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Methods to assess potential reduced exposure products

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The availability of tobacco products purported to reduce toxin exposure or potentially reduce health risks necessitates the development of methods and identification of biomarkers that can be used to assess these products. These assessments occur on multiple levels and stages, from identifying constituents in the tobacco products and smoke, to human exposure and health effects trials, to postmarketing surveillance. A conference of multidisciplinary experts was convened to present and discuss methods and biomarkers to assess these products and to consider the infrastructure necessary to facilitate the evaluation process. Although no currently available set of measures was thought to be sufficient for determining the relative health risk of potential reduced exposure products, this paper provides a blueprint for future research toward this end.

Introduction

Tobacco harm reduction, as a method to reduce mortality and morbidity, has been receiving increasing attention both in the United States and internationally. Harm reduction refers to "minimizing harms and decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use" (Stratton, Shetty, Wallace, & Bondurant, 2001). Although cessation and prevention should remain the primary methods for tobacco control, several reasons have been provided to support considering lowering tobacco toxin exposure and addictiveness as a strategy to reduce negative health consequences. First, although smoking rates have been decreasing consistently since the 1960s, the age-specific prevalence of cessation among ever-smokers (also known as quit ratio) has leveled off in recent years (Giovino, 2002). Second, even though the majority of tobacco users want to quit, few are successful on single quit attempts, and only 10%–20% are ready to quit in the immediate future (Etter, Paernegger, & Ronchi, 1997; Prochaska & Goldstein, 1991). Third, the number of cigarettes smoked demonstrates a dose–response relationship to disease (National Cancer Institute, 1997; Stratton et al., 2001), and recent modeling based on data from the American Cancer Society's Cancer Prevention Study I has suggested that the greater the reduction and the earlier the age of reduced smoking, the greater the number of years of life saved (Burns, 1997). Methods that have been proposed to reduce harm have ranged from modifying tobacco to reduce toxicants to long-term use of nicotine replacement products.

Because of the introduction of tobacco products that were marketed with implied or direct claims of reduced tobacco toxin exposure or reduced health risks, the Institute of Medicine (IOM) was charged in December 1999 by the U.S. Food and Drug Administration (FDA) to address four questions and to "formulate scientific methods and standards by which potential reduced exposure products (PREPs) could be addressed." The four questions were the following: (a) Does use of the product decrease exposure to the harmful substances in tobacco? (b) Is this decreased exposure associated with decreased harm to health? (c) Are there

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surrogate indicators of this effect on health that could be measured in a time frame sufficient for product evaluation? and (d) What are the public health implications of tobacco harm reduction products?

After reviewing the scientific evidence, the IOM report described the following conclusions: (a) "Reducing risk of disease by reducing exposure to tobacco toxicants is feasible," but it also stated that (b) "potential reduced exposure products (PREPs) have not been evaluated comprehensively enough to provide a scientific base for concluding they are associated with reduced risk of disease compared to conventional tobacco use." The report also concluded that (c) "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," (d) "currently available PREPs have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products," (e) "regulation of all tobacco products, including conventional ones as recommend 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," and (f) "the public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative."

These conclusions highlight the need for and urgency in developing a comprehensive strategy to evaluate these products and approaches. The currently existing PREPs include (a) modified tobacco products that contain reduced levels of one or more toxins (e.g., cigarettes with reduced tobacco-specific nitrosamines through new curing processes, the addition of catalysts to reduce polycyclic aromatic hydrocarbon carcinogens produced by smoke, the use of genetically modified plants to reduce nicotine or nitrosamines, or the use of filters to selectively reduce toxicants), (b) cigarette-like devices, such as those that heat rather than burn tobacco, and (c) oral noncombustible products, such as smokeless tobacco, that are modified to reduce exposure to specific toxicants. Other reduced exposure approaches include reduced tobacco use either through the use of medicinal products or other tobacco products (e.g., oral tobacco for cigarette smoking) and long-term maintenance on medicinal nicotine. The urgency for evaluation of PREPs is also highlighted by past experiences with low-yield cigarettes. Low-yield cigarettes were considered "safer" by consumers, in some cases leading to continued smoking and with no significant reductions in disease (National Cancer Institute, 2001).

Evaluation of these products must involve consideration of both individual risk and population effects (Hatsukami, Henningfield, & Kotlyar, 2004; Stratton et al., 2001). Individual risk involves assessing toxin exposure, addictiveness, and disease risk within individuals. Individual risk can be determined by conducting both short- and long-term clinical trials using biomarkers for exposure and for health effects. Population effects involve assessing tobacco use behavior such as the rate of uptake, maintenance, cessation, and relapse as a result of the introduction of the product and the effects of product use on morbidity and mortality. Population effects can also be determined by evaluating contributors to product use including consumer perception of the product, product promotion and placement in retail stores, cost, availability, policies such as tobacco use bans, and changes in normative beliefs.

Figure 1 offers a heuristic model illustrating the various components and steps in testing PREPs that takes into account both individual and population disease risk. This model is based on the principles for evaluating PREPs described in the IOM report (Stratton et al., 2001). Testing involves both premarket evaluation (step 1 and 2) and postmarket evaluation (step 3). At each step of this three-step model, testing results must be evaluated to determine whether sufficient evidence supports an appropriate risk–benefit ratio to permit proceeding to the next step or to eventual market distribution. This ratio can be based on the following:

- Extent of reductions in toxin exposure and addictiveness and any other heath claims associated with the product;
- Addictiveness or health risk compared with conventional brands of tobacco, including marketed brands with the lowest level of toxicity, and with cessation;
- Adequateness and accuracy of information provided to the consumer about the extent of toxic exposure from the product or relative health risk (e.g., adequacy of the evidence to support claims of reduced toxicity of a PREP, and if meaningful reductions of exposure or risk are found, then the accurate interpretation of the data by consumers);
- Effects of claims (if such claims are permitted), marketing, and promotion efforts on consumer perception of the product;
- Unintended and unwanted consequences such as increased morbidity or mortality as a result of increased prevalence of tobacco use or other changes in tobacco use behavior.

When the product is being offered for consumption, including in test marketing, evaluation of the risk–benefit ratio must be performed by an independent body of experts.

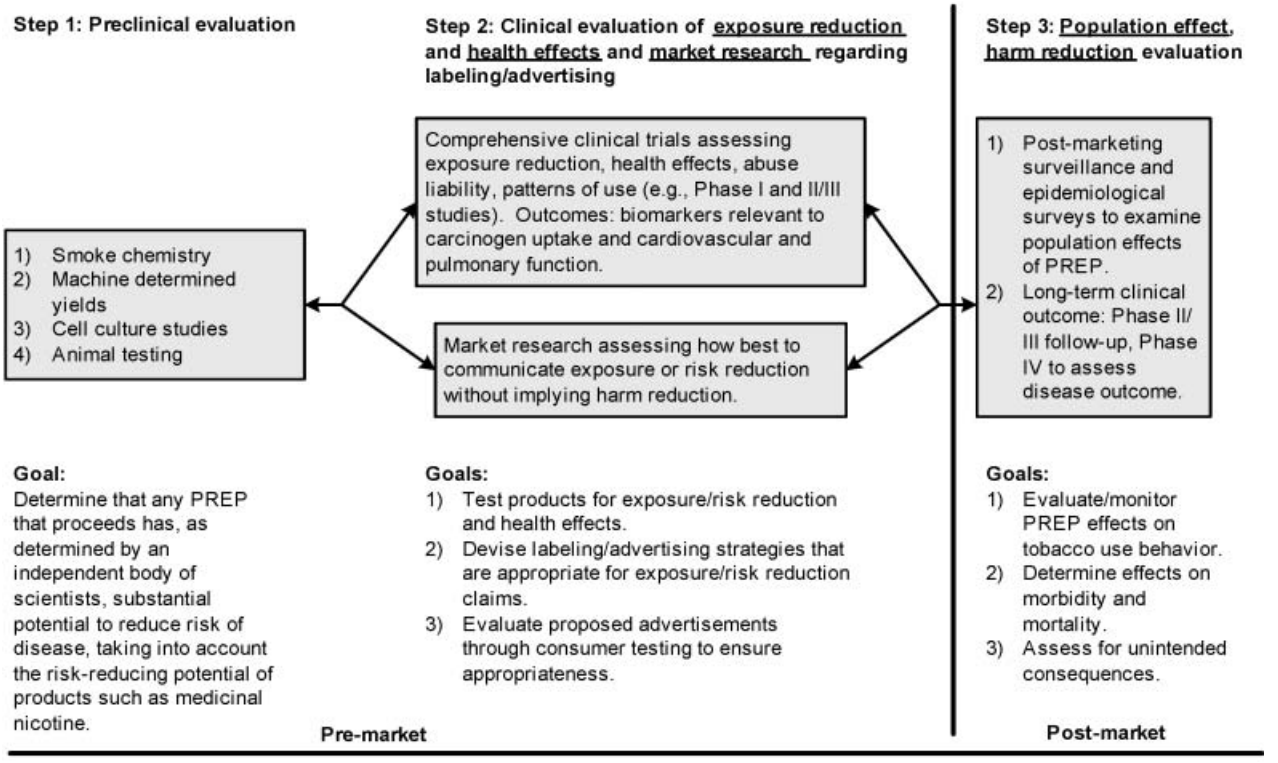

Figure 1. Three step model for potential reduced exposure product (PREP) evaluation with assessment occurring by an independent scientific panel or regulatory agency after each step.

A comprehensive strategy for testing PREPs initially involves testing for product toxicity or hazard identification, and preclinical cell and animal testing. According to the IOM report, hazard identification involves some of the following components: (a) Identifying toxicants in the PREP that are known to cause adverse health effects, (b) determining the extent to which the compounds targeted for reduced exposure are causally linked to tobacco-related disease, (c) determining how the contents of the PREP compare with those of conventional tobacco products, (d) identifying unique toxicants in the PREP compared with conventional tobacco products, and (e) identifying unique toxicants that may be associated with second-hand smoke. Once these toxicants are identified, then extent of exposure to toxicant ingredients (e.g., dose) should be measured based on machine-determined yields that simulate human smoking behavior. The range of doses that is observed can be applied to preclinical testing on cells or in animals (e.g., tests for cytotoxicity or mutagenicity) that will provide qualitative information about the toxicity of these ingredients. Future research goals should include the development of preclinical tests that can quantitatively measure relative toxicity between the comparison compounds. Furthermore, the extent of differences in exposure needed to result in meaningful differences in risk is a critical question that needs to be addressed. This task is made difficult and complex because of the frequent need to quantify the differences in risk between various highly toxic products and the vast number of constituents that need to be considered.

An independent group of scientists and regulators should use available preclinical data (a) to assess whether selected products are likely to substantially reduce risk, taking into account the risk reduction potential of products such as medicinal nicotine, and (b) to assess whether further premarket testing is worth pursuing (L. T. Kozlowski, Strasser, Giovino, Erickson, & Terza, 2001). However, the role of preclinical testing (animal or cell preparations) is extremely limited. Because preclinical testing cannot predict exposure or risk reduction when a product is used by humans, the results must not be used as a basis for advertising and promotion of PREPs.

After this first evaluation, human testing is necessary. The primary aim of human clinical testing is to determine individual risk, that is, the extent of exposure to toxins and health effects or the potential risk for disease resulting from use of the products, the potential for persistent use of the products, and the pattern of use of the products. Premarket consumer perception testing can help to determine potential individual as well as population harm. Perceptions of the health risks or harms associated with products can affect the individual's decision to use them and the extent to which the population participates in the purchase of the products. Premarket consumer

perception testing involves determining how the consumers perceive and interpret the information and images delivered to them, and if these perceptions and processing of information are accurate or misleading. The purpose of consumer product testing is to ensure that claims and marketing of a product will lead the consumer to make an informed decision based on an accurate understanding of valid information, and to ensure that the product does not appeal to youth, those who would have quit otherwise, or those who have previously quit.

Once the risk–benefit ratio is considered promising, then population effects of PREPs after they enter into the market need to be assessed. This assessment is accomplished through postmarketing surveillance and epidemiological studies. Postmarketing evaluation is conducted to ensure that PREPs do not result in increased initiation of tobacco use, maintenance of tobacco use in those who were interested in quitting, or relapse to tobacco use in former tobacco users. Furthermore, the use of PREPs should not result in an increase in morbidity and mortality. It is not acceptable to reduce individual risk at the expense of increasing population harm. Therefore, through the use of long-term, longitudinal surveys, the actual reduction in harm through the use of PREPs can be determined. An important point to remember is that the different stages involved in testing these products are bidirectional rather than unidirectional; that is, results from human evaluation can inform preclinical evaluation including product design. Similarly, postmarketing surveillance results can inform clinical or preclinical evaluation of products.

Because of the number of years required to determine whether PREPs result in harm to health, proxies for disease outcome are needed. Therefore, essential measures for determining the impact of PREPs are biomarkers for toxin exposure, injury, and disease risk. When comparing the health effects of a PREP, researchers must look for differences in the levels of biomarkers associated with the PREP and the currently used tobacco product, and ideally the impact of this difference on health must be determined. These biomarkers need to cover a broad range of tobacco-related diseases to ensure that products that decrease biomarkers for one disease category do not increase them in another category.

In an effort to facilitate development of research priorities and expand and update the IOM guidelines in the evaluation of PREPs, the National Cancer Institute, National Institute on Drug Abuse, National Institute on Alcoholism and Alcohol Abuse, and the Centers for Disease Control and Prevention convened a meeting to develop guidelines for the evaluation of PREPs on both individual and population levels. Both methods and biomarkers for evaluation were addressed. Although evaluation of product toxicity and preclinical evaluation of the products is an important step in assessing PREPs, this meeting focused primarily on human testing. A steering committee (Table 1) comprised of representatives from each of the government agencies and two university-based scientists developed the meeting agenda. Three topic were selected to examine methods for evaluation: Human clinical testing; premarket testing of consumer perceptions, product marketing, and promotion; and postmarketing evaluation. Biomarkers for four categories of diseases or negative health outcomes were also discussed: Cardiovascular disease, pulmonary disease, cancer, and fetal toxicity. A leader was selected for each topic, and this leader subsequently selected the team members for his or her topic (Table 2).

Table 1. Steering committee members.

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The members of the methods groups were asked to address the following questions for their assigned topics: (a) What are the primary issues associated with the evaluation of the products? (b) What are the methods and measures to address these issues? (c) What is the necessary infrastructure needed to evaluate the PREPs? The biomarker groups were asked to identify potential biomarkers that could be used to evaluate PREPs based on their mechanistic relationship to disease and evidence showing differences between smokers and nonsmokers, changes with cessation, a dose–response relationship with number of cigarettes per day, and changes with reduction in smoking. Ideally, changes in the levels of biomarkers should result in changes in the risks for disease. Unfortunately, limited data are available on the extent of biomarker change necessary to induce a beneficial health effect. Therefore, predictive validity, one of the hallmarks for determining a valid biomarker, was not included as a criterion for assessing biomarkers. The biomarkers groups also were asked to speculate on potentially promising biomarkers.

Each group was asked to present its finding at a meeting held on February 26 and 27, 2004, in Washington, D.C. This meeting included an invited expert panel (Table 3) and representatives from

Table 2. Topic leaders and workgroup members.

Methods
Human clinical trials
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Neil Weinstein, Ph.D., Rutgers University, New Brunswick, NJ
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Biomarkers
Cardiovascular
Neal Benowitz, M.D., [a] University of California, San Francisco, CA
Anne Burke, Ph.D., University of Pennsylvania, Philadelphia, PA
John Cooke, M.D., Ph.D., Stanford University, Stanford, CA
Pulmonary
Stephen Rennard, M.D., [a] University of Nebraska, Omaha, NE
Mark Frampton, M.D., University of Rochester, Rochester, NY
David Riley, M.D., Robert Wood Johnson Medical School, Piscataway, NJ
Cancer
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Steven Belinsky, Ph.D., Lovelace Respiratory Research Institute, Albuquerque, NM
Peter Shields, M.D., Georgetown University Lombardi Cancer Center, Washington, DC
Steven Tannenbaum, Ph.D., Massachusetts Institute of Technology, Cambridge,MA
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Theodore Slotkin, Ph.D., Duke University Medical Center, Durham, NC

Note. [a]Topic leader.

Table 3. Expert panel members.

David Ashley, Ph.D., Centers for Disease Control and Prevention, Atlanta, GA
David Burns, M.D., University of California, San Diego, CA
Greg Connolly, D.M.D., M.P.H., Massachusetts Department of Public Health, Boston, MA
Mirjana Djordjevic, Ph.D., National Cancer Institute, Bethesda, MD
Jefferson Fowles, Ph.D., Institute of Environmental Science and Research, Porirua, New Zealand
George Hammons, Ph.D., Philander Smith College, Little Rock, AR
Jonathan Samet, M.D., Johns Hopkins University, Baltimore, MD
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governmental agencies, and was also open to the public. After each presentation, the audience raised questions and provided feedback. After the meeting, each workgroup was responsible for integrating these comments into a written document. The final document was then sent to the expert panel for their review. The subsequent content of the two papers, one on methods and one on biomarkers, represents the deliberations of these groups. This article discusses issues and methods associated with testing PREPs, and a separate paper discusses biomarkers for testing PREPs (Hatsukami, Benowitz, Rennard, Oncken, & Hecht, in press). Note that the guidelines and issues outlined here can be used for evaluating all tobacco products.

Human clinical trials

Issues in clinical trials of PREPs

Clinical trials are part of the essential second step of evaluating PREPs (Figure 1). As described below, clinical trial design must account for moderating factors that can influence a PREP's impact, while incorporating methods and measures that allow the trial to address important questions such as (a) Does the PREP result in reduction in toxin exposure/uptake and harmful health effects? (b) What is the abuse liability of the PREP? (c) How is the PREP used? and (d) Does the PREP make future cessation attempts less likely? These questions can be answered in studies that approximate phase I–IV clinical trials, as defined by the FDA.

Methods

Moderating factors that can influence the impact of a PREP. Many moderating factors can influence the effects of a PREP (Table 4). These factors require consideration because they may affect tobacco use behavior and disease risk. Type of tobacco used is

Table 4. Moderating variables to consider for human clinical trials.

Characteristics of tobacco user
Type of tobacco use
Degree of dependence
Amount of tobacco use
Duration of tobacco use
Interest in quitting
Recent cessation activity
Gender
Ethnicity or race
Physical and mental health status
Physiological phenotype
Metabolic activations
Detoxification
Metabolism
Genotype
Disease
Addiction

one example, because oral tobacco confers less individual disease risk than does combustible tobacco (Hatsukami, Lemmonds, & Tomar, 2004). Degree of dependence, indexed with biochemical measures such as cotinine levels or self-report scales, such as the Fagerström Test for Nicotine Dependence or the Nicotine Dependence Syndrome Scale (Colby, Tiffany, Shiffman, & Niaura, 2000; Stratton et al., 2001), may influence key variables such as the extent or persistence of use and PREP-induced changes in smoking behavior. Amount and duration of tobacco use are also important; amount serves as an indicator of frequency of behavior whereas duration may be a better predictor of risk for some diseases (Doll & Peto, 1978; Flanders, Lally, Zhu, Henley, & Thun, 2003). Tobacco user gender influences sensitivity to nicotine, treatment outcomes, pharmacotherapy response, and extent of uptake of carcinogens and disease risk and outcome (Connett et al., 2003; Melikian et al., 2004; Perkins, 2001). Ethnicity and race can also affect the degree of dependence and disease outcome. For example, African American tobacco users report lower indicators of dependence and higher incidence of tobacco-related disease (Caraballo, Giovino, Pechacek, Mowery, & Richter, 1998; Emont, 1996; Pérez-Stable, Herrera, Jacob, & Benowitz, 1998; U.S. Department of Health & Human Services, 1998; Wagenknecht, Cutter, & Haley, 1990).

The effects of PREPs may differ based on users' mental or physical health status, with potentially less reduction in disease risk observed in populations with a history of disease or a current disorder. Concurrent medications may lead to induction of enzymes that influence toxin exposure. Other moderating variables include individual differences in physiological phenotypes (e.g., individual differences in metabolic activation or detoxification of toxins, capacity and efficiency of DNA repair; Stratton et al., 2001) and genotypes that confer susceptibility to disease or addiction (Lerman & Niaura, 2002). In sum, several potentially interrelated moderating variables can influence PREP effects.

Table 5. General methodological issues in human clinical trials.

Characterization of population
Random assignment of subjects to experimental conditions
Control group
Conventional brand of tobacco
Standardized brand of tobacco
Medicinal nicotine
Abstinent smokers or nonsmokers
Controlled vs. ad libitum smoking
Comprehensive set of biomarkers
Study duration
Dictated by study goal and outcome measures
Stabilization of tobacco use behavior
Verification of product use or reduction in tobacco consumption
Monitoring of adverse events
Clinical events
Other unexpected or unintended consequences

Methodological issues for evaluating PREPs. Several methodological issues are relevant to assessing PREP effects (Table 5). First, the study population should reflect the population of tobacco users likely to use the PREP. For example, many smokers of light and ultralight cigarettes are especially concerned about the health risks from smoking (Giovino et al., 1996) and thus may be most likely to use a PREP. Relative to smokers trying to quit, smokers primarily interested in reducing their cigarette intake may have more health, psychiatric, and alcohol use problems (Lemmonds, Mooney, Reich, & Hatsukami, 2004), which may limit the extent of beneficial effects from using a PREP. The smoker's cessation behavior, such as interest in quitting or past quit attempts, is likely to influence the use of the PREP and should be controlled for or stratified in the comparisons.

Second, unbiased assignment to carefully considered control conditions is critical. Control conditions for PREP evaluation might include use of (a) conventional tobacco products (Breland, Buchhalter, Evans, & Eissenberg, 2002; Hecht et al., 2004), (b) standardized products, although these types of products are not considered sufficient (e.g., Eclipse Expert Panel, 2000), (c) medicinal nicotine (Hatsukami, Lemmonds, Zhang et al., 2004), or (d) no tobacco or nicotine products (i.e., abstinent users or nonusers; Breland, Acosta, & Eissenberg, 2003). These conditions provide valuable reference points and allow consumers to understand the relative risks associated with PREPs.

Third, both controlled and ad libitum use should be considered in assessing PREPs. Controlled tobacco use allows a direct comparison of the toxin exposure associated with each PREP, whereas ad libitum use provides a more accurate picture of toxin uptake in the natural environment.

Fourth, a comprehensive battery of exposure, injury, or disease biomarkers is essential in PREP evaluation. Future research must identify a panel of biomarkers that reflect different disease states so that determinations can be made that reductions observed in one area (e.g., carcinogen exposure) are not achieved at the expense of increases in another (e.g., abuse liability or heart disease; Breland, Buchhalter et al., 2002; Breland, Evans, Buchhalter, & Eissenberg, 2002; Fagerström, Hughes, & Callas, 2002). A thorough assessment panel should include a general and uniform set of biomarkers that can be used in the evaluation of all PREPs, in addition to biomarkers that are specific to the products being assessed.

Fifth, it is important to consider goals, outcome measures (e.g., metabolic half-life of biomarkers), and in some cases, stabilization of PREP use

behavior when determining study duration. For example, in laboratory studies examining PREP acute effects, study duration may be a few hours (e.g., Breland, Buchhalter et al., 2002; Breland, Evans et al., 2002; Buchhalter, Schrinel, & Eissenberg, 2001). However, if the goal of the study is to examine human exposure and disease risk measures in a naturalistic environment, then a study may last days (e.g., Breland et al., 2003; Fagerström, 2000; Hatsukami, Lemmonds, Zhang et al., 2004) or months (Hecht et al., 2004; Keely, Hughes, & Hirsch, 2001).

Sixth, special attention should be given to assessment and verification of compliance with protocol-specific tobacco use restrictions. However, except in inpatient settings, compliance can be difficult to verify. On an outpatient basis, when the PREP involves tobacco reduction or abstinence, biochemical verification is possible (e.g., by assessing the tobacco alkaloid anatabine, or tobacco-specific nitrosamines such as total NNAL; Hecht et al., 2004). For PREPs that specifically involve tobacco use reduction, the extent to which anatabine, total NNAL levels, or other biomarkers should be lessened to indicate compliance is, to date, uncertain. If the PREP involves a continued normal rate of tobacco use (e.g., a tobacco-containing PREP intended to reduce toxin exposure), then investigators may need to identify procedures that maximize compliance while also encouraging accurate reporting of product intake (e.g., multiple compliance measures, return of used and unused product, contingent payment).

Finally, adverse events (e.g., increased blood pressure, higher than normal laboratory tests) need to be monitored to assess for unintended or unexpected consequences of PREP use.

Measures

Exposure and health effects. The measures related to potential harm involve assessing toxin exposure or health effects (Table 6). With regard to assessing the dose of toxin exposure, the most obvious measure is actual tobacco use, complemented with topographical features such as (in smokers) puff number, duration, volume, and velocity as well as interpuff interval. Generally, self-report measures are common (e.g., Bolliger et al., 2000; Carpenter, Hughes, & Keely, 2003; Etter, Laszlo, Zellweger, Perrot, & Perneger, 2002; Fagerström, Tejding, Westin, & Lunell, 1997; Hurt et al., 2000; Rennard et al., 2002; Wennike, Danielsson, Landfeldt, Westin, & Tonnesen, 2003) but can be confounded by changes in use topography (e.g., Hecht et al., 2004). Thus measures of actual toxin uptake, such as carbon monoxide, nicotine or cotinine, anatabine, and carcinogens, are essential (Breland et al., 2003; Hecht et al., 2004). Exposure assessments could also include examining PREP-delivered toxin pharmacokinetics, including metabolism and clearance rates.

Table 6. Measures for human clinical trials.

Exposure or chemical biomarkers
Frequency and amount of tobacco use
Tobacco use topography (e.g., number of puffs, puff duration, puff volume, puff velocity)
Biomarkers for exposure (e.g., nicotine, cotinine, carbon monoxide, carcinogen uptake)
Pharmacokinetics
Biomarkers of health effects
Early cellular or biological effects
Biologically effective dose
Biological injury
Other disease-related outcomes
Functional biomarkers
Directly observed biomarkers
Abuse liability measures
Subjective responses to product
Reinforcing effects
Mood effects
Side effects
Behavioral responses to product
Drug choice paradigm
Product self-administration
Duration of use
Dependence
Withdrawal suppression
Withdrawal symptoms

Biomarkers of health effects include early chemical, biological, and functional effects that are or should be related mechanistically to disease outcome. These measures incorporate biologically effective dose, injury, or other disease-related outcomes (Stratton et al., 2001). Examples of these measures would include carcinogen-DNA adducts, lipid peroxidation, chromosomal aberrations, mitochondrial mutations, lipids, F2 isoprostanes, white blood count, blood pressure, or FEV1. These biomarkers may describe components or mechanisms of the disease process and may be used as tools for further research to determine their relationship to disease risk. In addition to these types of biomarkers, directly observable measures such as visual inspection of airways or birth weight can be considered as biomarkers of health effects.

Abuse liability of PREPs. Another important component of assessing PREPs includes determining their abuse liability, that is, the potential for addiction (Table 6). No PREP should have increased abuse liability relative to existing conventional products. Abuse liability may be measured in several ways, including assessing the subjective effects that it produces (Griffiths, Bigelow, & Ator, 2003). Subjective effects measures include the Addiction Research Center Inventory (Houtsmuller, Fant, Eissenberg, Henningfield, & Stitzer, 2002; Houtsmuller, Henningfield, & Stitzer, 2003; Jasinski, 1977; W. R. Martin, Sloan, Sapiro, &

Jasinski, 1971; Schuh, Schuh, Henningfield, & Stitzer, 1997), the Duke Cigarette Evaluation Scale (Lee, Malson, Moolchan, & Pickworth, 2004; Rose, Behm, Westman, & Johnson, 2000; Westman, Levin, & Rose, 1992), the Profile of Mood States (McNair, Lorr, & Droppleman, 1992; Schuh et al., 1997), and a variety of items assessing the valence and magnitude of drug effects (e.g., Houtsmuller et al., 2002, 2003). In these studies, subjective responses have been compared across drugs or products being tested. Other studies have asked participants to indicate their preference for PREPs (e.g., Schneider et al., 2004; Schuh et al., 1997). Other measures have included assessment of palatability, pleasantness, satisfaction, sensory effects, and extent of feeling dependent on the product (e.g., Houtsmuller et al., 2002, 2003; Lee et al., 2004; Schneider et al., 2004; Schuh et al., 1997; West et al., 2000). Another method of measuring abuse liability involves determining behavioral responses, such as asking participants to choose PREPs they would like to self-administer after a sampling period (e.g., Fagerström et al., 2002). The extent to which participants use a PREP is presumed to be related directly to the PREP's abuse liability (Hughes et al., 1991; West et al., 2000). Duration of use ("How long do participants persist in the use of the product?") is also relevant (e.g., Shiffman, Hughes, Di Marino, & Sweeney, 2003; West et al., 2000). Finally, examining PREP effects on the suppression of tobacco-related withdrawal symptoms or craving is relevant, because withdrawal suppression is thought to maintain tobacco use (e.g., Breland et al., 2003; Breland, Buchhalter et al., 2002; Houtsmuller et al., 2003; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999; Schneider et al., 2004; West et al., 2000).

When examining PREP abuse liability, researchers should consider testing different doses (Houtsmuller et al., 2002, 2003; Hughes et al., 1991; Schuh et al., 1997) and the use of appropriate negative and positive control conditions (e.g., Houtsmuller et al., 2002, 2003).

Patterns of use. Because using multiple products (e.g., usual brand and a PREP) can lead to greater toxicity, an examination of naturalistic use patterns is important in assessing actual exposure (Keely et al., 2001). For example, use of smokeless tobacco instead of smoking may reduce individual disease risk (e.g., Levy et al., 2004). However, this beneficial effect may be lessened if smokeless products are used in conjunction with cigarettes (Hatsukami, Lemmonds, & Tomar, 2004) or are used to maintain contrived tobacco use under circumstances in which a smoker cannot smoke. Laboratory studies can also reveal factors that might contribute to the extent to which PREPs are used, compared with conventional tobacco products (e.g., instructions and information provided about the PREP, PREP cost and access, availability of alternatives; Hughes et al., 1991).

Evaluating PREP effects on maintenance of tobacco use. Understanding the extent to which long-term abstinence from all tobacco products is hindered or facilitated by PREPs is critical and can be ascertained by (a) assessing changes in motivation to quit on the Contemplation Ladder (Biener & Abrams, 1991; Carpenter et al., 2003; Kotlyar, Jensen, Li, & Hatsukami, 2004) or similar measures (Etter et al., 2002; Fagerström, 2000), (b) assessing whether subjects have progressed on their stages of change (Etter et al., 2002; Prochaska, DiClemente, & Norcross, 1992), (c) determining the number of quit attempts in which abstinence has been sustained for at least 24 hr (e.g., Bolliger et al., 2000; Carpenter et al., 2003), and (d) determining the total duration of abstinence. The gold standard is the abstinence rate associated with use of a PREP compared with conventional products. Studies should not rely solely on motivations to change as predictive of long-term abstinence. The ideal PREP may well be one that reduces toxin exposure and harmful health effects of tobacco in the short term and does not compromise complete tobacco abstinence in the long term.

Premarket consumer testing

Issues in premarket testing of product presentation characteristics

Premarket testing of consumer perceptions of PREPs is important to ensure that claims conveyed about these products or marketing efforts are accurate and not misleading. The importance of this type of testing is underscored by studies showing that many smokers were misled about the health benefits associated with light, mild, and ultralight cigarettes, and by reports indicating that because of this misperception, a number of smokers chose not to quit smoking (National Cancer Institute, 2001). Recently, studies have been conducted on the perception of claims that are made for PREPs. The results are of concern. In a study conducted by Shiffman, Pillitteri, Burton, and Di Marino (2004), the aim was to assess smokers' and ex-smokers' perceptions of PREPs and how PREP claims may affect interest in quitting among smokers or in resuming smoking among ex-smokers. A random-digit-dialed survey was used to contact 1,000 smokers and 499 ex-smokers. Risk reduction claims associated with R. J. Reynolds's Eclipse were read to the participants, and perception and potential effects of these claims were assessed. Examples of these claims

include "Best choice for smokers is to quit but Eclipse is the second best choice," "May present less risk of cancer," and "Contains far less of the many compounds found in cigarette smoke that are believed to contribute to the risk of cancer and other illnesses." Between 81% and 91% of smokers and ex-smokers thought Eclipse was safer than regular cigarettes, and 24%–26% believed Eclipse was completely safe (e.g., equivalent to not smoking). About 57% of smokers were interested in using Eclipse, with the greatest interest among contemplators (i.e., smokers who expressed interest in quitting within the next 6 months). The survey also showed that 21% of smokers lost interest in quitting after hearing about Eclipse, and 6.2% of ex-smokers were interested in Eclipse, with even a higher rate of interest (15.2%) among young adults who had stopped smoking within the past 2 years. Although one of the limitations of this study is that the survey assessed intent rather than actual behavior, it raises a cautionary note that promotion of PREPs, particularly without regulatory oversight for the scientific basis for making these claims, could have untoward effects on public health.

Ideally, tobacco companies would not be able to advertise their cigarette products, and it is debatable whether they should be allowed to advertise any claims for reduced exposure or reduced health risks. However, given the lack of current restrictions on advertisement and promotion, premarket testing is an important component of evaluating PREPs.

Evaluation of these products may entail two purposes: (a) Regulatory (i.e., Does this presentation and promotion of the product adhere to an agreed-upon standard including assurance that the claims are not false or misleading?) or (b) public health (i.e., Are the presentation and promotion likely to lead to beliefs or behaviors that tobacco control forces want to prevent, such as maintenance of tobacco use in those who would have quit otherwise?). The optimal situation is when these two purposes merge.

Methods

Testing of consumer perceptions of PREPs includes assessing reactions (a) to product characteristics presented via advertising (e.g., newspaper, magazine, Internet) and other promotional methods, images and text, and packaging and (b) to implicit and explicit reduced harm claims in these presentations. As a preliminary step, decisions by a regulatory agency must be made about what the science supports and whether labels should reflect reduced exposure to specific smoke constituents, based on human exposure methods, or go so far as to provide estimates of reduced risk of specific smoking-related diseases. Furthermore determining the text, format, and graphic representations of these data that best convey information in a way that is interpreted accurately is another important area of investigation. For example, the use of visual scales that show exposure from nonsmoking at one end and exposure to medium- or high-yield conventional cigarettes at the other end may be a readily comprehensible method of conveying the data to laypersons. Lessons may be learned from the experience of the FDA's development and testing of food labels. The necessity of this area of investigation is emphasized by studies showing that most smokers are unaware of the tar yield of their own cigarettes; could not correctly determine and understand the implications of the relative tar levels of cigarettes; and rely mostly on misleading labels such as light, ultralight, or mild (Cohen, 1996; Etter, Kozlowski, & Perneger, 2003; L. Kozlowski et al., 1998). Also, accurately perceived information on changes in specific components may nevertheless be misleading if not accompanied by information about components that have not changed.

Although no standard methods have been described for testing consumer perceptions of tobacco products, several methodological issues bear discussion. One important issue is the need to target the testing in a population that is potentially interested in these PREP products. Furthermore, recruiting smokers or other tobacco users who have diverse characteristics and describing these characteristics is necessary to determine how these attributes may influence their perceptions of PREPs. For example, participants need to be characterized on smoking status (e.g., never-smokers, former smokers), stage of smoking (experimenters vs. regular smoker), past and present efforts to reduce cigarette consumption or switch to a lower-yield cigarette, past quit attempts, difficulty in quitting smoking, stage of change (thinking about quitting in the next 6 months or within the next month), or motivation and intention to quit or decrease smoking. Perceived pressure from peers, family, or health care providers may also be a determinant of how PREPs are perceived. Other characteristics that bear consideration are the type of cigarettes currently smoked (e.g., ultra low yield, low yield, or regular), the degree of tobacco dependence and extent of smoking (occasional user vs. regular user), the degree of concern about smoking-related health, and the general and individual perceptions of risk associated with smoking. Concerted effort should be made to include individuals that represent a spectrum of ages (adolescents, young adults, adults, and older adults) and are from different ethnic and socioeconomic or educational backgrounds. Most of these variables, including gender, have been observed to influence perceptions and use of low-yield and ultra-low-yield cigarettes or PREPs (e.g., Etter et al., 2003; Gilpin,

Emery, White, & Pierce, 2002; Hamilton et al., 2004; Shiffman et al., 2004; Shiffman, Pillitteri, Burton, Rohay, & Gitchell, 2001a, 2001b).

Several avenues for consumer assessment of product presentation and labeling include focus groups; individual testing; mall-intercept interviews; and Internet, mail, and telephone surveys. Focus groups are most useful for initial exploration of the reactions elicited in consumers in response to product characteristics. Individual testing can be used for more in-depth understanding of message processing and preferences. It is recommended that some of the testing of the product presentation characteristics be performed in situ; that is, the content should be tested in the environment in which the consumer will encounter it. When consumers are explicitly directed to evaluate PREP characteristics and messages, they are likely to respond differently than if their attention had not been directed to these issues. This distinction between central and peripheral processing is well established in the persuasion literature (Petty, Haugtvedt, & Smith, 1995; Petty & Wegener, 1999). Although testing of print advertising intended for magazines or the Internet can be done in a laboratory setting, retail advertising will need to be tested in an actual retail environment, or within a virtual retail experience.

An innovative method of assessing the behavioral impact of a product is described in a study conducted by Shiffman, Burton, and associates (2001) using the ARS Persuasion test, a method to test the effectiveness of commercial television advertising. This test involves presenting the advertisement, which is embedded in a pilot television show that the participants are presumably reviewing, and determining the pre-post shift in brand choice in an environment that simulates product purchase. That is, the participants' shift in product choice offered as prizes is determined before and after viewing the advertisements. A control group that has no exposure to the advertisement is used as a comparison group. Ideally, the design should compare differences in postmessage choice only between the exposed and control groups. Making a premessage choice focuses attention on the advertisement and alters the way in which the message is processed. Conceivably, to assess the effects of PREPs on quitting behaviors, smokers who are in the preparation or action stage of quitting can be exposed to a PREP advertisement and the extent of PREP choices after exposure to the advertisement can be compared with those of a control group with no exposure to the advertisement.

Finally, population surveys can provide estimates for population impact, as described in the aforementioned random-digit-dialed telephone survey conducted to determine smoker and ex-smoker reactions to PREP cigarettes claiming reduced risk (Shiffman et al., 2004).

As an added area of research, product presentation characteristics may influence smokers' perceptions of the sensory and reinforcing effects of the PREPs and the experience of using them (Pollay & Dewhirst, 2002, 2003). For example, color, image, and extension of well-known brands may influence the perception of product taste (Pollay & Dewhirst, 2002). On the other hand, if after trying a PREP, the smoker rejects the sensory and hedonistic qualities of the PREP, he or she is unlikely to adopt it, in spite of any implicit or explicit reduced-harm claims. Furthermore several studies have demonstrated that the somatic or sensory sensations experienced by an individual may shape his or her perception of perceived health threat or protections (Brownlee, Leventhal, & Leventhal, 2000; Leventhal et al., 1997). Supporting the contributions of sensory effects on product perception are two studies finding that advertising information on the deceptiveness about the sensory effects of smoking light cigarettes had the greatest impact on changing beliefs about safety and toxin delivery of light and ultralight cigarettes, intent to quit, and preference for cigarettes (Shiffman, Burton et al., 2001; Shiffman, Pillitteri et al., 2001a). It is necessary then, in evaluating consumer perceptions of a PREP, to consider how the product presentation influences sensory and reinforcing qualities of the PREP and how the sensory experiences from the PREP influence perception of health benefits.

Measures

The assessment of consumer perceptions and assurance of adequate interpretation of information requires exposure to several methods of communication—print ads or packages, Internet, radio advertisements, retail store advertisements, and product placement. Participants in consumer testing should be asked both general questions about the product and specific questions about product presentation characteristics. In other words, how the individual is interpreting the information in the advertisement, packaging, and labeling should be assessed. More specifically, measures should include assessment of comprehension, beliefs, and behavioral intention (Bates, McNeill, Jarvis, & Gray, 1999; Cohen, 1996; Etter et al., 2003; Gilpin et al., 2002; Hamilton et al., 2004; L. Kozlowski et al., 1998; Pollay & Dewhirst, 2002; Shiffman, Burton et al., 2001; Shiffman et al., 2004; Shiffman, Pillitteri et al., 2001a, 2001b). Comprehension items include inquiring about whether harmful toxins have been reduced, to what extent, and the meaning of the reduction of specific toxins; whether risk for disease has been reduced, which diseases have been reduced, and to what extent; the potential addiction of the PREP and

whether the PREP affects motivation to quit and ease of cessation; and whether the product benefits the health of others (e.g., reduces second-hand smoke exposure to toxins). Belief items include asking if the participants actually believe that using the PREP is safer, healthier, or leads to beneficial health effects and the type and degree of these benefits; if using the PREP will make it easier for them to quit; if using the PREP is just as good as quitting; if using the PREP would lead to less harm or health benefits to others; and if using the PREP would allay the concerns of others over their tobacco use behaviors. Comprehension and belief questions can be asked to provide absolute or relative (compared with conventional marketed products such as regular, light, and ultralight cigarettes or compared with not smoking) ratings of safety, delivery of toxins, and other characteristics of the PREP. Behavioral intention items include measurement of the extent to which individuals are interested in trying the product, changes in their interest in quitting when the product becomes available, and if they would consider switching to the PREP from their own brand of cigarettes. Open-ended questions can also be asked, including "What are your thoughts and feelings about the PREP?", "What can you expect from this product?", and "How would you use this product?"

Finally, assessments can be conducted on the credibility of the message, who the participants believe the source of the message to be, and whether they believe that the government has given the product the stamp of approval.

Postmarketing surveillance and evaluation

Issues in postmarketing surveillance and evaluation of PREPs

Although premarket testing can screen out anticipated problems before a product goes to market, unanticipated developments are likely. A postmarketing system of surveillance and evaluation is needed to assess the actual population impact of the marketing of PREPs on the perceptions, behaviors, and health outcomes of relevant populations. The main concern in the tobacco control community is whether the marketing of PREPs will slow the decline in the use of conventional cigarettes and other tobacco products that has been observed since the 1950s (Giovino, 2002; Husten, Jackson, & Lee, 2004; Joseph, Hennrikus, Thoele, Krueger, & Hatsukami, 2004; E. G. Martin, Warner, & Lantz, 2004; Mendez & Warner, 2004; Warner & Martin, 2003). The ultimate question is whether tobacco-attributable morbidity and mortality will eventually be lower than they would have been had PREPs not been introduced into the market (Ferrence, Slade, Room, & Pope, 2000; Hatsukami et al., 2002). This is an extremely difficult question to resolve, partly because any conclusions drawn will rely on assumptions made when making projections. Nevertheless, a comprehensive postmarketing surveillance and evaluation system that provides information on product characteristics, environmental influences, relevant perceptions and behaviors, biological exposures, and health outcomes (Figure 2) for both the United States and comparison countries will maximize feedback potential and permit corrective action as early in the process as possible.

The ideal postmarketing surveillance and evaluation system will incorporate principles of public health surveillance. These principles include the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health. Data disseminated by a public health surveillance system can be used for immediate public health action, program planning and evaluation, and formulation of research hypotheses (Centers for Disease Control and Prevention, 2001a).

Many attributes are used to evaluate surveillance systems, including representativeness, timeliness, simplicity, flexibility, and sensitivity (Centers for Disease

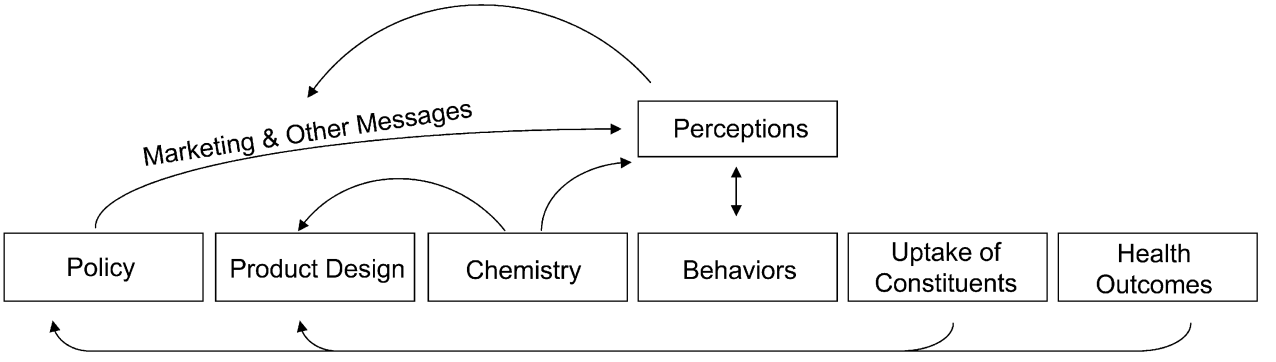

Figure 2. Elasticity/compensation model of policies influencing product design and chemistry and user behaviors, perceptions, uptake of constituents, and disease risk.

Control and Prevention, 2001a). A representative system will accurately describe the distribution of health events (e.g., behavior, disease) in a population by person, place, and time. A timely system minimizes the delay between the occurrence of an event and the collection of data and reporting of findings. The simplicity of a given system is a function of its structure and ease of operation. Ideally, a surveillance system will be as simple as possible and still meet all of its objectives. A flexible system can economically adapt to changing operating conditions or information needs. Sensitivity refers to the ability of a system to detect relevant health behaviors, perceptions, diseases, and conditions of interest.

Surveillance systems can be either passive or active. Passive systems generally collect information on health events reported by interested health professionals and others. Two examples of passive systems are the reporting of adverse drug events to the FDA via the Medwatch program and the Substance Abuse and Mental Health Services Administration via the Drug Abuse Warning Network (Arfken & Cicero, 2003; FDA, 2004; Substance Abuse and Mental Health Services Administration, 2004). Active surveillance systems are more resource intensive and for this application would involve data collection on the PREPs themselves; the people who use them, as well as potential users; the ways the products are marketed; and the environment in which they are marketed. Systems would need to monitor both pro- and anti-tobacco influences. An active surveillance system is urgently needed to properly assess the impact of PREPs at the population level (Stratton et al., 2001). Numerous surveys at the federal and state levels monitor tobacco-related variables, but their purposes differ, and none is dedicated to assessing the population impact of PREPs on tobacco use perceptions and behaviors and tobacco-attributable morbidity and mortality.

Key topics that need to be addressed include initiation and cessation rates, tobacco consumption patterns, and patterns of PREP use (e.g., whether they facilitate initiation to conventional cigarettes and whether they facilitate quitting). It is vital that we understand the characteristics of persons who adopt PREP use, for health outcomes will be influenced by factors such as age, duration of previous use of conventional tobacco products, and exposure to environmental tobacco smoke. We will need to know if current and potential users are adequately informed about the relative harms posed by various products (Cummings et al., 2004). Such assessments will be enhanced with adequate product surveillance (including the characteristics of the products themselves and how they are experienced by users), marketing surveillance (e.g., of both words and images), and environmental surveillance (of both pro- and anti-tobacco forces). Given that most, if not all, PREPs will be marketed at the national level and because regulation would most likely be implemented at the federal level, multinational comparisons will be needed to monitor PREP use, PREP users, and their environment.

Methods

Table 7 describes some of the methodological challenges associated with postmarketing surveillance. Table 8 details existing and new measures and methods needed for postmarketing surveillance. The current system of data collection on tobacco is complex and sophisticated. However, the integration and coordination needed to prevent unanticipated deleterious consequences of the marketing of PREPs are lacking.

Currently, information on the consumption of various tobacco products is available from the U.S. Department of Agriculture (2004) and from Federal Trade Commission (FTC) reports of aggregated data on the characteristics (e.g., length, menthol status) of cigarettes consumed in the United States (FTC, 2003a). However, none of this information is available on a variety-specific basis (i.e., at the sub-brand level), nor by geographic locale. Use of pharmaceutical aids to quitting is reported by a proprietary firm and used by researchers to understand patterns of quitting (Centers for Disease Control and Prevention, 2000).

No useful surveillance is conducted on the design of products, constituents in their tobacco, added ingredients, and the smoke they generate (Stratton et al., 2001). Until 1998, the FTC (2000) reported tar, nicotine, and carbon monoxide (TNCO) levels in the smoke of domestic varieties of cigarettes, but the testing system was not indicative of actual human smoking practices (National Cancer Institute, 2001). TNCO and additional constituents need to be measured in a manner that reflects how cigarettes are actually smoked.

Tobacco product marketing also is monitored inadequately. The FTC collects brand-specific marketing data for cigarettes and smokeless tobacco but

Table 7. General methodological issues in postmarketing surveillance.

Data integration
Testing products under conditions that mimic actual human topographies
Validity of self-reports of historical events (e.g., age at first use and first daily use, timing of use of various products and dose administered when using)
Declining response rates of telephone surveys in the United States
Finding biomarkers that predict disease outcomes
Comparability of American Cancer Society Cancer Prevention Study (CPS)-III to CPS-I and CPS-II
Adequate comparison groups (i.e., from other countries)

Table 8. Existing and new measures and methods for postmarketing surveillance.

Existing resources
Product consumption: U.S. Department of Agriculture, Federal Trade Commission reports
Tobacco product marketing: Federal Trade Commission; surveys on exposure to media messages such as the Youth Tobacco Survey, Monitoring the Future, Legacy Media Tracking Survey, and various state-based evaluations
Individual product use: Monitoring the Future, National Health Interview Survey, National Survey on Drug Use and Health, Tobacco Use Supplement to Current Population Survey
Health outcomes: Third National Health and Nutrition Examination Survey, American Cancer Society Cancer Prevention Survey I and II, national vital statistics system, cancer registries, hospital discharge survey, medical expenditure surveys
New methods and surveys that need developing
Product consumption: potential reduced exposure products (PREPs) and geographic locale of product consumption
Surveillance of tobacco product design, constituents of tobacco products, and actual human exposure
Surveillance of tobacco product marketing including television and magazine advertising, newspaper stories and editorials, television coverage and commentaries, sponsorship and promotions, text and images across various media outlets, product packaging and prices
Surveillance on antitobacco activities including cessation, school programming, ordinances, and policies
Surveillance on individual product use including a population-based surveillance that specifically measures who, what, when, and where of PREP use and how the products are perceived
Addition of biomarkers to existing surveys on health outcomes

can legally report only aggregated national marketing expenditures (FTC, 2003a, 2003b). Self-reported exposures to various media messages are obtained in several surveys (Bachman, Johnston, & O'Malley, 2001; Centers for Disease Control and Prevention, 2001b; Farrelly et al., 2002). Proprietary data on television and magazine advertising can be purchased, as can data on newspaper stories and prices of various products (Clegg Smith et al., 2002; Stillman, Cronin, Evans, & Ulasevich, 2001; Szczypka, Emery, Wakefield, & Chaloupka, 2003). The state of California supports activities that monitor sponsorship and promotions (Cruz & Jouharzadeh, 2003). Resources to expand these efforts are needed. Further monitoring needs involve work on text and images in newspapers and magazine advertising; direct mail marketing; retail environment advertisement and promotions; placement and portrayals of products in movies and on television; Internet messages (e.g., marketing, sales, chat rooms, corporate Web sites); product packaging; newspaper and magazine articles, editorials, and op-ed pieces; television stories and commentaries; tobacco industry anti-tobacco efforts; and tobacco industry efforts to counter tobacco control activities (G. A. Giovino et al., unpublished manuscript).

Monitoring of anti-tobacco activities will permit assessment of factors that reduce prevalence. For example, both media advocacy and paid media should be monitored, as should the availability of cessation aides, school programming, and the strength of smoke-free airs laws, ordinances, and policies (Stratton et al., 2001; Wakefield & Chaloupka, 1998).

Individual tobacco product use is assessed in numerous national surveys (Stratton et al., 2001). Although each survey is necessary for various components of public health surveillance, none of them collects all of the information needed to properly assess possible risks and benefits associated with the introduction of PREPs; further, all are cross-sectional in design (Stratton et al., 2001). Only limited information on perceptions regarding PREPs and other tobacco products (e.g., optimism bias) and on comorbidities is available from representative surveys. Therefore, a population-based surveillance system with adequate measures of variables needed to assess possible risks and benefits of PREP use is needed. This system would ideally be longitudinal in nature and provide comparisons with other English-speaking countries in the same stage of the tobacco use epidemic (e.g., Canada, United Kingdom, Australia) (Lopez, Collishaw, & Piha, 1994), similar in design to the International Tobacco Control Policy Evaluation Survey (Fong, Borland, Hastings, & Cummings, 2004). The declining response rates in telephone surveys conducted in the United States will need to be adequately accounted for and appropriate incentives provided to maximize participation rates.

Biological markers that are predictive of disease outcome need to be identified, perhaps by conducting follow-up studies of serum and urine from the Third National Health and Nutrition Examination Survey (conducted from 1988 to 1994; Stratton et al., 2001). The American Cancer Society's Cancer Prevention Study (CPS)-I and CPS-II have made enormous contributions to tobacco epidemiology, partly because of comparisons made between the two cohorts (Thun et al., 1997; Thun & Heath, 1997). The voluntary nature of this study facilitated the enrollment of large numbers of current, former, and never-smokers, yielding rates for a large number of diseases for each category of smokers. A third CPS wave is being planned. The recruitment and retention of smokers, particularly as smoking becomes proportionately more prevalent in lower socioeconomic groups (Husten et al., 2004), is a challenge for future cohort studies (Michael Thun, personal communication, June 28, 2004). A partnership between the federal government and the private sector may help solve this dilemma.

Sources of data on disease outcomes include the national vital statistics system, cancer registries, hospital discharge surveys, medical expenditures surveys, and the ACS Cancer Prevention Studies (Stratton et al., 2001). To facilitate reporting by consumers, a telephone number for reporting relevant symptoms (e.g., sore throat, coughing, irritation) could be placed on every package. These systems can be used to help calculate the population impact of PREPs.

Measures

Product design features can be assessed using visual inspection (e.g., for cigarette diameter and length, tobacco weight, filter type and weight, structural materials); optical scanning to assess blending; and machines for assessing characteristics such as ventilation, pressure drop, and paper porosity. Appropriate chemical analyses should be conducted on the products themselves and the smoke generated by those that are burned (or heated). Candidates for surveillance include TNCO, free nicotine, polycyclic aromatic hydrocarbons, and tobacco-specific nitrosamines. Ideally, variety-specific parameters for smoking-machine settings that mimic consumer behaviors should be determined and used in assessments.

Representative surveys of youth and adults should measure use (e.g., daily dose, brand history, topography); dependence; age and incidence of initiation and cessation; susceptibility to start; motivations and intentions to quit; perceptions of the risks and benefits associated with tobacco products and cessation treatments; awareness, use, and perceptions of and interest in PREPs; media exposures (e.g., cigarette advertising and promotions, anti-tobacco messages); home or work smoking bans; support and advice for quitting; health beliefs; alcohol and illicit drug use; mental health indicators; perceived stress; physical health; other risk factors; demographics; and biological fluids for biomarkers and genetic testing. One methodological concern raised in all epidemiological studies is the validity of documentation of exposure. Notably, age at initiation and the duration and dosage of each tobacco product used would need to be assessed accurately. Biomarkers should be measured as indicated by the science. For example, cancer biomarkers would include NNAL and NNAL-Gluc in urine and aromatic amine-Hb adducts (Hatsukami, Benowitz, Rennard, Oncken, & Hecht, in press). In sum, the proposed comprehensive surveillance system would do much more than monitor PREPs. It would also assess whether introduction of PREPs had any influence on smoking attitudes and behaviors in general.

Research will be needed to develop, test, and validate various environmental measures and indices of both tobacco promotional and tobacco control activities (e.g., state and local programs, media) across various communication channels (G. A. Giovino et al., unpublished manuscript). A coordinated system will be required to assess the nature, scope, intensity, and effectiveness of these strategies (G. A. Giovino et al., unpublished manuscript).

Measures of health status would include symptoms and syndromes (e.g., contact dermatitis among users of Eclipse), biological function, years of potential life lost, and health-related quality of life (Stratton et al., 2001).

Recommendations and conclusions

The recommendations put forward by this group are similar to those proposed by the World Health Organization Scientific Advisory Committee on Tobacco Regulation (2003) in a document entitled "Statement of Principles Guiding the Evaluation of New or Modified Tobacco Products." In the conclusions of that document, one of the principles stated, "Regulatory oversight of cigarette and cigarette-like products should include examination of at least five separate aspects of the new products: Physical chemical characteristics of the tobacco and tobacco smoke, uptake of toxicants (both by smokers and by non-smokers), toxicity, addiction potential, and disease risk (across a spectrum of disease states)." Similar aspects were proposed for the evaluation of smokeless tobacco products. These principles described the need for adequate scientific evidence to support the claims made on these products, with an independent regulatory agency determining the validity of the claims. Demonstration of reduction of smoke emissions or reduced uptake in toxins was not considered sufficient for a claim or implication that the product reduces toxicity or harm. Of final note, the principles described a need for postmarketing surveillance to monitor and further assess consumer perceptions of claims made on these PREPs.

Another document was developed by the World Health Organization Study Group on Tobacco Product Regulation (2003), formerly the Scientific Advisory Committee on Tobacco Regulation, entitled "Guiding Principles for the Development of Tobacco Product Research and Testing Capacity and Proposed Protocols for the Initiation of Tobacco Product Testing." The purpose of this document was to promulgate principles to implement articles of the WHO Framework Convention on Tobacco Control (FCTC) that are related to tobacco products testing. This document proposed guidelines for testing and measurement and for the regulation of the contents and emissions from tobacco products (Article 9 of FCTC), for the regulation of tobacco disclosures to both governmental authorities and the public about

the contents and emissions of tobacco products (Article 10), and for the packaging and labeling of tobacco products (Article 11), including assurance that packaging and labeling do not promote false or misleading impressions about the health effects or harmfulness of the products. The principles called for empirically verified standardized testing protocols and methods to assess product performance. It also emphasized that these methods must remain flexible and can be modified by the evolving research in product testing, by ongoing changes in tobacco products, and by assessing the impact of marketing messages and health effects of these products on populations. Further, the document described specific principles for testing and research as well as specific testing protocols particularly as they relate to measuring tobacco ingredients, emissions, and product design features.

The recommendations made by the panel of experts for this paper as well as the World Health Organization recommendations emphasize the importance of an infrastructure that allows for an integrated, comprehensive, and systematic evaluation of tobacco products, both conventional and PREPs (Table 9). This system would include a product registry, which would have necessary information on all nicotine-delivery products on the market. Optimal coordination of data collection and analyses will be facilitated by the creation and long-term support of a transdisciplinary research network that would include experts from both the public and private sectors (G. A. Giovino et al., unpublished manuscript). A comprehensive premarket evaluation program will likely require multiple testing sites, with each site using a valid, reliable, and uniform or coordinated set of measures (with additional measures as needed or desired).

The network also could facilitate the development and implementation of a multilevel cohort design dedicated to assessing the impact of PREPs on perceptions of these products and tobacco use behaviors. Such a study could involve multiple country controls and be based on a theory-driven mediational model to test hypotheses and answer research questions about the effects of product innovations and regulatory policies that influence the design of tobacco products (Fong, Borland, Hastings, & Cummings, 2004).

Table 9. Infrastructure needs.

Product registry
Transdisciplinary research network of independent researchers
Multisite clinical and premarketing testing centers
Valid, reliable, and uniform or coordinated test measures across sites
Linked survey data
Multilevel cohort designs assessing potential reduced exposure products (PREPs)
Rapid-response surveillance
Independent monitoring of data within a regulatory framework
Independent panel of expert reviewers

In addition to a set of planned evaluation and surveillance activities, the system would have the capacity to conduct rapid-response surveillance. Such a capability would permit flexible response to emerging developments that could limit possible untoward effects of the marketing and use of PREPs (G. A. Giovino et al., unpublished manuscript). Legislation that would provide marketing data disaggregated by variety and geographic locale would facilitate analyses of marketing influences. The research network should have access to a core group of methodological expertise to inform the data collection and analysis work (G. A. Giovino et al., unpublished manuscript).

Funding for this initiative could come from a modest increase in the federal excise tax. Given that about 20 billion packs of cigarettes were sold in the United States in 2003, a 1-cent per pack increase would raise $200 million. Approximately one-half of that amount could be dedicated to surveillance and evaluation, with the other half used for research on reducing tobacco use and associated harms. Furthermore, the information on product characteristics and industry marketing would be provided by the industry, with enough funds made available to have an independent panel of expert scientists verify industry reports. The oversight of this infrastructure would best be served by an independent regulatory body, such as the FDA. However, should FDA regulation over tobacco products not occur, other governmental agencies can provide appropriate forums for independently assessing these products and verifying the industry reports. With the growing introduction of PREPs, it is imperative that research and action be undertaken now to ensure that the public will be protected and to avoid a potential public heath disaster. But more important, to have a significant impact on public health, all tobacco products should be regulated and undergo comprehensive evaluation.

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References

Arfken, C. L., & Cicero, T. J. (2003). Postmarketing surveillance for drug abuse. *Drug and Alcohol Dependence*, *70*(Suppl. 3), S97–S105.

Bachman, J. G., Johnston, L. D., & O'Malley, P. M. (2001). Monitoring the Future: Questionnaire responses from the nation's

high school seniors. Ann Arbor, MI: Survey Research Center, Institute for Social Research.

Bates, C., McNeill, A., Jarvis, M., & Gray, N. (1999). The future of tobacco product regulation and labeling in Europe: Implications for the forthcoming European Union directive. *Tobacco Control*, *8*, 225–235.

Biener, L., & Abrams, D. (1991). The Contemplation Ladder: Validation of a measure of readiness to consider smoking cessation. *Health Psychology*, *10*, 360–365.

Bolliger, C. T., Zellweger, J.-P., Danielsson, T., van Biljon, X., Robidou, A., Westin, A., Perruchoud, A. P., & Sawe, U. (2000). Smoking reduction with oral nicotine inhalers: Double blind, randomised clinical trial of efficacy and safety. *British Medical Journal*, *321*, 329–333.

Breland, A. B., Acosta, M. C., & Eissenberg, T. (2003). Tobacco specific nitrosamines and potential reduced exposure products for smokers: A preliminary evaluation of Advance. *Tobacco Control*, *12*, 317–321.

Breland, A. B., Buchhalter, A. R., Evans, S. E., & Eissenberg, T. (2002). Evaluating acute effects of potential reduced-exposure products for smokers: Clinical laboratory methodology. *Nicotine & Tobacco Research*, *4*(Suppl. 2), 131–140.

Breland, A. B., Evans, S. E., Buchhalter, A. R., & Eissenberg, T. (2002). Acute effects of Advance: A potential reduced exposure product for smokers. *Tobacco Control*, *11*, 376–378.

Brownlee, S., Leventhal, E. A., & Leventhal, H. (2000). Regulation, self regulation and regulation of the self in maintaining physical health. In M. Boekartz, P. R. Pintrich & M. Zeidner (Eds.), *Handbook of self-regulation (pp. 369–416). San Diego: Academic Press.*

Buchhalter, A. R., Schrinel, L., & Eissenberg, T. (2001). Withdrawal-suppressing effects of a novel smoking system: Comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine & Tobacco Research*, *3*, 111–118.

Burns, D. (1997). *Estimating the benefits of a risk reduction strategy*. Poster presented at the Society for Research on Nicotine and Tobacco third annual scientific conference, Nashville, TN.

Caraballo, R. S., Giovino, G. A., Pechacek, T. F., Mowery, P. D., & Richter, P. A. (1998). Racial and ethnic differences in serum cotinine levels of cigarette smokers: Third National Health and Nutrition Examination Survey, 1988–1991. *The Journal of the American Medical Association*, *280*, 135–139.

Carpenter, M., Hughes, J., & Keely, J. (2003). Effect of smoking reduction on later cessation: A pilot experimental study. *Nicotine & Tobacco Research*, *5*, 155–162.

Centers for Disease Control and Prevention. (2000). Use of FDA-approved pharmacologic treatments for tobacco dependence in the United States: 1984–1998. *Morbidity and Mortality Weekly Report*, *49*, 665–669.

Centers for Disease Control and Prevention. (2001a). Updated guidelines for evaluating public health surveillance systems: Recommendations from the guidelines working group. *Morbidity and Mortality Weekly Report*, *50*(RR-13), 1–35.

Centers for Disease Control and Prevention. (2001b). Youth tobacco surveillance—United States, 2000. *Morbidity and Mortality Weekly Report*, *50*(SS-4), 1–84.

Clegg Smith, K., Wakefield, M., Siebel, C., Szczypka, G., Slater, S., Terry-McElrath, Y., Emery, S., & Chaloupka, F. J. (2002). *Coding the news: The development of a methodological framework for coding and analyzing newspaper coverage of tobacco issues*. Retrieved June 29, 2004, from www.impacteen.org/generalarea_PDFs/Newsmethodspaper_smithMAY2002.pdf.

Cohen, J. (1996). Smokers' knowledge and understanding of advertised tar numbers: Health policy implications. *American Journal of Public Health*, *86*, 18–24.

Colby, S. M., Tiffany, S. T., Shiffman, S., & Niaura, R. (2000). Measuring nicotine dependence among youth: A review of available approaches and instruments. *Drug and Alcohol Dependence*, *59*(Suppl. 1), S23–S39.

Connett, J. E., Murray, R. P., Buist, A. S., Wise, R. A., Bailey, W. C., Lindgren, P. G., Owens, G. R.; Lung Health Study Research Group. (2003). Changes in smoking status affect women more than men: Results of the Lung Health Study. *American Journal of Epidemiology*, *157*, 973–979.

Cruz, T., & Jouharzadeh, P. (2003). *Sampling, coupons, and other free stuff: What is the industry up to?* Presented at the 2003 National Conference on Tobacco or Health, Boston, MA.

Cummings, K. M., Hyland, A., Giovino, G. A., Hastrup, J., Bauer, J., & Bansal, M. (2004). Are smokers adequately informed about the health risks of smoking and medicinal nicotine. *Nicotine & Tobacco Research*, *6*(Suppl. 3), 333–340.

Doll, R., & Peto, R. (1978). Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and lifelong non-smokers. *Journal of Epidemiology and Community Health*, *32*, 303–313.

Eclipse Expert Panel. (2000). A safer cigarette? A comparative study. A consensus report. *Inhalation Toxicology*, *12*(Suppl. 5), 1–48.

Emont, S. (1996). Racial differences in the impact of smoking-attributable disease on health care costs in Indiana. *Indiana Medicine*, *89*, 161–164.

Etter, J., Kozlowski, L. T., & Perneger, T. V. (2003). What smokers believe about light and ultralight cigarettes. *Preventive Medicine*, *36*, 92–98.

Etter, J., Laszlo, E., Zellweger, J. P., Perrot, C., & Perneger, T. V. (2002). Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: A randomized trial. *Journal of Clinical Psychopharmacology*, *22*, 487–495.

Etter, J., Paernegger, T., & Ronchi, A. (1997). Distributions of smokers by stage: International comparison and association with smoking prevalence. *Preventive Medicine*, *26*, 580–585.

Fagerström, K. O. (2000). Nicotine-replacement therapies. In R. Ferrence, J. Slade, R. Room & M. Pope (Eds.), *Nicotine and public health* (pp. 199–207). Washington, DC: American Public Health Association.

Fagerström, K. O., Hughes, J., & Callas, P. (2002). Long term effects of the Eclipse cigarette substitute and the nicotine inhaler in smokers not interested in quitting. *Nicotine & Tobacco Research*, *4*(Suppl.), S141–S145.

Fagerström, K. O., Tejding, R., Westin, A., & Lunell, E. (1997). Aiding reduction of smoking with nicotine replacement medications: Hope for the recalcitrant smoker? *Tobacco Control*, *6*, 311–316.

Farrelly, M. C., Healton, C. G., Davis, K. C., Messeri, P., Hersey, J. C., & Haviland, M. L. (2002). Getting to the truth: Evaluating national tobacco countermarketing campaigns. *American Journal of Public Health*, *92*, 901–907.

Federal Trade Commission. (2000). *"Tar," nicotine, and carbon monoxide of the smoke of 1,294 varieties of domestic cigarettes for the year 1998*. Washington, DC: Author.

Federal Trade Commission. (2003a). *Federal Trade Commission cigarette report for 2001*. Washington, DC: Author.

Federal Trade Commission. (2003b). *Federal Trade Commission smokeless tobacco report for the years 2000 and 2001*. Washington, DC: Author.

Ferrence, R., Slade, J., Room, R., & Pope, M. (Eds.). (2000). *Nicotine and public health*. Washington, DC: American Public Health Association.

Flanders, W. D., Lally, C. A., Zhu, B. P., Henley, S. J., & Thun, M. J. (2003). Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: Results from Cancer Prevention Study II. *Cancer Research*, *63*, 6556–6562.

Fong, G. T., Borland, R., Hastings, G., & Cummings, K. M. (2004, February). *Evaluating and building an evidence base for the Framework Convention on Tobacco Control: Recent findings from the International Tobacco Control Policy Evaluation Survey*. Paper presented at the symposium presented at the Society for Research on Nicotine and Tobacco annual meeting, Scottsdale, AZ.

Food and Drug Administration. (2004). *Medwatch*. Retrieved June 28, 2004, from www.fda.gov/medwatch.

Gilpin, E. A., Emery, S., White, M. M., & Pierce, J. P. (2002). Does tobacco industry marketing of 'light' cigarettes give smokers a rationale for postponing quitting? *Nicotine & Tobacco Research*, *4*(Suppl. 4), S147–S155.

Giovino, G. A. (2002). Epidemiology of tobacco use in the United States. *Oncogene*, *21*, 7326–7340.

Giovino, G. A., Tomar, S., Reddy, M., Peddicord, J., Zhu, R.-P., Escobedo, L., & Eriksen, M. P. (1996). Attitudes, knowledge, and beliefs about low-yield cigarettes among adolescent and adults. In *The FTC cigarette test method for determining tar, nicotine, and carbon monoxide yields of U.S. cigarettes. Report of the NCI Expert Committee*. (Smoking and Tobacco Control Monograph No. 7; NIH Publication No. 96-4028; pp. 39–57). Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute.

Griffiths, R. R., Bigelow, G. E., & Ator, N. A. (2003). Principles of initial experimental drug abuse liability assessment in humans. *Drug and Alcohol Dependence*, *70*, S41–S54.

Hamilton, W. L., diStefano Norton, G., Ouellette, T. K., Rhodes, W. M., Kling, R., & Connolly, G. N. (2004). Smokers' responses to advertisements for regular and light cigarettes and potential reduced-exposure tobacco products. *Nicotine & Tobacco Research*, *6*(Suppl. 3), S353–S362.

Hatsukami, D., Benowitz, N. L., Rennard, S. I., Oncken, C., & Hecht, S. S. (in press). Biomarkers to assess potential reduced exposure tobacco products. *Nicotine & Tobacco Research*.

Hatsukami, D., Henningfield, J., & Kotlyar, M. (2004). Harm reduction approaches to reducing tobacco-related mortality. *Annual Review of Public Health*, *25*, 1–19.

Hatsukami, D., Lemmonds, C., & Tomar, S. (2004). Smokeless tobacco use: Harm reduction or induction approach? *Preventive Medicine*, *38*, 309–317.

Hatsukami, D., Lemmonds, C. A., Zhang, Y., Murphy, S. E., Le, C., Carmella, S. G., & Hecht, S. S. (2004). Evaluation of carcinogen exposure in people who used "reduced exposure" tobacco products. *Journal of the National Cancer Institute*, *96*, 844–852.

Hatsukami, D., Slade, J., Benowitz, N., Giovino, G., Gritz, E., Leischow, S., & Warner, K. (2002). Reducing tobacco harm: Research challenges and issues. *Nicotine & Tobacco Research*, *4*(Suppl. 2), S89–S101.

Hecht, S. S., Murphy, S. E., Carmella, S. G., Zimmerman, C. L., Losey, L., Kramarczuk, I., Roe, M. R., Puumala, S. S., Li, Y. S., Le, C. T., Jensen, J., & Hatsukami, D. K. (2004). Effects of reduced cigarette smoking on uptake of a tobacco-specific lung carcinogen. *Journal of the National Cancer Institute*, *96*, 107–115.

Houtsmuller, E. J., Fant, R. V., Eissenberg, T. E., Henningfield, J. E., & Stitzer, M. L. (2002). Flavor improvement does not increase abuse liability of nicotine chewing gum. *Pharmacology, Biochemistry, and Behavior*, *72*, 559–568.

Houtsmuller, E. J., Henningfield, J. E., & Stitzer, M. L. (2003). Subjective effects of the nicotine lozenge: Assessment of abuse liability. *Psychopharmacology*, *167*, 20–27.

Hughes, J. R., Gust, S. W., Keenan, R. M., Fenwick, J. W., Skoog, K., & Higgins, S. T. (1991). Long-term use of nicotine vs. placebo gum. *Archives of General Medicine*, *151*, 1993–1998.

Hurt, R. D., Croghan, G. A., Wolter, T. D., Croghan, I. T., Offord, K. P., Williams, G. M., Djordjevic, M. V., Richie, J. P., Jr., & Jeffrey, A. M. (2000). Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine & Tobacco Research*, *2*, 327–336.

Husten, C., Jackson, K., & Lee, C. (2004). Cigarette smoking among adults—United States, 2002. *Morbidity and Mortality Weekly Report*, *53*, 427–431.

Jasinski, D. R. (1977). Assessment of the abuse potentiality of morphine-like drugs (methods used in man). In W. R. Martin (Ed.), *Drug addiction I. Morphine, sedative-hypnotic and alcohol dependence. Handbook of experimental pharmacology* (Vol. 45, pp. 197–258), Heidelberg: Springer.

Joseph, A. M., Hennrikus, D., Thoele, M. J., Krueger, R., & Hatsukami, D. (2004). Tobacco control leaders' perceptions of harm reduction. *Tobacco Control*, *13*, 108–113.

Keely, J. P., Hughes, J. R., & Hirsch, T. S. (2001). *Effects of a cigarette substitute on ongoing smoking*. Poster presented at the Society for Research on Nicotine and Tobacco annual meeting, Seattle, WA.

Kotlyar, M., Jensen, J., Li, S., & Hatsukami, D. (2004). *Effect of smoking reduction on cardiovascular biomarkers and subjective measures*. Poster presented at the Society for Research on Nicotine and Tobacco Annual Meeting, Scottsdale, AZ.

Kozlowski, L., Goldberg, M., Yost, B., White, E., Sweeney, C., & Pillitteri, J. (1998). Smokers' misperceptions of light and ultra-light cigarettes may keep them smoking. *American Journal of Preventive Medicine*, *15*, 78–79.

Kozlowski, L. T., Strasser, A. A., Giovino, G. A., Erickson, P. A., & Terza, J. V. (2001). Applying the risk/use equilibrium: Use medicinal nicotine now for harm reduction. *Tobacco Control*, *10*, 201–203.

Lee, E., Malson, J., Moolchan, E., & Pickworth, W. (2004). Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. *Nicotine & Tobacco Research*, *6*, 95–102.

Lemmonds, C., Mooney, M., Reich, B., & Hatsukami, D. (2004). Characteristics of cigarette smokers seeking treatment for cessation vs. reduction. *Addictive Behaviors*, *29*, 357–364.

Lerman, C., & Niaura, R. (2002). Applying genetic approaches to the treatment of nicotine dependence. *Oncogene*, *21*, 7412–7420.

Leventhal, H., Benyamini, Y., Brownlee, S., Diefenbach, M., Leventhal, E., Patrick-Miller, L., & Robitaille, C. (1997). Illness representations: Theoretical foundation. In K. J. Petrie & J. A. Weinman (Eds.), *Perceptions of health and illness: Current research and application* (pp.19–45). Amsterdam, The Netherlands: Harwood Academic Publishers.

Levy, D. T., Mumford, E. A., Cummings, K. M., Gilpin, E. A., Giovino, G., Hyland, A., Sweanor, D., & Warner, K. E. (2004). The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: Estimates of a panel of experts. *Cancer Epidemiology, Biomarkers & Prevention*, *13*, 1–8.

Lopez, A. D., Collishaw, N. E., & Piha, T. (1994). A descriptive model of the cigarette epidemic in developed countries. *Tobacco Control*, *3*, 242–247.

Martin, E. G., Warner, K. E., & Lantz, P. M. (2004). Tobacco harm reduction: What do the experts think? *Tobacco Control*, *13*, 123–129.

Martin, W. R., Sloan, J. W., Sapiro, J. D., & Jasinski, D. R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. *Clinical Pharmacology and Therapeutics*, *12*, 245–258.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1992). *Profile of Mood States (manual)* (Revised ed.). San Diego: Educational and Industrial Testing Service.

Melikian, A. A., Djordjevic, M., Hosey, J., Zhang, J., Chen, S., Muscat, J. E., Zang, E., Stellman, S. D., & Richie, J. P. (2004). *Influence of gender on delivered toxins from cigarette smoke and metabolism*. Poster presented at the Society for Research on Nicotine and Tobacco annual meeting, Scottsdale, AZ.

Mendez, D., & Warner, K. E. (2004). Adult cigarette smoking prevalence: Declining as expected (not as desired). *American Journal of Public Health*, *94*, 251–252.

National Cancer Institute. (1997). *Changes in cigarette-related disease risk and their implication for prevention and control*. (Smoking and Tobacco Control Monograph No. 8; NIH Publication No. 97-4213). Rockville, MD: National Institutes of Health.

National Cancer Institute. (2001). *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine*. (Smoking and Tobacco Control Monograph No. 13; NIH Publication No. 02-5074). Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Pérez-Stable, E., Herrera, B., Jacob, P., III., & Benowitz, N. (1998). Nicotine metabolism and intake in black and white smokers. *The Journal of the American Medical Association*, *280*, 152–156.

Perkins, K. A. (2001). Smoking cessation in women. Special considerations. *CNS Drugs*, *15*, 391–411.

Petty, R., Haugtvedt, C., & Smith, S. C., Jr. (1995). Elaboration as a determinant of attitude strength: Creating attitudes that are persistent, resistant, and predictive of behavior. In R. E. Petty & J. A. Krosnick (Eds.), *Attitude strength: Antecedents and consequences* (pp. 93–130). Mahwah, NJ: Lawrence Erlbaum.

Petty, R., & Wegener, D. (1999). The elaboration likelihood model: Current status and controversies. In Y. Trope & S. Chaiken (Eds.), *Dual process theories in social psychology* (pp. 37–72). New York: Guilford.

Pickworth, W. B., Fant, R. V., Nelson, R. A., Rohrer, M. S., & Henningfield, J. E. (1999). Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine & Tobacco Research*, *1*, 357–364.

Pollay, R. W., & Dewhirst, T. (2002). The dark side of marketing seemingly "light" cigarettes: Successful images and failed fact. *Tobacco Control*, *11*(Suppl. 1), i18–i31.

Pollay, R. W., & Dewhirst, T. (2003). A Premiere example of the illusion of harm reduction cigarettes in the 1990s. *Tobacco Control*, *12*, 322–332.

Prochaska, J. O., DiClemente, C. C., & Norcross, J. C. (1992). In search of how people change: Applications to addictive behaviors. *American Psychologist*, *47*, 1102–1114.

Prochaska, J. O., & Goldstein, M. G. (1991). Process of smoking cessation. Implications for clinicians. *Clinics in Chest Medicine*, *12*, 727–735.

Rennard, S. I., Umino, T., Millatmal, T., Daughton, D. M., Manouilova, L. S., Ullrich, F. A., Patil, K. D., Romberger, D. J., Floreani, A. A., & Anderson, J. R. (2002). Evaluation of subclinical respiratory tract inflammation in heavy smokers who switch to a

cigarette-like nicotine delivery device that primarily heats tobacco. *Nicotine & Tobacco Research*, *4*, 467–476.

Rose, J. E., Behm, F. M., Westman, E. C., & Johnson, M. (2000). Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacology, Biochemistry, and Behavior*, *67*, 71–81.

Schneider, N. G., Olmstead, R. E., Nides, M., Mody, F. V., Otte-Colquette, P., Doan, K., & Patel, S. (2004). Comparative testing of 5 nicotine systems: Initial use and preferences. *American Journal of Health Behavior*, *28*, 72–86.

Schuh, K., Schuh, L., Henningfield, J., & Stitzer, M. (1997). Nicotine nasal spray and vapor inhaler: Abuse liability assessment. *Psychopharmacology*, *130*, 352–361.

Shiffman, S., Burton, S. L., Pillitteri, J. L., Gitchell, J. G., Di Marino, M. E., Sweeney, C. T., Wardle, P. A., & Koehler, G. L. (2001). Test of "light" cigarette counter-advertising using a standard test of advertising effectiveness. *Tobacco Control*, *10*(Suppl. 1), i33–i40.

Shiffman, S., Hughes, J. R., Di Marino, M. E., & Sweeney, C. T. (2003). Patterns of over-the-counter nicotine gum use: Persistent use and concurrent smoking. *Addiction*, *98*, 1747–1753.

Shiffman, S., Pillitteri, J. L., Burton, S. L., & Di Marino, M. E. (2004). Smoker and ex-smoker reactions to cigarettes claiming reduced risk. *Tobacco Control*, *13*, 78–84.

Shiffman, S., Pillitteri, J. L., Burton, S. L., Rohay, J. M., & Gitchell, J. G. (2001a). Effect of health messages about "light" and "ultra light" cigarettes on beliefs and quitting intent. *Tobacco Control*, *10*(Suppl. 1), i24–i32.

Shiffman, S., Pillitteri, J. L., Burton, S. L., Rohay, J. M., & Gitchell, J. G. (2001b). Smokers' beliefs about "light" and "ultra light" cigarettes. *Tobacco Control*, *10*(Suppl. 1), i17–i23.

Stillman, F. A., Cronin, K. A., Evans, W. D., & Ulasevich, A. (2001). Can media advocacy influence newspaper coverage of tobacco: Measuring the effectiveness of the American Stop Smoking Intervention Study's (ASSIST) media advocacy strategies. *Tobacco Control*, *10*, 137–144.

Stratton, K., Shetty, P., Wallace, R., & Bondurant, S. (Eds.). (2001). *Clearing the smoke: Assessing the science base for tobacco harm reduction*. Washington, DC: Institute of Medicine, National Academies Press.

Substance Abuse and Mental Health Services Administration. (2004). *Drug abuse warning network*. Retrieved June 28, 2004, from http://dawninfo.samhsa.gov.

Szczypka, G., Emery, S., Wakefield, M. A., & Chaloupka, F. J. (2003). *The adaptation and use of Neilsen media research commercials ratings data to measure potential exposure to televised smoking-related advertisements*. Retrieved June 29, 2004, from www.impacteen.org/generalarea_PDFs/Nielsenpaper_051403.pdf.

Thun, M. J., Day-Lally, C., Myers, D. G., Calle, E. E., Flanders, W. D., Zhu, B. P., Namboodiri, M. M., & Heath, C. W. (1997). Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959 through 1965) and II (1982 through 1988). In D. R. Shopland, D. M. Burns, L. Garfinkel, & J. M. Samet (Eds.), *Changes in cigarette-related disease risks and their implication for prevention and control* (Smoking and Tobacco Control Monograph No. 8; NIH Publication No. 97-4213). Rockville, MD: National Cancer Institute.

Thun, M. J., & Heath, C. W., Jr. (1997). Changes in mortality from smoking in two American Cancer Society prospective studies since 1959. *Preventive Medicine*, *26*, 422–426.

U. S. Department of Agriculture. (2004). *Tobacco outlook* (No. TBS-257). Washington, DC: Author, Economic Research Service.

U. S. Department of Health and Human Services. (1998). *Tobacco use among U.S. racial/ethnic groups—African Americans, American Indian and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics: A report of the surgeon general*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Wagenknecht, L. E., Cutter, G. R., & Haley, N. J. (1990). Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults Study. *American Journal of Public Health*, *80*, 1053–1056.

Wakefield, M. A., & Chaloupka, F. J. (1998). Improving the measurement and use of tobacco control "inputs." *Tobacco Control*, *7*, 333–335.

Warner, K. E., & Martin, E. G. (2003). The U.S. tobacco control community's view of the future of tobacco harm reduction. *Tobacco Control*, *12*, 383–390.

Wennike, P., Danielsson, T., Landfeldt, B., Westin, A., & Tonnesen, P. (2003). Smoking reduction promotes smoking cessation: Results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction*, *98*, 1395–1402.

West, R., Hajek, P., Foulds, J., Nilsson, F., May, S., & Meadows, A. (2000). A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler *Psychopharmacology*, *149*, 198–202.

Westman, E. C., Levin, E. D., & Rose, J. E. (1992). Smoking while wearing the nicotine patch: Is smoking satisfying or harmful? *Clinical Research*, *40*, 871A.

World Health Organization Scientific Advisory Committee on Tobacco Product Regulation. (2003). *Statement of principles guiding the evaluation of new or modified tobacco products*. Retrieved from http://whqlibdoc.who.int/publications/2003/9241590513.pdf.

World Health Organization Study Group on Tobacco Product Regulation. (2003). *Guiding principles for the development of tobacco product research and testing capacity and proposed protocols for the initiation of tobacco product testing*. Retrieved from www.who.int/tobacco/global_interaction/tobreg/goa_2003_principles/en.