a natural experiment to determine the impact of this policy on consumer perception of the product and related change in smoking behavior. Furthermore, international policies have varied across countries, again affording the opportunity to capitalize on natural experiments to determine the effects of these policies on prevalence of smoking (including initiation, maintenance, cessation, and relapse across PREPs and conventional tobacco products), reduced frequency of smoking, and product uptake. For example, some countries in Europe ban tobacco advertisement, some ban the use of smokeless tobacco, whereas other countries promote it and others have differing degrees of access to different products, including medicinal nicotine. Therefore, the workgroup recognized the need to capitalize on already existing databases or to collaborate internationally to develop databases that would allow addressing the following research areas:

a. Studies on how different policies, regulations, and availability of programs impact the use of PREPs and conventional products, and how these different policies affect tobacco use behavior and resulting mortality and morbidity.

b. Examination of the accessibility of these various products across states and countries and of how the extent of accessibility impacts uptake and amount of use.

c. Determination of how the costs of PREPs, conventional tobacco products, and medicines for smoking cessation affect uptake and amount of use.

d. Studies on how these factors interact with each other.

Exposure and Toxicity Assessment for Reducing Tobacco Harm

The ultimate goal of tobacco harm reduction is to reduce human disease related to tobacco use. As mentioned previously, interventions to reduce harm may include both novel tobacco products and medications aimed at reducing tobacco use. Assessing the direct outcome of such interventions, that is, reduction in tobacco-induced disease, is difficult for most tobacco-related diseases because the diseases take many years to develop. It would not be feasible in general to do a clinical evaluation of new harm reduction interventions (such as would be required for a new medication) in a suitable time frame. To assess the benefits of harm reduction strategies in a reasonable time frame one must rely on indirect measures – that is, measures of exposure to toxins and/or measures of surrogate disease end points.

As with medications, harm reduction interventions could have detrimental effects. Such effects could result from the intrinsic toxicity of the harm reduction products, or from changes in tobacco use. Assessment of toxicity, however, should not solely occur on an individual level. Population effects must also be examined to assess accurately the benefits of harm reduction. The issue of harmful effects of harm reduction strategies on the population as a whole is addressed by another working group. The present working group considered the type of research necessary to assess exposure to tobacco toxins and toxicity directly related to product use by an individual. The research needs were addressed in the form of four research recommendations.
1. Examine how changes in tobacco product exposure affect disease risk

Key unanswered questions are which disease processes are altered as a result of reduced tobacco exposure? And, how much reduction in tobacco smoke exposure is necessary to realize a meaningful reduction in disease risk? Another way to conceptualize the problem is to determine the dose-response for cigarette smoking vs. disease risk, and what part of this risk is reversible when smoke exposure is reduced.

Specific research needs in this area include the following:

a. Studies of the effects of reducing cigarette consumption on exposure to tobacco smoke toxins and biomarkers of toxic effects.
b. Studies of the relationship between cigarette consumption and disease risk, addressing the question of how much cigarette smoke reduction is needed for a meaningful reduction in various disease risks. A related question is how long a period of time of reduced tobacco exposure is needed to reduce risk.
c. Animal toxicology studies are needed to construct dose-response data and to inform the problem of reversibility of tobacco smoke-related injury.
d. Both individual and population studies are needed to assess the relationship between cigarette consumption/smoke exposure and disease risk.
e. Studies are needed to assess changes in behavior when people switch from cigarettes to other major tobacco types (pipes, cigars, and smokeless tobacco products), the toxicity from these products, and the effect on biomarkers and disease risk.

2. Identify and validate biomarkers that predict reduction in disease

Most tobacco-related diseases develop after many years of smoking. For most tobacco-related diseases, it is impossible to conduct clinical trials of adequate duration to see how new products would affect disease risk. Therefore, biomarkers of tobacco toxin exposure and early indicators of tobacco-caused tissue injury that predict risk for development of disease are needed. Specific research questions and issues in this area include the following:

a. Studies on the mechanisms of injury from tobacco smoke toxins and whether there are some changes in tissue structure and/or function that occur early but predict later development of disease.
b. Animal toxicity studies are needed to better characterize tobacco-caused disease pathophysiology and relevant biomarkers of injury. Novel biomarkers of tissue injury, such as markers of early genetic injury and associated change in protein expression, need to be investigated.
c. Animal toxicity studies should include studies of mixtures of toxins. Data on toxicity of mixtures and relevant biomarkers of injury are needed to guide regulation of novel tobacco products that have different proportions of various tobacco toxins.
d. Biomarkers of exposure and/or disease risk need to be validated against actual development of disease. This might be done initially in animal studies, but ultimately will need to be confirmed in human epidemiology studies. However, the challenge will be how to undertake these epidemiological studies with the evolving and changing tobacco products.

3. Examine whether there are special populations that can provide new insights into harm reduction

There is considerable individual variability in susceptibility to tobacco-related disease. Sources of such variability may include genetics, age, socioeconomic status, physical environmental factors, and physiological state (for example, pregnancy and presence of diseases). Likewise, there are likely to be individual differences in benefits gained by particular harm reduction strategies. Studying different responses to harm reduction in different populations might lead to a better understanding of tobacco-related disease mechanisms. Some research issues related to special populations include the following:

a. Gender and ethnic differences in response to harm reduction interventions.
b. Genetic influences on harm reduction responses.
c. Mechanistic explanations of different responses in different populations to harm reduction interventions.
d. Studies of how different harm reduction strategies might be selectively beneficial for different groups.
e. Studies of how harm reduction strategies may have a differing impact depending on periods of vulnerability within an individual (i.e., during pregnancy, after myocardial infarction, etc.).

4. Examine how behavior and product characteristics interact to affect dose reduction and disease risk

When nicotine yield characteristics of cigarettes change, smokers smoke their cigarettes differently, potentially changing the chemical composition of the smoke compared with standard smoking machine tests. Likewise, novel cigarette-like tobacco products may be smoked in different ways by different smokers, resulting in different amounts and patterns of toxic exposures. Specific research needs in this area include the following:

a. Studies of constituents of products smoked with different puffing parameters. That is, testing should be done with puffing parameters that reflect low, medium, and high intensity smoking. Smoking
machines and/or parameters that more realistically reflect how people actually smoke the particular products need to be developed.

b. The effects of cigarette design on toxic exposures should be characterized. For example, when nitrosamine levels are reduced in cigarette tobacco, there may be an increase in generation of polycyclic aromatic hydrocarbons. Thus, when products are changed, patterns of toxic exposures need to be examined. Likewise, when there are changes in a product such as filter ventilation, which might be expected to reduce yield in standard smoking machine tests, such ventilation is also likely to change how cigarettes are smoked. Therefore, the effects of different intensity of smoking and their interaction with cigarette designs need to be studied.

c. Comparison of toxicity of different products is an important aspect of product regulation related to harm reduction. Research is needed on ways to compare toxic exposures from different products, considering interactions between product design and smoking behavior of those products.

d. Since smoking introduces multiple toxins that lead to a variety of diseases, each likely with varying susceptibilities, risk is not a single parameter, but a composite. An important research need is the development of an appropriate model, which can compare relative risks of various toxins. This is particularly important as some potential harm reduction products might reduce some exposures while increasing others (e.g., a product which resulted in a reduction of polycyclic aromatic hydrocarbons but an increase in carbon monoxide might reduce cancer risk but increase risk of acute cardiovascular events). Such a model should also be able to account for new toxins introduced by such products.

1. Examine the interests and impact of PREPs
It is important to understand the nature and extent of interest in PREPs and the reason for such interest. Addressing the following questions will help provide insight about the impact of these products and methods, and for whose health they may contribute positively or negatively.

a. Studies on the effect of PREPs on quitting. To what extent will current smokers view PREPs as an alternative to quitting? What factors influence switching to PREPs instead of quitting? To what extent will the availability of PREPs interest former smokers to use them? Conversely, will PREPs facilitate quitting for some smokers?

b. Studies on the influence of PREPs on tobacco use initiation and product selection. To what extent will PREPs interest persons who have never tried tobacco in any form? Will the use of PREPs among people who otherwise would never have used tobacco lead to eventual conversion to more dangerous tobacco products? To what extent will PREPs be chosen instead of conventional tobacco products among new users who would have used tobacco anyway? Studies in test-market locations and comparison communities could be especially illustrative.

2. Marketing and communication: Determine how messages affect knowledge, attitudes, and behaviors of relevant target groups
Research indicates that misperceptions exist about low-yield cigarettes and that correcting such misperceptions can influence intentions and may influence use (Giovino et al., 1996; Kozlowski & Pillitteri, 2001; National Cancer Institute, 2001; Shiffman, Burton, et al., 2001; Shiffman, Pillitteri, Burton, Rohay, & Gitchell, 2001). Improved understanding of knowledge, attitudes, and behaviors regarding conventional tobacco products and PREPs will facilitate the development of appropriate communications. Improved understanding of effective message development will serve to optimize the overall benefit to the public’s health. Researchers will need to improve our understanding of both the cognitive and affective nature of communications and how individuals process these components. Furthermore, these research endeavors must take into account the variability of the effects of these messages, dependent on relevant target groups (e.g., tobacco use status, ethnicity, age, sex, and socioeconomic status). They need to address some of the following study areas to discover how we can make PREPs more attractive than more dangerous products, without crossing over the risk/use equilibrium.

Considerations for ensuring the public health: Communication, surveillance, and regulation
The ultimate question for ensuring the public health is whether or not the introduction of PREPs into various markets will have a net benefit on the health of the populations in those markets. Net benefit should be considered not only in terms of the baseline situation, but also in terms of what would have occurred in the absence of PREPs. Net benefit can occur even if more people use nicotine-containing products and other PREPs over time, as long as the harm posed to individual users is reduced enough to make up for the increased number of users (Kozlowski, Strasser, Giovino, Erikson, & Terza, 2001; Stratton et al., 2001). Conversely, net harm can result even if the toxicity of PREPs is reduced if the amount of use of nicotine products rises more than toxicity declines.

This workgroup recognized that research needs in this general area could involve both empirical and non-empirical methodologies. For example, many workgroup members argued that analyses of regulation and ethics that do not involve data are required.
a. Studies on the relative influence of words and of images used in marketing on both cognitive and affective processing of messages.

b. Studies on the effects of avenues and sources of messages. What is the relative influence of traditional marketing, other media (e.g., coverage in newspapers and magazines, on television or radio, television shows, movies, Internet), word-of-mouth, and mass mailings on consumer knowledge? Does the source of the message (e.g., tobacco companies, government, voluntary organizations such as the American Cancer Society, and medical and other health professionals) matter? If so, how?

c. Studies on influences of tobacco and pharmaceutical industry marketing. How does marketing influence perceptions and misperceptions of both consumers and health professionals? Will marketing of PREPs influence health professionals’ behaviors regarding the provision of clear and unequivocal messages to quit (Kottek, Battista, DeFriese, & Brekke, 1988)? If so, how? Will marketing of PREPs influence policy makers’ behaviors regarding the provision of proven health promoting strategies (i.e., funding of anti-tobacco media campaigns, provision of smoke-free areas, increasing excise taxes to raise the price of tobacco products)? If so, how?

d. Studies on the influences of product characteristics and packaging. How do product characteristics influence perception of safety? For example, is a cigarette that is perceived as smooth and mild interpreted as being less hazardous than one that is harsh? How do individuals process words such as light, mild, and smooth? How will individuals process other words (e.g., ‘reduced carcinogens, premium taste’) used directly or indirectly to convey a purportedly safer product? What is the relative influence of product packaging? What is the relative influence of various warning labels? What is the relative influence of package inserts and onserts (i.e., folded information sheets attached to the outside of the package)? What are the effects of disclosures and disclaimers?

All of the above research should contribute to the process of developing communications to produce maximum net benefit. A challenge will be to communicate relative degrees of hazard. For example, currently, many consumers have inaccurate beliefs regarding the health effects associated with the use of medicinal nicotine, frequently believing that these products cause cancer or overestimating the abuse potential of these products. These misperceptions lead to unnecessary concern over the use of these products (Cummings, Giovino, Bansal, Hyland, Hustrup, & Yost, 2001; Shiffman, Mason, & Henningfield, 1998), deterring the use of the least toxic nicotine delivery-device that is currently available and that can assist in cessation. As PREPs emerge in the market and are demonstrated to reduce toxin exposure significantly, serious thought and effort need to be expended on how best to convey the relative risk and the recommended use of these products and methods to both consumers and health care providers. This area is particularly challenging because of the shifting of the perceptions of safety. In Finland, for example, various tobacco products were classified as either dangerous or very dangerous. Eventually, however, many members of the public considered the products, classified as dangerous, to be safe (Tapani Piha, personal communication to Judy Wilkenfield; May 2000). Research is needed to ensure accurate communication and perception of relative hazards of products. At the same time, messages must continue to emphasize the importance of cessation and prevention.

a. Examination of how relative degrees of hazard can be communicated without misleading the consumer. For example, would pictograms in advertisements and on packaging improve understanding? Would varying the type and amount of images used in advertisements and on packaging influence perceptions and use? What cognitive and affective strategies must be incorporated to maximize net benefit?

b. Studies on messaging from health care providers. For example, how, when, and with what populations of tobacco users should health care providers recommend the use of reduced-risk products or methods for tobacco reduction? How do health care providers effectively communicate the importance of cessation and prevention of smoking initiation, while discussing the alternatives to these approaches?

3. Surveillance of people, products, and promotions

Examine who is using what products, where, when, how, for how long, and to what effect.

Surveillance systems in epidemiology and public health can provide timely information from relevant populations on the prevalence of use of tobacco products and PREPs; factors influencing use patterns; incidence, prevalence, and mortality from tobacco-related diseases; and the impact of tobacco control programs and policies (Stratton et al., 2001). The population perspective provides focus on the entire community and the totality of the burden of tobacco products and PREPs. Detailed documentation (e.g., brand specific) from survey data of use patterns will help provide insights. The following surveillance studies and data collection methods will address some of these important topic areas:

a. Surveys on who is using what products, where, when, how, for how long, and to what effect.

b. Detailed survey data could also provide baseline data if survey participants agree to participate in cohort studies, which include outcome measures such as
lifelong usage patterns, morbidity, and mortality. Survey participants or subsamples of participants could provide biological samples to permit testing of biomarkers that may predict health consequences and genetic factors that may influence use and predict health consequences.

c. Information from existing data collection efforts (e.g., the vital statistics system, disease registries, hospital discharge surveys, medical record surveys) could be expanded to answer questions related to the influence of tobacco products and PREPs on disease outcomes, both short- and long-term in nature. Indeed, research on chronic diseases will be limited, because users likely will try several conventional tobacco products and PREPs, making identification of the specific role of a given PREP extremely difficult (Stratton et al., 2001). Studies of PREPs with short-term outcomes may be useful, such as wound healing and pregnancy outcomes. Trials comparing the effects of PREPs on short- and long-term consequences are needed.

Survey how products have changed or are changing over time, the impact of these changes, and product acceptability

Currently, we have insufficient information on the nature of tobacco products—specifically the chemical constituents of tobacco and tobacco smoke, as well as structural materials such as fibers or fiber fragments (Pauly, Allaart, Rodriguez, & Streck, 1995; Pauly et al., 1998; Pauly, Stegmeier, Mayer, Lesses, & Streck, 1997; Stratton et al., 2001). Information reported by the Federal Trade Commission is limited, in part because it does not measure consumption under normal human conditions and because the constituents measured (i.e., tar, nicotine, carbon monoxide) need to be expanded to include specific chemicals inherent in tobacco and tobacco smoke, as well as chemicals added in the agricultural and manufacturing processes (Stratton et al., 2001). The workgroup believed that the tobacco companies have more data than the Federal Trade Commission provides and that industry data may prove useful. The following areas of investigation were considered important.

a. Studies on the characteristics of tobacco products. For example, how have products changed and how will they continue to change? What can tobacco industry documents tell us about changes in products? What can patent tracking tell us about future considerations for products? The workgroup recommended document tracking for past findings and patent tracking for more proactive monitoring. Presentations and published reports from industry scientists should be independently verified.

b. Studies on the impact of new brands on overall tobacco consumption.

c. Studies on product acceptability. What products are acceptable to consumers? What factors influence consumer acceptability?

Surveillance of messages

Current information on promotion messages is extremely limited, existing in the form of annual Federal Trade Commission reports that only provide overall information on total expenditures for various broad marketing categories (Federal Trade Commission, 2001). Adequate monitoring would cover themes of messages, imagery, geographic boundaries, channels of communication, and duration and reach of exposure. Research on the influence of such messages on use patterns would be facilitated by such surveillance. The primary research areas include:

a. Surveys on what messages are being promoted, where, how, for how long, and to what effect.

b. Examination of how ongoing tobacco control policies and programs might impact or interact with these messages.

4. Policy, regulation, law, and ethics

If harm reduction is to have any chance of working effectively, a sound regulatory framework needs to be established and sufficient resources for surveillance and regulatory needs will have to be provided (Stratton et al., 2001). Research on relevant topics involves three areas—policy/regulation, law, and ethics—that could require both empirical and nonempirical work. The workgroup believed that such research would contribute to enhancing the public’s health, regardless of the method of inquiry. Addressing some of the issues listed below may first require addressing the research questions raised by the Products and Methods as well as Toxicity and Exposure Assessment workgroups.

Policy and regulation

Explore and examine the optimal policy/regulatory elements for tobacco harm reduction. Determine the infrastructure additions that need to be made to permit optimal policy/regulation:

a. Examination of the optimal policy/regulatory elements for tobacco harm reduction, using the recommendations of the Institute of Medicine report (Stratton et al., 2001) as a foundation. For example, how can and should communications by manufacturers be regulated? Can and should a regulatory body require the industry to provide detailed marketing and/or product formulation data? If so, what data should be made available to the public? What is the minimal set of tests that should be done for assessing toxicity of conventional products and PREPs? What standards should be set? What benefits might manufacturing standards (e.g., requiring the industry to remove all nitrosamines) have? What actions should be taken if standards aren’t met? What is the role for individual states if the Federal government assumes regulatory authority?
b. Exploration of the infrastructure additions that need to be made to permit optimal policy/regulation. For example, who will collect necessary data and pay for the costs of surveillance and regulation? What is the core set of regulatory tools that the FDA, or whatever agency assumes regulatory authority, should have to oversee the manufacture and distribution of tobacco products and PREPs?

**Law: Examine legal burdens of proof for regulation**

As PREPs become introduced, the legal climate may facilitate the development of new standards for toxicity of tobacco or tobacco-like products. This would focus on examination of the impact of and ways to facilitate a regulatory scheme. For example, could a regulatory scheme influence the pharmaceutical and tobacco industry’s incentives in a positive direction? What legal burdens of proof are needed to support regulatory action, such as restricting/banning certain types of marketing or additives?

**Ethics: Explore and examine ethical issues evolving around the use of PREPs**

The optimal balance of individual rights to information on and access to PREPs versus the need to protect the public from harm has not been adequately explored (Kozlowski, this issue). Furthermore, the type and extent of product information that is necessary for the individual to make a fully informed choice is not clearly known. In the research realm, Institutional Review Board and Data Safety and Monitoring issues related to harm reduction research need careful consideration.

a. The cigarette industry often claims that smokers are ‘fully informed.’ However, the definition of a truly fully informed tobacco user needs to be clarified and the number of users that are fully informed assessed.

b. Studies on what information the public health and medical authorities think tobacco users need to be optimally informed (regardless of whether they are ‘fully informed’) and how we can optimally inform consumers.

c. Examination of the balance of human rights with protection of public health. How can the government adequately maintain an individual’s right to information on and access to PREPs and yet also protect the public health? What lessons can be learned from previous controversies involving government regulation? For example, does the laetrile experience (an alternative therapy promoted as a cure for cancer and which had a large following, but was scientifically determined as ineffective) provide a useful case study? Are there others?

d. Studies on how human subjects can be optimally protected and what IRB issues need to be considered as agencies and universities proceed with research on PREPs. For example, for what population of smokers should PREPs be targeted in research studies without compromising quitting attempts? How can the subject population be adequately informed about new PREPs, particularly when risks may be increased for some diseases, but not for others? Are researchers obliged to encourage the participants to sustain the use of tobacco-related PREPs or to return to the previous conventional tobacco products?

**Discussion**

The deliberations and research questions raised by the workgroups reflect the vast amount of research knowledge that we are lacking in this area. On the other hand, past research results and lessons learned from experience with low yield cigarettes have informed the scientific and tobacco control community of the pitfalls that can occur when tobacco products that are purported to be ‘safer’ are released onto the market. These lessons have helped to formulate future research directions.

Currently, consideration of tobacco regulation by the Food and Drug Administration has been raised by a few members in Congress as well as by the tobacco industry. One of the key reasons why regulatory oversight of the industry seems particularly important is the number of emerging reduced toxin exposure and potentially ‘safer’ tobacco products that will be and are being marketed and claims, either direct or indirect, that are being made about them. A focused and comprehensive science database must be developed to guide policies and regulatory initiatives. Although ideally all the identified research areas would be addressed concurrently, the following lists those that we believe require the most immediate attention.

1. Determine valid biomarkers and predictors of reduced toxin exposure in vitro, in animals and humans, taking into account the multiple number of toxin constituents and their interaction.

2. Estimate the extent of reduction in tobacco toxin exposure that would lead to reduced harm in health.

3. Examine compensatory smoking behavior and its impact on exposure and harm reduction approaches.

4. Explore multiple methods to reduce toxin exposure and harm from nicotine-delivery devices, ranging from product development to policies.

5. Develop a comprehensive surveillance system that will monitor PREP marketing, penetration, uptake, and consequences (i.e., health and prevalence of use of PREPs and conventional tobacco products). A system needs to be developed that includes rapid and long-term assessments.

6. Examine the impact of messages and marketing of PREPs on consumer and healthcare provider attitudes, knowledge, perception, and beliefs. Find ways and avenues to communicate information that will lead to the greatest net public health benefit.
7. Consider the regulatory framework and requirements that are necessary to oversee and monitor PREPs.

Across these research areas, the workgroups emphasized the need to take into account individual and ethnic group differences.

To ensure valid and timely assessment of PREPs, the workgroup strongly believed that infrastructures need to be developed that would allow for rapid response capabilities. These assessment programs need to be independent of the activities of the tobacco industry and would involve toxicological assays, immediate surveillance capabilities, rapid testing of PREPs from basic product characterization to the use of animal and human models to determine exposure and effects, and a repository for tobacco industry information. Furthermore, standing panels of representatives from various sectors of the population may provide an efficient way to test market communication messages. Finally, systems of research that involve multidisciplinary teams may foster more rapid translation of basic science work to preclinical testing to human clinical testing to eventual policy development, and also produce a more cohesive and systematic approach toward these scientific issues.

Currently, we have the opportunity to conduct research and develop policies and products that can significantly reduce morbidity and mortality associated with cigarette smoking and tobacco use. However, for this approach to be embraced by the public health community, sufficient information needs to be provided to ensure that these ‘harm reduction’ approaches do not result in poorly informed decision making and increased aggregate harm. Furthermore, the message that no use is better than any use must be clearly heard and understood.

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### Appendix 1  Products and methods for reduced tobacco toxin exposure and harm reduction

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### Appendix 2  Exposure and toxicity assessment for reducing tobacco harm

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### Appendix 3  Consideration for ensuring the public health: Communication, surveillance, and regulation

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<td>Mitch Zeller</td>
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