VOLUME 5

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Surveillance for the Health and Behavioral Consequences of Exposure Reduction

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

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

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

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

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

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

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

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

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

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

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

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

EXISTING TOBACCO SURVEILLANCE SYSTEMS

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

Consumption of Tobacco Products and PREPS

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

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

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

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

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

Tobacco Product Marketing

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

Biomarkers of Exposure to Tobacco Products

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

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

Personal Tobacco Product Use and Related Behavioral Patterns

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

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

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

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

continues

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TABLE 6-1 Continued

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

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

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

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

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

Disease Outcomes

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

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

Other Surveillance Activities: The Social and Legislative Environment

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

PROPOSED SURVEILLANCE SYSTEM ENHANCEMENTS

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

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

Consumption of Tobacco Products and PREPs

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

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

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

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

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

Tobacco Product Marketing

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

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

Biomarkers of Exposure to Tobacco Products

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

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

Personal Tobacco Product Use and Related Behavioral Patterns

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

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

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

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

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

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

Disease Outcomes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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SUMMARY AND RECOMMENDATIONS

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

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

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Implementation of a Science-Based Policy of Harm Reduction

Scientific evidence establishes unequivocally that tobacco use causes serious adverse health effects in humans and that the nicotine delivered by tobacco is a highly addictive drug. The ultimate public health goal of tobacco policy is to eliminate the excess morbidity and mortality associated with tobacco use. The only scientifically proven way to accomplish this is to eliminate tobacco use by preventing initiation by those who have never used tobacco, achieving cessation for those who currently use tobacco, and preventing relapse by former users of tobacco. Achieving this goal will protect tobacco users themselves and those affected by environmental tobacco smoke (ETS). But because nicotine is a highly addictive drug, quitting tobacco use is extremely difficult for many people. Despite overwhelming evidence and widespread recognition that tobacco use poses a serious risk to health, some tobacco users cannot or will not quit. For those addicted tobacco users who do not quit, reducing the health risks of tobacco products themselves may be a sensible response. This is why many public health leaders believe that what has come to be called "harm reduction" must be included as a subsidiary component of a comprehensive public health policy toward tobacco.

Some public health officials oppose the adoption of harm reduction strategies because of concerns that promoting this approach will not, over the long term, prove to be beneficial to public health or to the individual tobacco users who might otherwise have quit (Ferrence et al., 2000; Warner et al., 1997). Whatever the merits of this position, marketplace forces already at work have put this issue on the public policy agenda, and new

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products are being developed and offered as harm-reducing alternatives to conventional tobacco products. The task before this committee is to address the science base for implementing a harm reduction approach, and for assessing the impact of such an approach on public health. The committee's task is not to recommend whether or not tobacco harm reduction should be pursued. Furthermore, the committee's effort to carry out its charge should be understood as only one component of a comprehensive tobacco control policy.

This report shows that the prospect of harm reduction presents both promise and uncertainty. For tobacco and pharmaceutical companies to be investing in products that reduce exposure to tobacco toxicants could be a salutary development. Nonetheless, despite advances in understanding tobacco toxicology and the pathophysiology and epidemiology of tobacco-related diseases, little is known about the health effects of using products that reduce exposure to one or more tobacco toxicants or about the public health consequences of promoting tobacco-related products or pharmaceutical products as potential reduced-exposure products (PREPs). It will take many years of research to develop definitive data. It is also clear, however, that action must be taken now, even as better data are being developed, to respond to the already emerging market for PREPs and to ensure that the necessary data are developed, that consumers are accurately informed, and that the public health is fostered.

Until adequate data are available, individual and regulatory choices will by necessity have to be made on the basis of predictions of risk and harm reduction based on inference from indirect evidence. Action should therefore be taken not only to monitor the market, but also to shape it as scientific knowledge unfolds. Despite continuing ambivalence among some health officials about the wisdom of embracing harm reduction as a public health policy, numerous consumers will be taking steps in this direction, with or without scientific guidance. The aggregate effect of these decisions might make an important contribution to public health—or might further exacerbate the problems posed by tobacco products. Policy makers must use the best that science has to offer to ensure that the harm reduction strategies pursued by tobacco and pharmaceutical manufacturers and by individual consumers will truly reduce harm, and to the greatest extent possible.

The committee was drawn by its charge into considering how best to implement the scientific and policy recommendations in this report and, in so doing, was necessarily required to address some features of a regulatory framework for PREPs. The regulation of tobacco products is most certainly controversial and many approaches have been proposed. Tobacco regulation conceivably includes taxation, access by minors, point of sales, etc. For the purposes of this report the regulatory framework

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considered is narrow and focused exclusively on evidence and any necessary powers required to assess harm reduction products, be they pharmaceutical or tobacco-related. Other aspects of possible tobacco regulation are outside of the charge of this committee.

The committee did come to conclude that regulation of PREPs is necessary and feasible. First, effective regulation is a necessary precondition for advancing scientific knowledge on the toxicology and clinical effects of these products, for developing the data necessary for systematic risk assessment, and for monitoring the impact of such products on the public health through appropriate postmarketing surveillance and the collection of long-term epidemiological data. Second, regulation is needed to ensure that the product labeling and advertising do not mislead consumers and accurately describe the products' risks, including the uncertainties that can only be resolved after long-term use. Consumers should not use these new products on the basis of explicit or implicit claims that these products carry less risk than traditional tobacco products unless such claims are true. Absent careful regulation of industry claims about these products, informed choices by consumers will not be possible, the potential benefit of a harm reduction strategy is likely to go unrealized, and the long and unsettling saga of light cigarettes may well be repeated. Finally, regulation is also needed to foster integrated, coherent, and equitable policies with respect to the scientific testing, labeling, and advertising of the diverse array of PREPs marketed by tobacco and pharmaceutical companies.

NEXT STEPS: AN OVERVIEW

Although the science base for tobacco harm reduction (summarized in Chapter 5 and described in detail in Chapters 9-16) is extensive, the committee identified many gaps and limitations. To improve the science base for a harm reduction strategy for tobacco products and to protect public health, the committee's scientific findings and conclusions must be translated into a comprehensive policy framework that includes the following elements:

- a substantial and sustained *research* program to address the critical unresolved questions that are susceptible to scientific resolution, as identified in this report;
- a strong *surveillance* program that will serve both as an "early warning system" for identifying problems associated with PREPs and as an epidemiological tool for evaluating long-term health consequences;
- a well-designed program of public health *education* (including media campaigns) to help people understand that preventing the

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initiation of smoking and assisting smokers to quit constitute the only proven methods of minimizing tobacco-related harm, that the health benefit of using PREPs remains uncertain, and that this uncertainty will not be resolved for many years; and

- an integrated program of federal *regulation* of both tobacco-related PREPs and pharmaceutical PREPs designed to protect public health and to facilitate the research, surveillance, and public education activities described above.

The remainder of this chapter will set forth the committee's recommendations regarding the regulation of PREPs. As discussed in Chapter 4, the current regulatory situation leaves conventional tobacco products essentially unregulated while imposing stringent regulatory controls on the development and marketing of pharmaceutical PREPs. Modified tobacco products with exposure reduction claims currently fall into a twilight zone of regulatory uncertainty.

Previous reports of the Institute of Medicine (IOM, 1994,1998) have recommended that Congress enact a comprehensive regulatory statute delegating to an appropriate agency, preferably the Food and Drug Administration (FDA), "the necessary authority to regulate tobacco products for the dual purpose of discouraging consumption and reducing the morbidity and mortality associated with use of tobacco products." The need for comprehensive tobacco regulation, as recommended in these previous reports, is reinforced by the Supreme Court's ruling, on March 21, 2000, that the FDA lacks comprehensive authority over tobacco products under the Federal Food, Drug and Cosmetic Act (Food and Drug Administration, et al. v. Brown & Williamson Tobacco Corporation et al., 2000). These reports also recommended that the designated agency be authorized to regulate the design and constituents of tobacco products—for example, by adopting "performance standards" that set limits for the levels of toxicants in all tobacco products and/or by regulating the levels of, or exposure to, nicotine. This committee endorses these recommendations.

This committee's charge focuses specifically on products that purport to reduce exposure to tobacco toxicants. In this context the need for federal regulation is made more urgent by the recent introduction of Advance and the expansion of Eclipse into the marketplace and by the likely introduction of other tobacco-related PREPs, including oral nicotine and Swedish snus, in the future. The FDA already has the authority to regulate certain of these new or modified tobacco products as drug-delivery devices or as "drugs" if the manufacturer claims that the product prevents disease by reducing the health risks of using tobacco. The scope of the FDA's jurisdiction is unclear, though, if the manufacturer goes no further than claiming that the product reduces exposure to known tobacco

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toxicants (Page, 1998). Whatever the reach of FDA's current jurisdiction over modified tobacco products, the existing regulatory framework for all tobacco products, including tobacco-related PREPs is inadequate to provide a basis for informed consumer choice and to protect the public health. Accordingly, **the committee recommends that Congress enact legislation enabling a suitable agency to regulate tobacco-related products that purport to reduce exposure to one or more tobacco toxicants or to reduce risk of disease, and to implement other policies designed to reduce the harm from tobacco use.**

Regulatory classifications are traditionally based on the use(s) of a product and/or the claims associated with it. The outline of a sensible regulatory classification is therefore as follows:

1. conventional tobacco products and modified products that are marketed without claims of reduced exposure to tobacco toxicants or reduced risk of disease;
2. modified tobacco products or tobacco-like products, whether tobacco containing or not, that are marketed with such claims; and
3. pharmaceutical products and medical devices, whether nicotine containing or not, that are marketed with a claim of effectiveness for cessation of, or significant reduction in, smoking.

The committee's charge is directed to products in categories 2 and 3 (all PREPs). The legal structure for regulating pharmaceuticals in category 3 is already fully in place under the federal Food, Drug and Cosmetic Act (FDCA) and administered by the FDA. The committee has therefore largely focused on products in category 2, a classification that encompasses any tobacco-related product marketed as a PREP—that is, with claims of reduced exposure to tobacco toxicants or reduced risk of disease—presumably involving a novel design or a modification of a conventional tobacco product. In the interest of placing recommendations concerning the regulation of tobacco-related PREPs in the larger regulatory context, the committee has embraced several recommendations in previous reports of the IOM (1994, 1998) with respect to conventional tobacco products (category 1 above). Thus, several of the principles outlined below apply to conventional tobacco products as well as to tobacco-related PREPs.

Taken together with the drug and device laws already in place, the overall regulatory system should be sufficiently broad and flexible to encompass all relevant product innovations and to respond to new scientific knowledge in the years ahead. Manufacturers of tobacco products and pharmaceuticals should be encouraged to develop and introduce new products that will reduce the burden of tobacco-related disease. How-

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ever, manufacturers of new products should not be allowed to escape regulatory oversight by claiming that their products are dietary supplements, herbals, botanicals, or foods or that they make no explicit claims.

PRINCIPLES FOR REGULATING POTENTIAL REDUCED-EXPOSURE PRODUCTS

In the remainder of this chapter, the committee offers its judgment for consideration of the challenging scientific issues presented by the complex array of new products offered with claims bearing on tobacco harm reduction. Specifically, the committee proposes 11 principles that it believes should govern the regulation of new or modified tobacco products and pharmaceutical products with harm-reducing potential. The overall regulatory structure builds on the foundation of existing regulatory law, with appropriate adaptations to take into account the unique history and toxicity of tobacco products. The committee's approach reflects the following general configuration:

- All tobacco products would be subject to requirements for certain testing and reporting and to the regulation of labeling and advertising.
- A manufacturer who wishes to market a new tobacco product as a PREP—a product with a claim, whether explicit or implicit, of reduced exposure to one or more tobacco toxicants or of reduced risk of adverse health effects (compared with conventional products)—would be required to receive from the regulatory agency prior approval of the claim based on scientific evidence presented by the manufacturer that the claim is not false or misleading; products for which risk reduction claims are made would be subject to postmarketing epidemiological studies.
- New brands and modifications of conventional tobacco products without health claims would be permitted to enter the market without prior regulatory approval if they are certified to present "no greater risk" than products already on the market.
- Pharmaceutical products and medical devices, whether nicotine containing or not, with health claims for reduction of smoking would continue to be subject to the current requirements of the FDCA.

The committee believes that the agency charged with regulating tobacco PREPs should have a public health orientation and should be given authority over all tobacco products, including conventional ones. The scientific expertise needed to regulate both categories of products is similar. This agency will require a competent scientific review staff, including

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molecular biologists, pharmacologists, toxicologists, physicians, epidemiologists, statisticians, and scientists experienced in the technology of tobacco product design and manufacture. In addition, it will need social scientists and marketing experts experienced in the evaluation of product labeling and the regulation of advertising. The agency must also have an analytical laboratory capable of testing a wide range of conventional and modified tobacco products and a product surveillance program staffed with epidemiologists and data management experts. Finally, it will need an enforcement and legal staff and appropriate administrative and information technology personnel.

Some of these functions already exist for tobacco products at the Food and Drug Administration (disease claims), at the Federal Trade Commission (FTC; regulation of advertising and enforcement staff), and at the Centers for Disease Control and Prevention (CDC; analytical laboratory). But no agency currently has the comprehensive mandate or staff necessary to fulfill the policies recommended by the committee. This committee, like previous IOM committees (IOM, 1994, 1998), believes that the FDA would be an appropriate site for this regulatory function, but other administrative locations are certainly possible. The important point is that the requisite authority be lodged in a suitable federal regulatory agency with sufficient expertise and resources to execute the mission successfully.

The committee notes the efforts of some states, notably Massachusetts in particular, to take on some of the regulatory challenges created by the federal government's failure to establish comprehensive regulatory authority over tobacco products. However, patchwork state legislation is not a satisfactory long-term response to the problem. The only adequate response is for Congress to confer comprehensive authority on a suitable federal agency.

Summary of Regulatory Principles

A science-based regulatory framework for implementing tobacco harm reduction should conform to the following 11 principles:

1. Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.
2. All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various constituents of tobacco

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smoke should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

3. Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models and appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency.
4. Manufacturers should be permitted to market tobacco-related products with exposure reduction or risk reduction claims only after agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that independent scientific experts would anticipate finding a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies.
5. The labeling, advertising, and promotion of all tobacco-related products with exposure reduction or risk reduction claims must be carefully regulated under a "not false or misleading" standard, with the burden of proof for the claim resting on the manufacturer not the government. The responsible agency should have the authority and resources to conduct surveys of consumer perceptions relating to these claims.
6. The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct postmarketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.
7. In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to increase the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects, or other adverse health effects, compared to similar conventional tobacco

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products, as judged on the basis of the most current toxicological and epidemiological information.

8. All added ingredients in tobacco products, including those already on the market, should be reported to the agency and be subject to a comprehensive toxicological review.
9. The regulatory agency should be empowered to set performance standards (e.g., maximum levels of toxicants; definitions of terms such as "low tar") for all tobacco products, whether conventional or modified, or for classes of products.
10. The regulatory agency should have enforcement powers commensurate with its public health mission, including the power to issue subpoenas.
11. Exposure reduction and risk reduction claims for drugs and devices that are supported by appropriate scientific and clinical evidence should be allowed by the FDA.

The following sections elaborate on each of these principles.

Principle 1: Disclosure of Product Ingredients

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

The manufacturers of tobacco products have detailed and extensive knowledge of the composition, curing, and blending of tobacco; the ingredients of their products; and the composition of tobacco smoke. They also have detailed quantitative information on the tobacco in each of their brands of cigarettes and smokeless products, since each is blended to achieve the desired taste and levels of nicotine and other ingredients. Manufacturers also conduct major research and development programs aimed at developing new products. Currently, there is no requirement for disclosure of this information to an appropriate regulatory body. Such disclosure is prerequisite to any meaningful scientific appraisal of the comparative risks of different tobacco-containing products or the potential for risk reduction offered by modified products. For smoked products, analytical information on the smoke and the concentrations of smoke components that are absorbed under actual smoking conditions may be even more important than knowledge of the product ingredients themselves. For smokeless tobacco products, whether conventional or modified, similar information on the concentrations of major ingredients in saliva and blood are equally important. The disclosure of quantitative information on ingredients (with appropriate safeguards to protect trade secrets) is a standard requirement in regulatory laws relating to drugs,

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biologics, devices, food additives, toxic chemicals, and environmental contaminants and should be required of all tobacco products, whether conventional or modified.

Although FTC regulation requires public reporting of some constituents in cigarette smoke, manufacturers are not required to report brand-specific information about the nicotine content or other properties (e.g., nitrosamine level) of the material that forms the tobacco rod. Under legislation enacted in 1986, manufacturers of smokeless products are required to report total nicotine content to the secretary of the Department of Health and Human Services (HHS), but the secretary may not release the data. Under the same legislation, tobacco manufacturers are required to submit lists of additives to the tobacco (but not to filters or papers) to the secretary of HHS. Information about the quantity of additives and their presence in specific brands is not required, and the secretary is bound to safeguard the information from public disclosure. In 1993, attorneys for six cigarette manufacturers released a combined list of 599 additives. The following year, ten manufacturers of smokeless products released a list of additives in their products. Three states have enacted legislation requiring disclosure of additives in tobacco products (U.S. DHHS, 2000).

Principle 2: Yield Assessment

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

The actual yield—that is, the amount of toxicants inhaled by an individual—from particular cigarettes varies considerably among smokers. As discussed in Chapter 11, this is because the standard yield is measured by a machine that smokes cigarettes in a mechanical and standardized way, whereas smokers can and do smoke their cigarettes with different numbers of puffs and different depths of inhalation. As a result, for any product, the temperature of combustion and the composition of the smoke varies among smokers depending on the pattern of smoking. The information required to address the relative harmfulness of tobacco products will be available only if an improved methodology for ascertaining the range of actual toxicant yields in human consumers is developed and applied; only then will there be a scientific basis for developing some of the features of a harm reduction program, including, for example, accurate labeling, meaningful definition of terms such as "low tar", and reasonable standards for yields of tar, carbon monoxide (CO), or nicotine.

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Although the limitations of the FTC's current methodology for assessing cigarette yield is generally acknowledged, no definitive steps have been taken to replace it. In 1994, the President's Cancer Committee and the National Cancer Institute (NCI) issued a report criticizing the current approach and recommending adoption of a new one. In 1997, the FTC issued a proposed revision of the methodology and a proposed format for disclosing test results in advertising and labeling. However, many proponents of a new approach urged the FTC to defer action pending judicial clarification of the FDA's authority and possible congressional enactment of comprehensive regulation for tobacco products. It is time for the FTC—or, ideally, an agency with regulatory authority over tobacco products—to adopt a new standardized methodology to assess the range of toxic exposures to smokers under actual conditions of human smoking.

Although the focus of yield assessment has been smoked tobacco, an analogous methodology should also be developed for smokeless products. Without quantitative information on the absorption of various constituents under normal product use, it is impossible to assess comparative exposures and comparative risks.

The committee embraces the conclusions and recommendation on this issue set forth in the IOM (1994) report *Growing Up Tobacco Free*:

> [T]he regulatory agency, as its first step, should develop a sound methodology for ascertaining the actual yields of nicotine, tar, or any other constituents of tobacco products, based on human consumption. Human exposure to some constituents of tobacco smoke can be assessed by use of biochemical markers of exposure to those constituents, although at present this methodology is technically difficult and still imprecise; however, it is likely that better exposure measures will be developed in the future. In any case, even the currently available measures of human exposure are likely to provide a better indicator of relative risk than do the standard cigarette smoking machine yields. At a minimum, the smoking machine tests can be modified to reflect the range of ways in which people actually smoke, including numbers of puffs and blocking of ventilation holes, to determine likely *ranges* of delivery. In addition, the manufacturers of tobacco products could be directed to submit information to the regulatory agency regarding the actual yields of their products in humans for particular brands of tobacco products, based on use of prescribed protocols.
>
> A variety of regulatory initiatives relating to tar and nicotine yields can be envisioned. At a minimum, the regulatory agency should take steps to assure that consumers are informed about the meaning of statements regarding tar and nicotine yields, about the behavioral influences on exposure, and about the relative importance of the characteristics of the cigarette and the way it is smoked. The agency might also require that tar and nicotine yields be presented in a standard format, such as

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absolute content together with a statement of the range of expected systemic yield determined according to number of puffs or other behavioral factors. Currently, marketed cigarettes typically *contain* 8-9 mg nicotine in the tobacco rod, and have an expected actual yield to the smoker of 0.5-3.0 mg nicotine. Stating the nicotine content of the tobacco contained in the cigarettes is important because the content reflects the maximum possible yield, and reduction of content would be expected to result in a reduction in actual yield. Manufacturers might be required to convey this information on the package or through package inserts. In order to avoid misunderstanding, the agency might require consumers to be told that small differences in nominal yield do not reflect significant differences in health risks. Regulations of this nature will improve risk perception among consumers, and will correct any misleading impression about the relative hazards of cigarettes containing different levels of tar and nicotine. From the same perspective, the agency should be authorized to ban or regulate use of misleading terms (such as "light") in advertising or on packaging, and should be authorized to require the use of standard terms.

Principle 3: Toxicity Testing

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

Under the regulatory arrangements recommended by the committee, tobacco manufacturers would have to obtain appropriate toxicological data from the scientific literature or conduct toxicological testing in connection with any new product or modification of an existing product (1) to support a claim of reduced exposure or reduced risk (see principle 5), (2) to demonstrate that a new ingredient does not increase the product risk (see principle 7), or (3) to satisfy the requirements of the added-ingredients review described in principle 8.

Because clinical trials on the long-term health risks of individual ingredients in tobacco-related PREPs cannot reasonably be conducted in humans, any scientific assessment of the risks, except perhaps low birthweight and sudden cardiac death, of added ingredients must necessarily be based on animal studies, short-term human studies, and epidemiological studies. For ingredients that have not previously been used in conventional or modified tobacco products, animal studies to support their safety should be conducted by the manufacturer prior to human exposure to those ingredients. The committee believes that the practice of introducing new ingredients into smoked products without full and adequate testing of such ingredients, as judged by a competent regulatory agency, poses a substantial risk to the consumer and should cease. A requirement for

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adequate preclinical testing of potentially toxic ingredients is a basic feature of all regulatory laws relating to drugs, biologics, devices, food additives, toxic chemicals, and environmental contaminants and should apply as well to conventional and modified tobacco products.

Principle 4: Premarket Approval of Claims

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

Products accompanied by explicit or implicit claims of reduced exposure to tobacco toxicants or reduced risk of adverse health effects should be subject to premarket approval of the specific claim. Under this approach, manufacturers would be permitted to market products with claims of reduced exposure or reduced risk (compared with whatever benchmark product is stated in the labeling) as long as the claim is approved on the basis of appropriate scientific data by the regulatory agency before marketing and, where judged necessary for risk reduction claims, appropriate plans for postmarketing surveillance are also approved.

When the committee refers to a "reduced risk" claim in this chapter, it is referring to any statement, however qualified, indicating that use of the product presents or may present a reduced risk of disease or other adverse health effect, compared with use of some other tobacco product.

Premarket approval of tobacco-related PREPs with claims of reduced exposure or reduced risk is essential to ensure that full information is presented to potential consumers. Under the current regulatory system, manufacturers may, in the absence of drug claims, introduce new or modified tobacco products into the marketplace without any prior regulatory review, subject only to the FTC's authority to enjoin "deceptive acts and practices" after the deception has already occurred. The result has been the long history, cited elsewhere in this report, of promotional practices by tobacco manufacturers that have, at the least, obscured the adverse health consequences of tobacco use. The committee considers it highly unlikely that tobacco-related PREPs marketed under this system would be labeled and promoted with appropriate caution, especially if the market becomes competitive.

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The premarket approval model used for the review of new drugs, while not now applied to new brands and modifications of conventional tobacco products marketed without disease claims, in fact provides the only fail-safe procedure for the review of exposure reduction or risk reduction claims relating to tobacco products, whether made on behalf of novel products like Eclipse or in connection with products already on the market (e.g., smokeless products). The committee thus recommends that any new legislation must provide for premarket approval of claims of exposure reduction or risk reduction. The medical device provisions of the FDCA provide a model for this policy in that high-risk products are subject to premarket approval, while products of lesser risk are subject only to premarket notification. The marketing of a new tobacco-related product with an unsubstantiated claim of reduced disease risk (including a claim of reduced exposure that implies a reduced disease risk) is probably a greater threat to public and personal health than the marketing of a product already known to be dangerous, unless the claim is proven to be accurate. The scientific evidence behind such a claim thus deserves full and independent scrutiny.

The committee judges that exposure reduction and risk reduction claims for tobacco-related PREPs should be treated as analogous to "effectiveness" claims for drugs and devices. Just like drug claims, they are intended to assure consumers of a potential health benefit if the product is used as directed, and just like drug claims, they should be presented accurately and supported by appropriate scientific data. As discussed in Section II of this report, the committee is not aware of a sound scientific basis at the present time for an unqualified risk reduction claim for any tobacco-related PREP. Although the potential for reduced-risk products exists, data supporting such claims have never been subject to comprehensive, independent scientific scrutiny or regulatory review. In no case has the degree of potential risk reduction been estimated from animal or human studies, nor have surveillance programs been implemented to monitor the long-term outcome of the use of any of these products. Uncertainty about the health effects of all PREPs will therefore continue for years even if an effective regulatory framework is created in the near term. If no such framework is created, consumers will continue to act on deficient information.

With respect to the tobacco-related PREPs known to the committee, the most that can reasonably be said today on the basis of the publicly available data supplied by manufacturers is that these products reduce exposure to some but not all of the toxic ingredients in cigarettes, assuming no increase in the total number of cigarettes smoked or in other forms of compensatory smoking. Direct evidence will not be available for many years, if ever, to prove that the degree of exposure reduction achieved, if

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maintained over years, is sufficient to result in a significant reduction in morbidity and mortality. The use of reduced-nitrosamine tobacco, for example, seems likely to reduce the exposure of smokers to nitrosamines, but whether this will reduce lung cancer rates, given the other carcinogens in tobacco smoke, is unknown (see Chapter 12). Similarly, the use of the cigarette-like product Eclipse may reduce exposure to carcinogens but increase exposure to CO. Whether these and similar products, if smoked chronically like cigarettes, will provide a net benefit in terms of all-cause mortality is unknown and can only be determined by long-term epidemiological studies.

Products that increase exposure to one or more tobacco toxicants while reducing exposure to others will present a complex challenge to the regulatory agency. At a minimum, approved claims of reduced exposure should be accompanied by warning statements regarding any increased exposure. Moreover, in the committee's view, reduced-risk claims should be permitted for such a product only if the agency finds, based on scientific evidence, that the use of the product can reasonably be expected to reduce the overall risks of tobacco-related disease or death. While recognizing that the proposed premarket approval requirement raises the possibility of regulatory delays and may inhibit the marketing of new tobacco-related PREPs, the committee believes that undue delay can be minimized by an efficiently administered agency for the following reasons:

- The body of scientific information submitted for review of each new product is likely to be substantially less than that in a typical new drug application to the FDA. For most such products the scientific evidence supporting exposure reduction claims will come from in vitro studies, animal studies, and pharmacokinetic studies in humans. Depending upon the claim, evidence may also come from short-term clinical studies of pulmonary function and/or cardiovascular function. The huge clinical trial programs required to show the effectiveness and safety of drugs in humans would not be necessary to support exposure reduction claims for tobacco-related PREPs.
- Only a handful of tobacco-related PREPs are currently known to be under development, suggesting a relatively low volume of new applications compared with the hundreds of applications for drugs and devices that are handled annually by FDA.
- The success at FDA of the user fee mechanism, in combination with a budgetary appropriation, in providing resources to support an adequate staff suggests a model of public-private funding for the review of claims for tobacco-related PREPs.

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Principle 5: Labeling, Advertising, and Promotion

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

Labeling requirements and restrictions on advertising and other promotional activity are core elements of product safety regulation. In a previous report focusing on preventing initiation of tobacco use (IOM, 1994), another IOM committee recommended that warnings concerning the risks of using tobacco products be strengthened and made more salient, that advertising be restricted to a text-only format, and that many types of promotional activity be severely curtailed. These measures are still needed to reduce youth uptake, to promote cessation, and—most pertinent to this committee's charge—to ensure that public understanding of the dangers of tobacco use is not obscured or compromised by the marketing and promotion of a new generation of modified tobacco products purporting to be "safer" than conventional products. From this perspective, adequate regulatory authority to promote accurate public understanding of the health effects of tobacco-related PREPs is perhaps the single most important feature of effective regulation.

The burden of proving any claim of reduced exposure or reduced risk should rest on the manufacturer. The evidentiary base for such claims must meet contemporary scientific standards and be fully available for independent review by a responsible regulatory body. Independent review and replication of key findings—the "gold standard" for validating scientific assertions—is a compelling necessity for assessing health-related claims associated with tobacco products. Unfortunately, in today's regulatory environment for tobacco products, this proper burden of proof is reversed. Manufacturers are free to market new tobacco products with explicit or implied health claims until challenged by the FTC, which must then show in court, through expert testimony and consumer surveys, that a particular advertising claim is deceptive and not adequately substantiated. Regulation of claims through this process may take years and offers no chance for prompt correction of misleading advertising. The committee anticipates that under the current regulatory conditions, tobacco manufacturers are no more likely to present—accurately and with appropriate caveats, warnings, and uncertainties—what is known, and unknown, about the potential health effects of PREPs than they have been to describe accurately the risks of conventional cigarettes.

The committee therefore strongly recommends that new legislation be enacted to ensure that the labeling, advertising, and promotion of all

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tobacco-related products are carefully regulated so that exposure reduction and risk reduction claims are supported by adequate scientific evidence and are not false or misleading. Claims made in the product labeling should be subject to premarket approval by the regulatory agency, as explained in connection with principle 4. Although a routine requirement for prior approval of advertising might not be constitutionally permissible, the agency should have the authority to take prompt action against specific advertising or promotional campaigns or practices that are false or misleading. This authority should include the power to require corrective advertising.

The committee considered the alternative of recommending that the advertising and promotion of tobacco-related PREPs be included under the present system of regulation for tobacco products in general. For the reasons noted previously, however, the committee considers this system to be insufficient to the task. In the judgment of the committee, a harm reduction strategy using tobacco-related PREPs cannot be implemented successfully unless consumers are fully informed through accurate labeling and advertising about the health consequences of using all types of tobacco products and about the substantial gaps in scientific knowledge. The committee finds no justification for continuing the current situation in which pharmaceutical products intended to aid smoking cessation—the desired public health goal—must be labeled and promoted truthfully under a "not false or misleading" standard, while tobacco products claiming to reduce exposure or risk—at best a partial and uncertain step toward disease reduction—can be promoted under generic consumer deception laws, with the burden of proof on the FTC to police violations after the fact. Unless this imbalance in the regulation of labeling and advertising is corrected, the committee finds it likely that aggressive promotion of tobacco-related PREPs, accompanied by incomplete and possibly inaccurate or misleading health-related claims, may well undermine other public health efforts to promote cessation of smoking and other forms of tobacco use. In short, unless the regulation of labeling and advertising of all tobacco-related products with health claims can be brought to parity, the impending availability of tobacco-related PREPs could cause more harm than good.

As a corollary, the committee concludes that the evidentiary base for regulating labeling and advertising must include not only scientific studies related to toxicology and human biology but also scientific analyses of the impact of particular claims, as well as messages and images in advertising and promotional activity, on risk perception and risk communication. Such analyses should take into account the overall public health goal of reducing tobacco-related morbidity and mortality both in individuals and in the population as a whole as well as the goal of enhancing the

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capacity of each adult to make an informed decision concerning the use of tobacco. The regulatory agency should have the resources and funding to conduct relevant consumer surveys and analyses as well as the authority to require such studies from manufacturers.

The committee has aimed to balance two possible types of errors: (1) allowing reduced-risk claims that turn out to be erroneous, and (2) deterring the development of modified products that would reduce exposure to known toxicants (and that would eventually be shown to reduce disease risk) if they were marketed. The committee acknowledges that manufacturers might forego the necessary investment in product development because of doubts that the accuracy of their claims can be defended successfully to unduly skeptical regulators.

However, the most important considerations are unproven or premature reduced-risk claims and reduced-exposure claims that are mistakenly interpreted as reduced-risk claims. The regulatory process should not discourage or impede scientifically grounded claims of reduced exposure, as along as steps are taken to ensure that consumers are not misled into believing (in the absence of sound evidence) that smoking the modified product is (or is likely to be) less hazardous than smoking the conventional product. How the complex of claims and caveats associated with PREPs can best be articulated in labeling is one of the major challenges facing the regulatory agency. On the one hand, the public health is not well served by the continued use of poorly defined terms such as "light," "low tar," or other phrases that imply a benefit when none has been proven to exist. On the other hand, neither is the public health served if smokers are discouraged by unduly cautionary language from using a new product with the potential for real risk reduction. The problem of conveying balance in communicating health benefits and risks is not unique to tobacco-related PREPs, and the large body of experience in other areas of health and safety regulation may be applicable to these products as well.

The agency will have to direct its attention to the language used as well as the labeling format. Some illustrations, based on existing formats, follow:

- Current cigarette labeling contains warnings that smoking causes lung cancer, heart disease, and emphysema and may cause birth defects. If warranted by scientific evidence, such warnings could be accompanied by a statement that the modified product might carry a reduced risk of one or more of these conditions.
- Current food labeling has on each package a table displaying a quantitative analysis of nutritional content. This approach could be applied to selected ingredients and constituents of tobacco products or tobacco smoke, such as known carcinogens and CO.

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- Food-labeling tables express nutritional content not only as grams per serving but also as a percentage of average daily intake. One could envision tobacco product labeling with a similar table that shows exposure or yield ranges for particular toxicants or perhaps ranks the levels of exposure or yield as high, average, or low. These terms could be specifically defined and would perhaps be less misleading than such terms as "light."
- One could also envision the use of words such as "high," "average," or "low," again carefully defined, in a "risk" column in such a table. Pictograms, such as those that appear in poison control warnings, or icons might be used instead of words. It is essential that such labeling in the end be perceived as denoting degrees of risk, not as signifying or implying safety. The message that cessation is the only safe choice must not be obscured or lost.
- The agency should also consider requiring that labels for PREPs that make exposure reduction claims disclose that the reduction in exposure depends upon the user not compensating for the reduction by increasing use or by inhaling more deeply. Consideration should also be given to a disclosure that the health benefits of the product's exposure reduction have not yet been established in scientifically recognized tests or ongoing studies. Such a disclosure would guard against consumer confusion that risk reduction benefits have been proven. Furthermore, such a disclosure would provide an incentive to manufacturers to do more research on the health effects of exposure reduction. The FTC should consider requiring similar disclosures under its existing authority if new legislation is not adopted.

The committee does not have recommendations on the specific form of labeling that is optimal for tobacco-related PREPs. (The formats cited in the foregoing examples are meant only to be illustrative.) This topic deserves the sustained attention of experts in communication and marketing, with the intent of identifying the optimal approach for conveying in a simple format specific information on exposure reduction, the potential for risk reduction, and the associated uncertainty. This information must be balanced, accurate, informative, and not misleading.

Growing Up Tobacco Free (IOM, 1994) reviewed the history of mandated tobacco health warnings; called attention to the inadequacy of the existing warnings (both in content and format); reviewed recent initiatives in other countries, especially Canada; and recommended a number of legislative measures to increase the salience and effectiveness of health warnings on packaging and in advertising. Specifically, the IOM (1994) report made the following recommendations:

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> Based on current knowledge, Congress should enact specific warning and format requirements now, and should delegate regulatory responsibility for future modifications to the secretary of health and human services. The secretary should ensure that ongoing research is conducted on the effectiveness of prescribed warnings. Congress lacks the institutional expertise and flexibility to monitor the efficacy of regulatory innovations and to respond to new information. Authority to amend the warnings should be delegated to an appropriate regulatory agency. The secretary should be empowered to modify the format or content of existing warnings and to prescribe additional warnings, whenever such action is reasonably necessary to achieve effective communication of significant information regarding the health consequences of tobacco use or to discourage consumption of tobacco products.

The committee endorses this recommendation. The need to implement this approach is all the more evident now in light of the emerging market for products that purport to reduce the risk of tobacco use.

One of the recurrent questions in the regulation of health claims is when to permit a claim that a product *may* reduce the risk of disease. Such a statement may be misleading even though it is not false. Assuming substantial proof of exposure reduction, what type of evidence must be produced in support of a claim that the product *may*, as a result, reduce the risk of disease? Is inference based solely on the existence of a dose-response relationship sufficient? How strong must the evidence be? What is the significance of counterevidence? How much weight should be given to favorable changes in biomarkers that are biologically rational but not yet proven to be true surrogate end points? Although these are questions that will have to be addressed by the regulatory agency in due course, the committee itself is disinclined to permit claims that the product "may" or "might" reduce the risk of disease (or that "growing evidence suggests that the risk is reduced") unless, as judged by the regulatory agency after review of data by an independent scientific advisory committee, the degree of exposure reduction is likely to result in a meaningful decrease in tobacco-related morbidity or mortality that can be measured in subsequent epidemiological studies.

Another question must then be faced. Assume that the agency finds insufficient evidence under such a demanding standard to support a claim that the exposure-reducing product "may reduce the risk" of a particular disease. Should the manufacturer be permitted to make the statement (which is not false) as along as it is accompanied by a disclaimer to the effect that the regulatory agency has not approved the statement? This approach is receiving increasing attention in other regulatory contexts in light of a few judicial decisions holding that regulatory agencies must allow manufacturers to make the unproven statement, together with a

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disclaimer, under the First Amendment (Gilhooley, 2000). The committee assumes that the First Amendment does not require such a permissive approach and is inclined to be much more cautious in light of the history of public health mistakes in tobacco product innovation. In the committee's judgment, in the absence of sufficient scientific evidence to support a claim that a product may reduce the risk of disease, any claim of reduced exposure to tobacco toxicants should be accompanied by a statement that the health consequences of the change are unproven (or unknown).

Given that considerable time will be needed to enact appropriate legislation, to staff a new regulatory agency, and to bring whole classes of products into a new regulatory system, a number of modified tobacco products with risk-reduction claims may enter the marketplace in coming years without regulatory review, assuming they are positioned not to fall under the drug or device laws. The committee views this situation with alarm but cannot offer a ready solution. Perhaps tobacco manufacturers would be willing to demonstrate their good faith by agreeing to voluntarily submit claims of reduced exposure or reduced harm to FDA, FTC, CDC, or some other appropriate agency for its review and comment, and to conform to agency suggestions pending legislative action. The committee emphasizes, however, that any purported harm-reducing products that have been put on the market before enactment of regulatory legislation should not be grandfathered or exempted from rigorous scientific and regulatory scrutiny.

Principle 6: Postmarketing Surveillance

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

The committee has repeatedly emphasized that since definitive information on the ultimate value of a PREP cannot be determined at the time of its initial marketing, the true extent of its long-term benefit (or possible harm) will remain uncertain unless specific surveillance and epidemiological studies are conducted after the product is marketed. The FDA already has the authority to require pharmaceutical manufacturers to conduct such studies for the purpose of monitoring drug-related health risks. The designated regulatory agency for tobacco-related PREPs should have equivalent authority to require manufacturers who seek to make reduced-risk claims to sponsor surveillance and epidemiological studies in appropriate cases. These studies should be designed to assess not only the

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benefit of the product in reducing the risk of smoking but also the degree to which the product has served to maintain as smokers those who might otherwise have quit and/or to recruit new smokers. The quality of these studies should be high so that the results can permit modification of claims as knowledge evolves.

The committee envisions that a plan or protocol for such a study (or studies) would commonly be required at the time of approval of the claim. Whether a postmarketing study is necessary should be judged by the regulatory agency on a case-by-case basis. The agency can also be expected to take steps to ensure the scientific integrity of such studies by requiring appropriate monitoring and, where necessary, an independent safety monitoring board. In addition to the authority to require manufacturers to sponsor postmarketing studies, the regulatory agency should also have in-house expertise in epidemiology. Such expertise is needed to deal competently with scientists in industry and peers in the field, to operate an adverse event reporting system, and to sponsor selected studies when necessary. As discussed in Chapter 6, the regulatory agency, in collaboration with other public health agencies, should conduct an active program of surveillance for all tobacco products, including conventional ones, modified products that are not accompanied by health claims, and PREPs. It is particularly important for public health authorities to monitor patterns of initiation and progression of use, including the interactions of product use (substitution and supplementation), for all PREPs.

Principle 7: "No Increased Risk" Threshold for All Tobacco Products

In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and upon certifying that the product could not reasonably be expected to increase the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects, or other adverse health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information.

Conventional tobacco products are well established in the marketplace, and the committee recognizes that, regardless of the adverse health consequences of using these products, this situation is likely to continue for the foreseeable future. These products are already subject to a limited regulatory system that includes certain health warnings and other labeling requirements and some restrictions on advertising and promotion. The committee considered whether modified versions of established tobacco products, or new brands, that are marketed without health claims should be required, on public health grounds, to satisfy any new regulatory

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requirements and, if so, whether manufacturers should continue to be permitted to put such conventional products on the market without prior agency approval.

The committee concludes that any new regulatory system should ensure that all newly marketed tobacco products pose no increase in health risks, and ideally a new system should move products toward reduced potential for harm. To this end, the committee recommends that manufacturers be permitted to introduce a new product or make significant changes to an already marketed conventional tobacco product only if, on the basis of currently known toxicological and epidemiological information, the product could not reasonably be expected to increase the risk of disease. Implementation of this regulatory principle requires the definition of a standard for comparison. Although the responsibility for developing such a standard will rest with the regulatory agency, the committee can envision several possibilities: the most popular brand, the most (or least) harmful brand on specified dimensions, a toxicity profile that is representative of a sales-weighted average brand, or a standardized product of known composition. Because toxicant yields do not necessarily reflect health effects and because different standards may be appropriate for different products, the establishment of standards or reference products may require the type of information that would evolve from the regulatory agency's experience with the disclosure of ingredients in individual products (principle 1) and the added-ingredients review (principle 8). Such standards might be promulgated through guidelines and performance standards (principle 9).

To implement this approach, manufacturers should be required, before marketing a product, to submit ingredient information to the agency and to certify that the criterion of no increased risk is met (premarket notification). Whatever comparative standard is adopted for the product, the committee believes that a judgment of no increased risk should be based on the most current toxicological and epidemiological data. Manufacturers should not use the most dangerous products of the past as an appropriate standard for any new product. Consumers should rightfully expect that all new tobacco products, even those marketed without health claims, are at least no more hazardous than similar contemporaneously marketed products.

The committee considered whether premarket approval by the regulatory agency should be required for modifications and new brands of conventional tobacco products without claims of reduced exposure or reduced risk, and rejected this approach in favor of premarket notification and certification by the manufacturer. Although some product modifications may be undertaken to improve taste or other features linked to consumer satisfaction, future innovation in the tobacco market in this

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country is likely to focus on changes that purport to reduce risk. Because the main regulatory purpose of a requirement for no increased risk is to help establish the baseline for future comparisons and to stimulate development and use of protocols for tobacco product risk assessment, premarket notification is sufficient. The committee also did not want to see the regulatory agency burdened with a high volume of premarket approval decisions for products that have no claims of and no potential for improving the public health. Nevertheless, the regulatory agency should have the authority to seek the removal of a product from the market in the event that the "no increased risk" standard is not met.

Principle 8: Added-Ingredient Review

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

The ingredients added to tobacco products should be subject to a review that is similar to the FDA review of food additives conducted more than two decades ago to determine if those additives were generally recognized as safe and not subject to additional regulation. Although many of the ingredients added to tobacco products are generally recognized as safe when used as food additives, such an understanding may not apply when these substances are combusted and/or inhaled in smoke. A review of added ingredients would establish a baseline of knowledge about the ingredients, including chemicals, papers, and filters, as well as the toxicological testing that has been conducted on them; it would thereby facilitate an informed appraisal of the potential effects of product modifications. This review should be conducted by independent panels of experts reporting to the regulatory agency, with the objective of identifying those ingredients that add no significant toxicity to tobacco products and therefore can be considered safe in the context of this use. Sufficient knowledge of the toxicity of many of the constituents and ingredients of tobacco products may already be available (see Chapter 10) to begin this review. If adequate information is not yet available, the regulatory agency should have the authority to require the in vitro and animal testing that is judged necessary by the expert panels conducting the review. Such a review would begin to rationalize the risk assessment of ingredients in tobacco products. It would also open this field to the same scientific discourse that is now applied to food additives, environmental contaminants, and toxic chemicals, substances that are no longer introduced into use without independent scientific scrutiny or regulatory review. Tobacco products are the last remaining legally marketed toxic products in our marketplace that are tolerated without such review. A review of

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added ingredients would provide a scientific basis for guidelines or performance standards to limit possible toxicants like pesticides or filter fibers, if such limits are judged necessary for health reasons. It would also facilitate the review of new products by establishing conditions under which added ingredients, such as flavoring agents and papers, would be considered safe for use without additional data or review.

An added-ingredients review would be a large administrative undertaking requiring several years of effort. It would also require the cooperation of the tobacco industry in submitting data. The committee believes that such a review would be in the interests of both manufacturers and consumers. It would permit credible scientific judgment regarding the extent to which nontobacco ingredients in tobacco products contribute to overall toxicity, would build scientific bridges between the tobacco industry and the toxicology community at large, and as noted above, would facilitate the regulatory review of new products. The committee notes that the review of food additives has been conducted without public disclosure of trade secrets, such as the composition of spices and flavoring agents, and believes that this principle should be respected in any review of the ingredients added to tobacco products.

Principle 9: Performance Standards

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

Performance standards, including maximum permissible levels, are promulgated under many regulatory laws, including those related to drugs, medical devices, and environmental pollutants. As noted above, successful implementation of a harm reduction strategy as an element of the nation's tobacco policy will require proactive government efforts in research, education, and surveillance as well as regulation of specific products. Accordingly, as scientific knowledge evolves regarding product risks and consumer preferences, the regulatory authority should be empowered to require product modifications to eliminate unreasonable risks. (A similar recommendation appears in the 1994 IOM report.) The committee has not attempted to draft precise statutory criteria to guide the agency's discretion in adopting performance standards. However, the committee does assume that the agency would not be empowered to ban nicotine from tobacco products.

Performance standards might take the form of limits on the concentrations of toxic ingredients in the product or the smoke; sets of limits that taken together would qualify a smoked product to be labeled as high, average, or low on a risk scale; or a list of reviewed ingredients that could

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be used without challenging the no increased-risk standard. A performance standard cannot be adopted without good scientific data, deliberate planning, and careful monitoring to ensure that it is achieving the desired goal. As the FTC test for tar and nicotine illustrates, even well intended performance standards can sometimes be subverted, with perverse and unintended health consequences. Performance standards aimed at setting definitions for terms must therefore be thought through with great care and be subject to change as experience is gained. Such standards will undoubtedly require a public rule-making process, meaning considerable time for their adoption.

Principle 10: Enforcement Powers

The regulatory agency should have enforcement powers commensurate with its public health mission, including the power to issue subpoenas.

The committee envisions that any regulatory agency for tobacco-related products would need the usual enforcement authorities conferred on public health regulatory agencies, such as the FDA, FTC, CPSC, and Environmental Protection Agency (EPA). The committee anticipates that this agency would also have an appropriate technical and legal staff concerned with issues of enforcement.

The committee specifically recommends that the agency have among its powers the authority to require the monitoring of scientific studies sponsored by manufacturers and to inspect manufacturers, investigators, and contractors to verify the data submitted in these studies. Such powers are necessary to ensure the quality and integrity of these studies. The agency should also have the authority to remove from the market ingredients or products that do not meet the test of no increased risk; to prohibit claims that are not supported by adequate scientific data; to seize products that are improperly labeled; to act promptly against advertising campaigns and promotional materials that are false or misleading; and to require corrective action.

Principle 11: Regulation of Drugs and Devices

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

The committee recommends no new legislation regarding the regulation of pharmaceutical products and medical devices intended to assist people to stop smoking. What will be needed is effective policy coordination between FDA regulators responsible for drugs and devices and whatever agency is charged with administering any new legislation related to tobacco products.

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The committee also recommends that the FDA be prepared attitudinally and technically to approve both exposure reduction and risk reduction claims for drugs, when such claims are supported by appropriate scientific data. It is clear that the current FDA standard for all approved smoking cessation products is "quit rates" and that long-term use of pharmaceutical PREPs with cigarettes, which might be employed in a harm reduction strategy, is discouraged by the labeling approved for these products (Hughes et al., 1999). While the committee again emphasizes that cessation of smoking is the desired goal for all smokers, it also concludes that drugs with exposure reduction and risk reduction claims, if properly regulated and proved efficacious, have a place among the treatment modalities that should be available to current smokers. The committee judges, for example, that statements such as "helps recruitment into treatment clinics" or "reduces the use of cigarettes without compensation" are appropriate indications if supported by adequate data from clinical trials. The committee also concludes that for persons addicted to nicotine, a nicotine-containing drug product is preferable to a cigarette or other tobacco-containing product as a chronic source of nicotine. The FDA should therefore be prepared to consider the chronic administration of nicotine products as a reasonable exposure reduction strategy, again if supported by valid clinical data.

Transitional Regulation of Tobacco-Related PREPs as Drugs

Although the committee believes that adequate regulation of tobacco-related PREPs requires new legislation conforming to the preceding principles, the potential utility of the existing authority of the FDA and FTC should not be overlooked, and some of the committee's recommendations could be implemented by these agencies in the absence of new authority. The FDA presently has the authority to regulate any product, including new or existing tobacco products, as drug-delivery devices or as drugs, on the basis of an expressed or implied claim by the manufacturer that the product prevents disease by reducing the health risks of tobacco (Page, 1998). FDA can find that a manufacturer intends to make such a claim by looking at any relevant source, including advertising. See United States v. "Sudden Change" (United States v. "Sudden Change," 1969) and National Nutritional Foods Assn. v. FDA (National Nutritional Foods Assn. v. FDA) (objective evidence). Claims that PREPs respond to concerns about smoking-related illnesses or cancer can be regarded as disease prevention claims.

In its recommendations for regulating the risk reduction claims for PREPs, this report identifies the type of testing and post-approval studies that should be conducted. The committee recommends that FDA use these

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testing standards under its existing authority in regulating PREPs that make claims for reduced risk of disease. FDA can regulate products that are both drugs and devices under its authority over medical devices. In the case of medical devices that require premarket approval, the agency can determine what testing needs to be done to provide a "reasonable assurance" of safety and effectiveness and can set performance standards for class II devices where appropriate (21 U.S.C.; Page, 1998). The products can be considered safe on a relative basis in light of their capacity for risk reduction, even though tobacco itself was not considered safe in FDA v. Brown & Williamson (Food and Drug Administration, et al. v. Brown & Williamson Tobacco Corporation, et al., 2000). Post-approval testing has been allowed and required for new drugs (Page, 1998).

Exposure reduction claims, such as low tar, have not been regulated by FDA as disease claims, and its authority to do so is uncertain (Page, 1998). A new law designed specifically to regulate tobacco-related PREPs can give a regulatory agency clear authority with respect to exposure-related and smokeless claims. Even for disease prevention claims, new legislation can confirm the agency's authority and the type of tests and manner in which the agency should regulate claims. Moreover, the legislation recommended by the committee would provide the agency new authority to obtain data on ingredients of all tobacco products, permit additional disclosures to consumers about toxicants in tobacco, give enhanced authority (and review when needed) over advertising and labeling claims for PREPs, guard against increased risks from new or modified tobacco products, and authorize a toxicology review and performance standards for tobacco products.

FDA's authority with respect to disease claims would continue if the new authority recommended under this report were given to FDA, with whatever modifications were made by statute. If the authority were given to a new agency, FDA's authority over disease claims for PREPs should be revoked only if the new agency has authority that is at least as extensive as FDA's present authority.

SUMMARY

In this chapter, the committee has addressed key elements of a regulatory framework for implementing the scientific and policy recommendations made in the body of the report. In the committee's judgment, harm reduction is a feasible and justifiable public health policy—but only if it is implemented carefully to achieve the following objectives:

- manufacturers have the necessary incentive to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease;

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- consumers are fully and accurately informed of all of the known, likely, and potential consequences of using these products;
- promotion, advertising and labeling of these products are firmly regulated to prevent false or misleading health claims, whether these claims are explicit or implicit;
- health and behavioral effects of all PREP use are monitored on a continuing basis;
- basic, clinical, and epidemiological research is conducted to establish with reasonable scientific certainty the actual health benefits of PREPs to individuals and the population as a whole; and
- harm reduction is implemented as a component of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

The committee nevertheless acknowledges that a regulatory system of the type outlined in this report will require sustained congressional support and substantial public funding. It will also impose new direct and indirect costs on the tobacco industry. The committee emphasizes, however, that the regulatory system proposed in this report is not to be viewed in isolation. It is proposed as an essential component of a package of public policy initiatives (including research, education, and surveillance) that this committee believes is necessary to realize whatever benefit tobacco or pharmaceutical product innovation can offer in reducing the nation's burden of tobacco-related illness and death. The committee notes again that public health benefits may not emerge, even if the public and private investment in these initiatives is made. In the absence of this investment, however, the hoped-for benefits are highly unlikely to materialize.

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8

Principal Conclusions

The science base for assessing tobacco harm reduction is incomplete. Nonetheless, the presence of potential reduced-exposure products (PREPs) on the market suggests an urgent need for proactive plans to evaluate the potential risks and benefits. The potential for reduction in morbidity and mortality that could result from the use of less toxic products by those who do not stop using tobacco justifies inclusion of harm reduction as a component in a broad program of tobacco control. To date there are two general types of PREPs: pharmaceuticals and modified tobacco products. The pharmaceuticals include, for example, nicotine replacement therapy (NRT) and bupropion, while modified tobacco products include products with modified tobacco and those with modified delivery systems.

Having identified conceptual and operating precepts as stated at the end of Chapter 1, the committee concludes that there can be a successful, scientifically-based harm reduction program that is justifiable and feasible—but only if implemented carefully and effectively and only if:

- manufacturers have the necessary incentive to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease;
- consumers are fully and accurately *informed* of all of the known, unknown, likely, and potential consequences of using these products;

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- promotion, advertising and labeling of these products are firmly *regulated* to prevent false or misleading claims, explicit or implicit;
- health effects of using PREPs are *monitored* on a continuing basis;
- basic, clinical, and epidemiological *research* is conducted to establish the potential use of PREPs for reducing risks for disease in individuals and for reducing harm to the population as a whole; and
- harm reduction is implemented as a component of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

The 7 chapters of the committee's report that precede this and the extensive reviews found in Section II provide the documentation for the following principal conclusions regarding the four questions posed within the charge, as outlined in Chapter 1. Specific recommendations can be found within the body of the report.

Conclusion 1. *For many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible.* This conclusion is based on studies demonstrating that for many diseases, reducing tobacco smoke exposure can result in decreased disease incidence with complete abstinence providing the greatest benefit. Key to this conclusion is the assumption that compensatory increase in exposure does NOT occur with the use of these products.

Conclusion 2. *PREPs have not yet been evaluated comprehensively enough (including for a sufficient time) to provide a scientific basis for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use.* (One exception is the use of nicotine replacement therapy for maintenance of cessation in the Lung Health Study. See Chapters 13 and 14.) Carefully and appropriately conducted clinical and epidemiological studies could demonstrate an effect on health. However, the impact of PREPs on the incidence of most tobacco-related diseases will not be directly or conclusively demonstrated for many years. Tobacco use causes very serious morbidity and mortality due to several different diseases. Cancer (e.g., of the lung, oral cavity, esophagus, and bladder), cardiovascular disease, chronic obstructive pulmonary disease, and low birthweight are all well-established effects of tobacco use. The conditions can be diagnosed, the natural history of the diseases is reasonably well understood, and scientifically appropriate studies of tobacco users who switch to PREPs could be designed. See Chapters 4 and 11-16 for supporting material.

However, such research will be difficult. For example, tobacco users may not use a particular PREP for long enough to see health impact; tobacco PREPs will undoubtedly change substantially over

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the next decade; many subjects would be required for adequate statistical power. For all these and other reasons, conclusive proof of the health effects of PREPs will not be available in the near future, as new PREPs are entering the marketplace. Thus, for purposes of educating the public about PREPs and for purposes of regulating health claims, surrogate measures of health effects must be considered.

Conclusion 3. *Surrogate biological markers that are associated with tobacco-related diseases could be used to offer guidance as to whether or not PREPs are likely to be risk-reducing.* However, these markers must be validated as robust predictors of disease occurrence, and should be able to predict the range of important and common conditions associated with conventional tobacco products in order to be useful for PREP evaluation and regulation. PREPs may differentially affect risk of tobacco-related diseases. Furthermore, the efficacy of PREPs will likely depend on user population characteristics, e.g., those defined by gender, genetic susceptibility, ethnicity, tobacco history, and medical history. Chapters 12-16 describe clinical studies using surrogate indicators that could be conducted to better understand whether or not PREPs would decrease specific adverse health outcomes. The potential studies vary in terms of the length of time that would be required to document the effect, the number of patients, and the power of the study to predict disease outcome. There is no one panel or group of tests that the committee could recommend at this time that would, as a whole, serve to assure that morbidity and mortality would decrease with use of PREPs.

Conclusion 4. *Currently available PREPs have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.* There are many techniques to assess exposure reduction, but the report contains many caveats about the use of all of them, including usually an unknown predictive power for harm. Long-term use of pharmaceutical preparations for maintenance of tobacco cessation will clearly achieve exposure reduction. The safety of these products for long-term use, however, is not well established. For example, it is well known that nicotine affects the autonomic nervous system, with uncertain long-term consequences. However, even if NRT use for maintenance of cessation results in nicotine exposure equivalent to that achieved with conventional tobacco products, exposure to the most harmful tobacco toxicants is avoided. See Chapters 4, 9, and 11 for supporting material.

There is insufficient evidence to decide whether concomitant use of NRT or bupropion with decreased tobacco use will lead to signifi-

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cantly decreased exposure to tobacco toxicants such as tar and carbon monoxide. Nor is there sufficient evidence to determine how much this PREP strategy will decrease conventional tobacco use or how much compensation will occur. However, there are exposure assessment tools to assess this issue, as described in Chapter 7.

Tobacco-related PREPs pose different exposure assessment problems. PREPs characterized by the reduction (or, conceivably, elimination) of one class of toxicants, such as the reduced-nitrosamine preparations in varying stages of development and marketing, do result in decreased exposure per cigarette to specific toxicants. Analytic techniques exist to demonstrate this. However, the smoking behavior of people who use these PREPs has not been researched well enough to know whether or not compensation occurs (thus increasing net exposure to other toxicants and possibly maintaining exposure to the potentially reduced chemical). Furthermore, there are insufficient data to allow scientific judgement or prediction of the health effects of removal of one class of chemicals from tobacco products.

The cigarette-like PREPs that use heat or reduced burn temperature of tobacco and deliver aerosolized nicotine pose other exposure assessment problems. The prototypes available now have only just begun to be studied by researchers other than the manufacturers. It is clear that the yield of some of these products is different from that of conventional cigarettes. The pattern of yield changes suggests differential reduction in exposure to toxicants. Some preliminary data suggest increased yield of specific toxicants concomitant with no change or decreases in others.

There does not exist a standard reference product for comparison with tobacco-related PREPs. Assessment of the risk from use of a PREP requires comparison to the risk of the product avoided AND to the risk of the product (including no product, or abstinence) the PREP user would switch to if the PREP were NOT available.

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

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which it substitutes, regulation is needed to assure that the claim is supported by scientifically sound evidence and that pertinent epidemiological data is collected to verify that claim. The regulation proposed by this committee is narrowly focused on assuring that the products reduce risk of disease to the user and accumulating data that would indicate whether or not the products are harm-reducing for the population in the aggregate. Other potential regulatory approaches to tobacco control are not addressed within this report. See Chapter 7 for supporting and explanatory material.

Conclusion 6. *The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.* The effect on public health will depend upon the biological harm caused by these products and the individual and community behaviors with respect to their use. Assessing the public health impact will be difficult and will require classic public health tools of surveillance, research, education, and regulation to assure that the impact is positive. The major concern for public health is that tobacco users who might otherwise quit will use PREPs instead, or others may initiate smoking, feeling that PREPs are safe. That will lead to less harm reduction for a population (as well as less risk reduction for that individual) than would occur without the PREP, and possibly to an adverse effect on the population. PREPs should be a last resort only for people who absolutely can not or will not quit. Population-based research and surveillance can determine whether the intended impact is achieved. However, measurements of health impact at the population level can take years to document, as described in previous sections of this chapter and in the report as a whole.

Regulation of PREPs can only assure that a specific PREP could be risk-reducing for a person who uses it compared to the conventional product it replaces. Regulation cannot assure that the availability of risk-reducing PREPs will lead to reduced tobacco-related disease in the population as a whole. However, a regulatory agency can assure that data are gathered that would permit the population effects to be monitored. If population tobacco product use increases or tobacco-related disease increases, these data would serve as a basis for developing and implementing appropriate public health interventions. See Chapters 3, 6, and 7 for supporting material.

Studies using surrogate indictors of population impact could be designed. For example, monitoring the perception that the public, particularly tobacco users and adolescents, has of the risks and benefits of PREPs is possible. Research indicating that people perceive PREPs to be more beneficial than scientific judgment indicates would

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provide early evidence of the risk for an adverse public health impact. Action of various sorts (e.g., regulatory review of claims, public health education campaigns) could then be taken.

Chapters 1 and 5 include discussions of the utility of a risk assessment framework for organizing the scientific basis for evaluation of PREPs. It is useful to return to that framework to put the committee's conclusions and recommendations into the proper light. Although the committee did not perform a risk assessment for any existing PREP, the committee's conclusions and recommendations provide a means to assure that a risk assessment can be done in the future. As Table 8-1 illustrates, the committee's principal conclusions (discussed in a preceding section of this chapter) assume use of the conventional risk assessment framework, and the conclusions and recommendations for surveillance and regulation point a way to develop the necessary data for such an evaluation.

Hazard identification is inherent in the first question of the committee's charge, Does the product decrease exposure to the *harmful substances* in tobacco? The principal conclusions that harm reduction is feasible and that exposure reduction can be demonstrated require identification of the toxicants within or produced by use of the PREP. The element of the proposed surveillance system related to specific tobacco constituents and several of the regulatory principles (#1, #3, #7, #8, #9) will assure that the necessary toxicology data are gathered, validated, and made available to scientists, public health officials, and regulators.

Dose-response assessment is inherent in the second question of the charge, Is decreased exposure associated with decreased harm to health? An important issue when considering this question in the context of PREP assessment is that while some data are available when assessing a dose-response relationship, there are virtually no data describing the change in response due to dose reduction after a period of higher exposure. This data would reflect the extent of disease reversibility or halting of disease progression possible from exposure reduction. Dose-response assessment is also inherent in the third question of the charge, Are there useful surrogate indicators of disease that could be used? The principal conclusion that surrogate measures could be used to predict harm reduction requires the development of surrogate disease indicators (response) so that a dose-response assessment (and therefore a risk characterization) could be made in some reasonable timeframe, without waiting decades to assess cancer morbidity and mortality. The surveillance system component addressing disease outcomes will help provide some of these necessary data and the regulatory principle #6 requiring postmarketing surveillance and epidemiologic studies for PREPs with claims will assure that the data are collected.

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TABLE 8-1 Relationship of Conclusions and Recommendations for PREP Risk Assessment

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Committee charge	1. Does product decrease exposure to the **harmful substances** in or produced during use of tobacco?	2. Is decreased exposure associated with decreased harm to health? 3. Are there useful surrogate indicators of disease that could be used?	1. Does product **decrease exposure**?	4. What are the public health implications?	4. What are the public health implications?
Principal conclusions	1. Risk reduction is feasible 4. Exposure reduction can be demonstrated	3. Surrogate measures could be used to predict risk reduction	4. Exposure reduction can be demonstrated	1. Risk reduction is feasible 2. Risk reduction not yet demonstrated 6. Public health impact is unknown	5. Regulation is a necessary precondition for assuring a science base and for assuring protection of the health of the public
Elements of surveillance system	Specific tobacco constituents of both the products and the smoke they generate	Disease outcomes	Consumption of tobacco products and of PREPs Biomarkers of exposure to tobacco products Personal tobacco product use and related behavioral patterns	Disease outcomes	Tobacco product marketing, including PREPs

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TABLE 8-1 Continued

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Regulatory principles (all refer to tobacco-related PREPS, except for 11)	1. Ingredient disclosure 3. Preclinical testing required to support health-related claims 7. Evidence for no increased risk 8. Added ingredient review 9. Performance Standards	6. Products with claims would require post-marketing surveillance and epidemiological studies	2. Yield assessment 4. With specific claims, no increased exposure to unclaimed compounds 9. Performance standards 11. Exposure reduction claims for pharmaceutical PREPs	5. Labeling for products with claims cannot be false or misleading	10. Enforcement power
Research and other recommendations	3. Develop appropriate animal models and in vitro assays of pathogenesis	1. Sufficient data to allow estimation of dose-response 2. Develop validated biomarkers of disease	4. Clinical and epidemiological studies in human are required	Comprehensive surveillance is recommended	Regulation is recommended

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Exposure assessment is inherent also in the first question of the committee's charge. The principal conclusion that exposure reduction can be demonstrated is fairly straightforward. Several components of the proposed surveillance system will provide important exposure information and at least four regulatory principles (#2, #4, #9, #11) would assure that relevant data are collected.

Risk characterization is the central question of the report and, indeed, of harm reduction writ large. The fourth question of the committee's charge regarding the public health impact of the products is perhaps the most important asked of the committee. The principal conclusions that harm reduction is feasible but not yet convincingly demonstrated and that a beneficial public health impact is not assured are two that are most easily misunderstood as contradictory if not carefully considered. They drive important considerations of the report—harm reduction should be pursued and encouraged but every aspect of it should be watched and studied vigilantly. Appropriate tools of public health must be available and must be powerful. Surveillance of personal tobacco product use and related behavioral patterns and of disease outcomes will provide some of the data necessary to assure a positive population impact. The regulatory principle that labeling for PREPs with claims cannot be false or misleading is another necessary safeguard against a negative public health impact.

Risk management, the culmination of the risk assessment process, is directly related to the committee's principal conclusion that regulation is a necessary precondition for advancing knowledge and for ensuring a public health benefit. Two of the most important tools for a risk manager, are knowledge, which will be developed if the research and surveillance recommendations are followed and if the regulatory principles #1-9 are adhered to, and enforcement power, which is called for in regulatory principle #10. A properly conducted risk assessment outlines gaps in the knowledge required by the risk manager and the assumptions used for the risk characterization in the absence of complete data. Explicit description of these assumptions can help identify the research that will most significantly improve understanding of risk and, thereby, affect public policy.

Questions asked by a risk manager help to integrate the scientific data and assumptions provided by the formal risk assessment into the desired public policy. The questions also assure that regulation, a risk-management tool for tobacco harm reduction proposed by this committee, is based on and informed by the risk assessment process. Questions might include:

- Which of the thousand known tobacco-related toxicants are most important to consider in the assessment of risk? Is the scientific data available for adequate hazard identification?

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- Are the data presented by the manufacturer based on assays reflecting the manner in which the product is actually used by the consumer?
- Are the claims by the manufacturer adequately supported by the scientific data? Is the risk characterization accurately conveyed in a manner understandable to the consumer?
- What constitutes a substantial degree of overall risk reduction?
- Who has the burden of proof for each type of claim? Is the burden of proof sufficient to assure the products will provide a benefit to the user? Is the burden of proof so high that innovation will be stifled and the possible benefit never realized?
- What can be done immediately to manage the possible risks of these products, given that the science base is currently inadequate?
- Are there parties responsible for assessing and assuring harm reduction outside this regulatory agency? And if so, are the boundaries of risk-management responsibility and authority clear to all parties?

The data presented and scientific limitations identified in Chapter 5, the surveillance system outlined in Chapter 6, and the regulatory framework described in Chapter 7 provide a sound basis for the risk management for tobacco harm reduction.

In summary, tobacco harm reduction could lead to reduced risk of disease for those who cannot give up tobacco. Unfortunately, without the appropriate public health tools of research, surveillance, education, and regulation, tobacco harm reduction could result in a personal and public health disappointment.

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Section II

Evidence for the Science Base

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9

Nicotine Pharmacology

BASIC AND HUMAN PHARMACOLOGY

It is some 550 years since the eponymous Jean Nicot sent tobacco and seeds from Portugal to Paris, passing *Nicotiana tabacum* from the Americas to Northern Europe by way of the Iberian peninsula. Nicotine itself was subsequently extracted and synthesized, culminating in the identification of the spatial orientation of the natural *(S)* isomer in the late 1970s (Domino, 1999). Up to 10% of the nicotine in tobacco smoke is the *(R)* isomer, probably arising from racemization during combustion (Benowitz, 1986). Nicotine has gained particular prominence as the addictive constituent of most tobacco based products and, to a lesser extent, as an effective insecticide.

Nicotine, 3-(1-methyl-2-pyrrolidinyl) pyridine, has a molecular weight of 162.23 and is a volatile, colorless base (pK_a=8.5) that turns brown and acquires the typical odor of tobacco on exposure to light. Roughly 69% of its pyrrolidine nitrogen is ionized (positively charged) at pH 7.4 and 37°C, whereas its pyridine nitrogen is un-ionized. This feature of nicotine renders its absorption and renal excretion highly pH dependent, because uncharged lipophilic bases pass easily over lipoprotein membranes and charged organic bases do not. For example, nicotine is primarily ionized at the pH (5.5) of smoke from the flue-cured tobaccos in most American cigarettes, and buccal absorption is minimal (Gorrod and Wahren, 1993). By contrast, smoke from air-cured tobaccos in pipes, cigars, and many European cigarettes is less acidic and is well absorbed through

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the mouth (Armitage et al., 1978; Gori et al., 1986). Nicotine constitutes about 95% of the total alkaloid content of commercial cigarette tobacco (Gorrod and Jenner, 1975).

The mechanisms by which nicotine exerts its actions at a molecular level are complex. Dale (Dale, 1914) noticed the structural similarity between nicotine and acetylcholine (Ach) and the resemblance of the effects of nicotine in vivo to those of Ach after pretreatment with the muscarinic antagonist atropine. The muscarinic effects of Ach are now recognized to be mediated via one of the five heptahelical muscarinic receptors (M1-M5). Ligation of these receptors may activate downstream signaling pathways via their interaction with diverse G proteins. Nicotinic receptors (nAchRs), by contrast, are ligand gated ion channels (Domino, 1999; Lena and Changeux, 1998). These pentamers are comprised of various combinations of α, β, γ, and δ subunits. Recent studies have demonstrated that specific configurations of these subunits mediate the diverse effects of nicotine. Although this area of research is evolving, the neuronal subunits that appear to be primarily responsible for the effects of nicotine contain $\alpha_{3,4,7}$ and $\beta_{2\text{ and }4}$ subunits. The $\alpha_4\beta_2$ subtype is particularly prevalent in the brain and may be responsible for the self-administration of nicotine. Mice deficient in the β_2 subunit do not self-administer nicotine (Cordero-Erausquin et al., 2000), suggesting that this subunit in particular may be important in reinforcing the effects of nicotine. In addition, some preliminary evidence suggests that the α_7 subunit may play a significant role in withdrawal and sensory gating functions of schizophrenics (Adler et al., 1998; Nomikos et al., 2000; Panagis et al., 2000). Localization studies have identified nAchRs in the brain, neuromuscular junctions, autonomic ganglia, and adrenal medulla (Gundisch, 2000). Ligation of nAchRs by nicotine opens the channel, and the ionic influx activates signal transduction pathways, culminating in release of a number of different neurotransmitters, which have been related to nicotine's pharmacodynamic effects. These include dopamine (pleasure and appetite suppression), serotonin (appetite suppression and mood modulation), epinephrine and norepinephrine (arousal and appetite suppression), Ach (arousal and cognitive enhancement), vasopressin (memory improvement), glutamate (improvement in learning), β-endorphin (mood modulation and analgesia), and δ-aminobutyric acid. Nicotine also increases nAchR expression. For example, prenatal nicotine exposure upregulates the pulmonary expression of the α_7 receptor subunit and consequently affects fetal lung development in monkeys (Sekhon et al., 1999). Nicotine caused lung hypoplasia and reduced surface complexity of developing alveoli in this model. Collagen surrounding the large airways and vessels was increased, as was the number of type II cells and neuroendocrine cells in neuropepithelial

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bodies. Many animal studies have also demonstrated that nicotine administration upregulates expression of nAchRs in the brain. Similarly, ligand-binding studies have demonstrated an increase in binding sites for nicotine analogues in the cerebral cortex and hippocampus of smokers compared to nonsmokers (Perry et al., 1999), although the extent to which this may contribute to the differential central effects of nicotine observed in smokers is unknown.

Dopamine is believed to be the dominant neurotransmitter in the maintenance of drug-taking behavior (DiChiara, 1999; Koob, 1992). The area of the brain that is responsible for the reinforcing effects of all drugs of abuse is the mesolimbic pathway, which contains the ventral tegmental area (VTA), nucleus accumbens, amygdala, cingulate gyrus, and frontal lobe and is rich in dopamine. The VTA and nucleus accumbens seem particularly important in nicotine's reinforcing effects. Activation of nAchRs in the VTA and other parts of the midbrain, modulates the ascending mesolimbic dopamine system, including the nucleus accumbens (George et al., 2000; Yu et al., 2000). Nicotine self-administration behavior is diminished by either surgical or chemical ablation of dopaminergic pathways or by treatment with dopamine antagonists (Kameda et al., 2000). Nicotine evokes an increase in dopamine levels in brain microdialysis studies (Fu et al., 2000). In addition, monoamine oxidase A and B, responsible for the metabolism of dopamine, are reduced by a compound in tobacco smoke that also results in higher levels of neurotransmitters (Quattrocki et al., 2000).

The release or inhibition of other transmitters may also play a role in nicotine addiction. They may be responsible for mood modulation, the modest enhancement of performance, and the weight-reducing effects of nicotine (Benowitz, 1999; Chiodera et al., 1990; Chowdhury et al., 1989; U.S. DHHS, 1988). Mood modulation by nicotine has been a controversial topic, since laboratory studies do not validate the smoking-induced enhancement of mood self-reported by smokers. Furthermore, individuals experience greater positive affect when smoking after a period of abstinence. The relief of negative affect by tobacco use may be more a function of abating withdrawal symptoms (Cinciripini et al., 1997; RCP, 2000). Finally, in addition to its traditional pre- and postsynaptic actions at synapses and at chemoreceptors in the carotid and aortic bodies, nicotine also evokes the release of epinephrine from the adrenal medulla and may act directly to activate ion channels distinct from nAchRs. For example, nicotine has been shown to block directly inward rectifier potassium channels, an effect of potential relevance to cardiac arrhythmogenesis (Wang et al., 2000b).

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PHARMACOKINETICS

Absorption

Although buccal absorption is influenced by the pH of tobacco or tobacco smoke, tobacco smoke from all sources is rapidly absorbed from the large surface area of the small airways and the alveoli, following dissolution in the pulmonary fluid at pH 7.4 (Zevin et al., 1998). Nicotine is also readily absorbed from the skin; this property has been exploited in the use of patch delivery in nicotine replacement therapy (NRT) for cigarette smokers (Figure 9-1). Nicotine is well tolerated as a dermal application, even in individuals who suffer from irritant skin disorders (Benowitz, 1995).

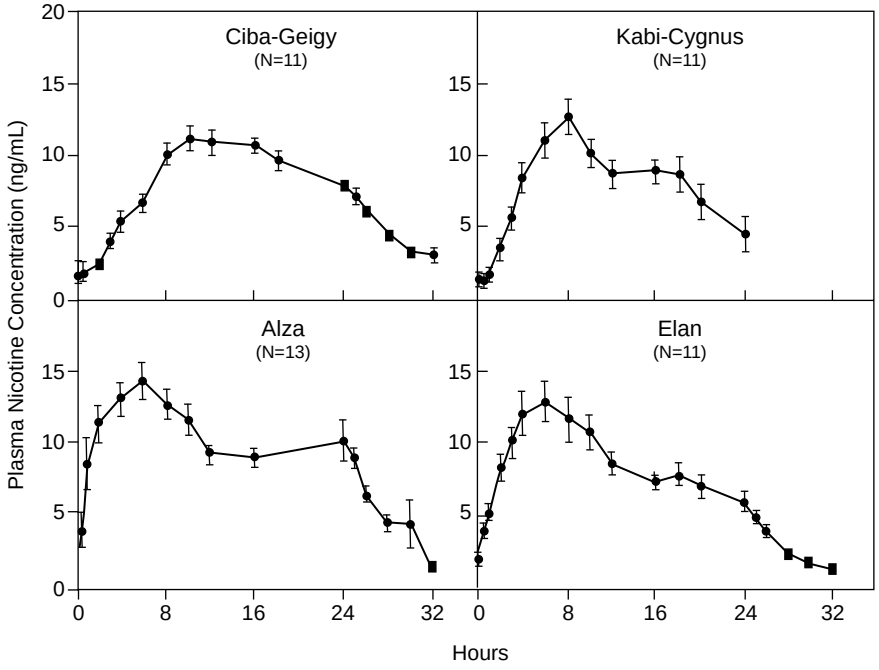


FIGURE 9-1 Time curves of plasma nicotine concentrations.

NOTE: Time curves of plasma nicotine concentration after application of four different transdermal nicotine delivery systems. The Ciba-Geigy Habitrol, the Alza (SmithKline Beecham) Nicoderm, and the Elan Prostep patches were worn for 24 hours, while the Kabi-Cygnus (Pharmacia) Nicotrol patch was worn for 16 hours.
SOURCE: Benowitz, 1993. Reprinted from *Drugs* 1993; 45(2):157-170 with permission. © Adis International, Inc.

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Following ingestion, as with chewing tobacco, the pH dependence of nicotine ionization favors its absorption by the small intestine, rather than the stomach, although a timed-release preparation, which permits colonic absorption (Green et al., 1999), has also been developed for use in ulcerative colitis as discussed below. Although the peak levels of nicotine attained after chewing tobacco may approximate those after smoking, the shape of the curve of plasma concentration versus time is quite different (Figure 9-2). Thus, after smoking a cigarette, plasma levels of nicotine rise rapidly to a peak, which is maintained transiently after the cigarette is inhaled, rather than the more gradual and sustained elevation after oral

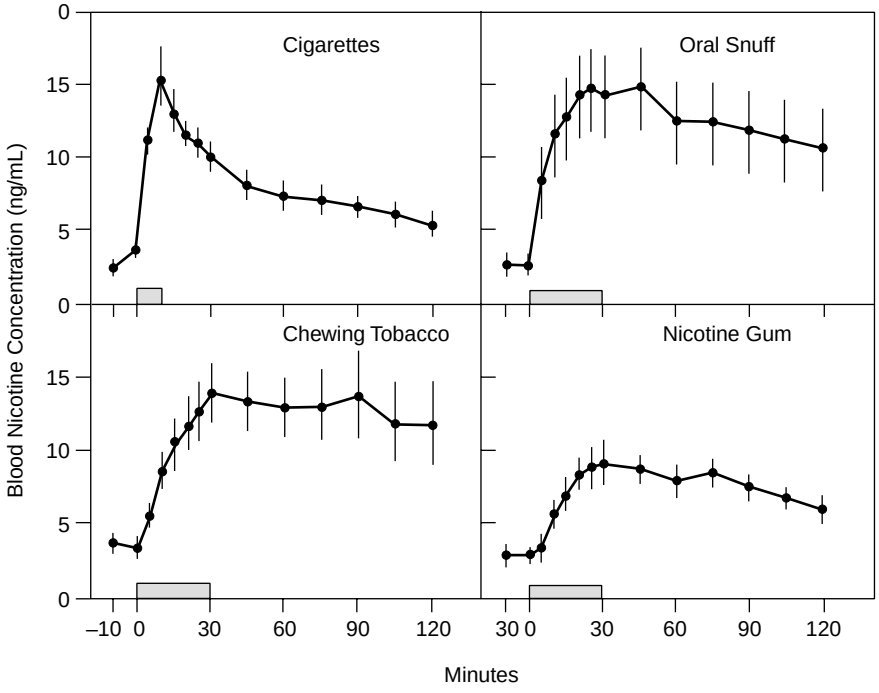


FIGURE 9-2 Blood nicotine concentrations.

NOTE: Blood nicotine concentrations during and after cigarette smoking for nine minutes, oral snuff (2.5 grams), chewing tobacco (average 7.9 grams), and nicotine gum (two 2 mg pieces). Data represent average values for 10 subjects (±SEM). Horizontal bars above time axis indicate period of tobacco or nicotine gum exposure.
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ingestion. The evoked liking, systemic response, and addiction potential of the former pattern of nicotine delivery exceed those of the latter (Benowitz et al., 1988). It takes roughly 10-15 seconds for nicotine, inhaled by puffing a cigarette, to reach the brain, and puffing is associated with a marked arterial-venous gradient of nicotine (Benowitz, 1995; Benowitz et al., 1988; Guthrie et al., 1999). This rapid central nervous system (CNS) delivery permits the smoker to adjust the nicotine dosage to a desired effect, reinforcing self-administration and facilitating the development of addiction (Benowitz, 1995). This contrasts with the slower increase and lesser increment in brain nicotine attained after transdermal delivery, which facilitates the development of tolerance (see below). The average cigarette contains 10-15 mg of nicotine and delivers, on average, roughly 1-2 mg of nicotine systemically to the smoker. However, smoking habit—puff intensity, duration, and so forth—can markedly alter nicotine bioavailability. By comparison, the systemic doses of nicotine from other delivery systems are roughly 1 mg from a 2 mg gum; 5-22 mg per day from transdermal patches; 0.5 mg per dose from one spray per nostril; 3.6 mg from 2.5 grams of snuff, held in the mouth for 30 minutes and 4.5 mg from 7.9 grams of chewing tobacco chewed for 30 minutes (Benowitz and Jacob, 1999).

Following its absorption, nicotine circulates with roughly 60% in the ionized form. It is poorly (around 5%) protein bound (Benowitz et al., 1982) and widely distributed, at least in rats and rabbits, particularly in liver, lungs, and brain (Benowitz et al., 1990).

Distribution and Metabolism

The presence of both aromatic and aliphatic carbon and nitrogen atoms in nicotine affords multiple sites for metabolic oxidation and subsequent conjugation reactions (Figure 9-3). The disposition of nicotine has been reviewed in depth elsewhere (Benowitz and Jacob, 1999; Gorrod and Schepers, 1999). Briefly, roughly 80% of the metabolic inactivation of nicotine involves oxygenation of the 5'-carbon to yield cotinine. This appears to involve an intermediate cytochrome P-450 (CYP)- derived 1',5'-imminium ion, which is further metabolized by aldehyde oxidase to yield cotinine (Brandange and Lindblom, 1979; Gorrod and Hibberd, 1982; Murphy, 1973). This iminium ion is an alkylating agent and has been speculated to have relevance to the carcinogenicity of tobacco, although this is not established (Hibberd and Gorrod, 1983). Oxidation of this radical may also yield nornicotine or 4-(3-pyridyl)-4-oxo-*N*-methylbutylamine. CYP2A6 and, to a lesser extent, 2B6 appear to play the predominant roles in nicotine carbon oxidation in humans (Benowitz and Jacob, 1999; Nakajima et al., 2001; Nakajima et al., 2000; Yamazaki et al., 1999). Although roughly

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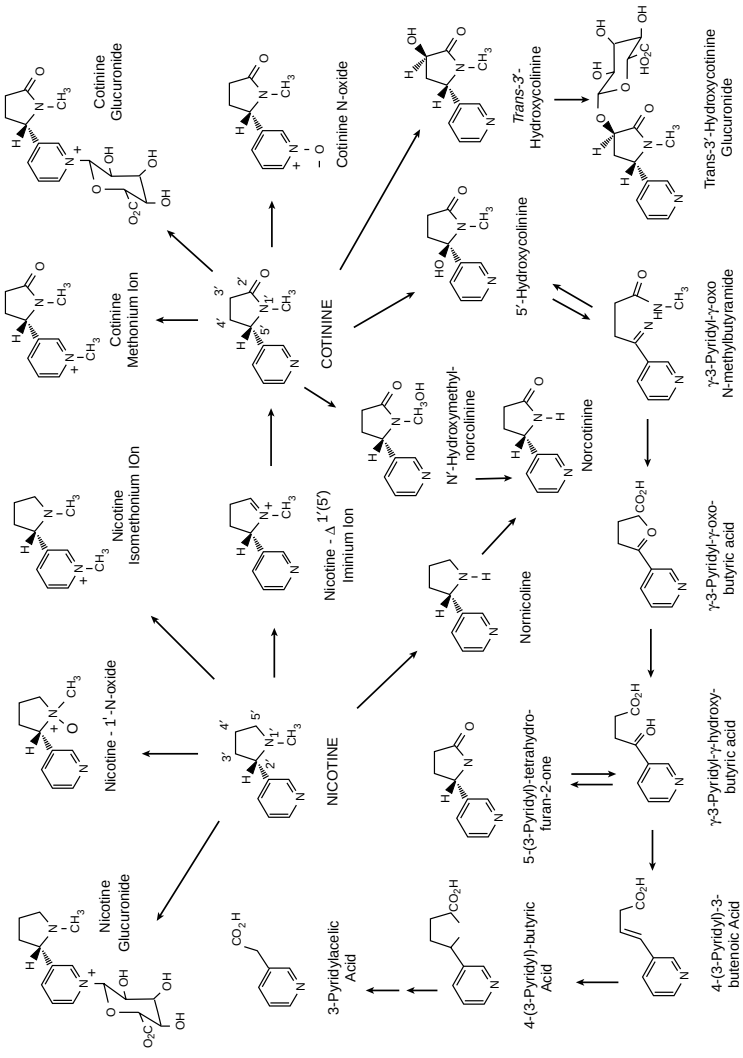


FIGURE 9-3 Nicotine metabolic pathways.

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15% of a nicotine dose is excreted in human urine unchanged, all of the primary metabolites, including cotinine, are subject to further oxidation reactions. Oxidation appears to involve only the alicyclic pyrrolidine nitrogen in biological systems (Gorrod and Schepers, 1999). Nicotine-1'-*N*-oxide may be reduced to nicotine in man by gut bacteria (Dajani et al., 1975).

Phase two metabolites can be formed by methylation, glucuronidation, sulfation, or glutathione conjugation reactions with primary oxidation metabolites. Formation of such polar, water soluble molecules facilitates excretion. Although great interindividual variation is noticeable, glucuronides may account for roughly 40% of the urinary nicotine metabolites in humans. This variability may also be apparent among ethnic groups. Thus, the most abundant phase 2 metabolite in the urine of North Americans is the *N*-glucuronide of cotinine, whereas in Europeans the *O*-glucuronide of *trans*-3'-hydroxycotinine predominates (Gorrod and Schepers, 1999). Similarly, the metabolism of nicotine is slower in African Americans than in Caucasians, due to both slower oxidative metabolism of nicotine to cotinine and slower *N*-glucuronidation (Benowitz et al., 1999; Caraballo et al., 1998; Perez-Stable et al., 1998). Asian Americans also metabolize both nicotine and cotinine more slowly than do Caucasians. Nicotine clearance declines with age (Molander et al., 2001). Although there is some evidence for differences between men and women in the pharmacodynamic response to nicotine (Pomerleau et al., 1991), this does not appear to reflect systematic differences in nicotine pharmacokinetics. Nicotine readily crosses the placental barrier, although there is no apparent conversion of nicotine to cotinine by placental tissues or microsomal fractions (Pastrakuljic et al., 1998). Although the potential for fetal toxicity must be considered in women undergoing NRT (as discussed below), this consideration usually occurs in the context of relativity. Thus, the hazard to the fetus of maternal cigarette smoking is well established (Oncken et al., 1998; Robinson et al., 2000), whereas the theoretically much smaller risk of NRT remains entirely notional.

Clearance of nicotine falls with hepatic blood flow during sleep (Gries et al, 1996) and a circadian pattern in both circulating nicotine and cotinine is evident (Figure 9-4). Although the half-life of nicotine is about 2-3 hours when based on plasma levels, it approximates 11 hours when based on urinary excretion (Benowitz and Jacob, 1994, 1999), so circulating levels tend to accumulate during the day. The afternoon levels of nicotine in the plasma of smokers generally range from 10 to 50 ng/ml, whereas steady-state levels with patches range from 10 to 20 ng/ml and with the nasal spray from 5 to 15 ng/ml (Benowitz and Jacob, 1999).

Sophisticated approaches to analysis not just of nicotine and cotinine, but of minor oxidative metabolites and many phase 2 metabolites, have

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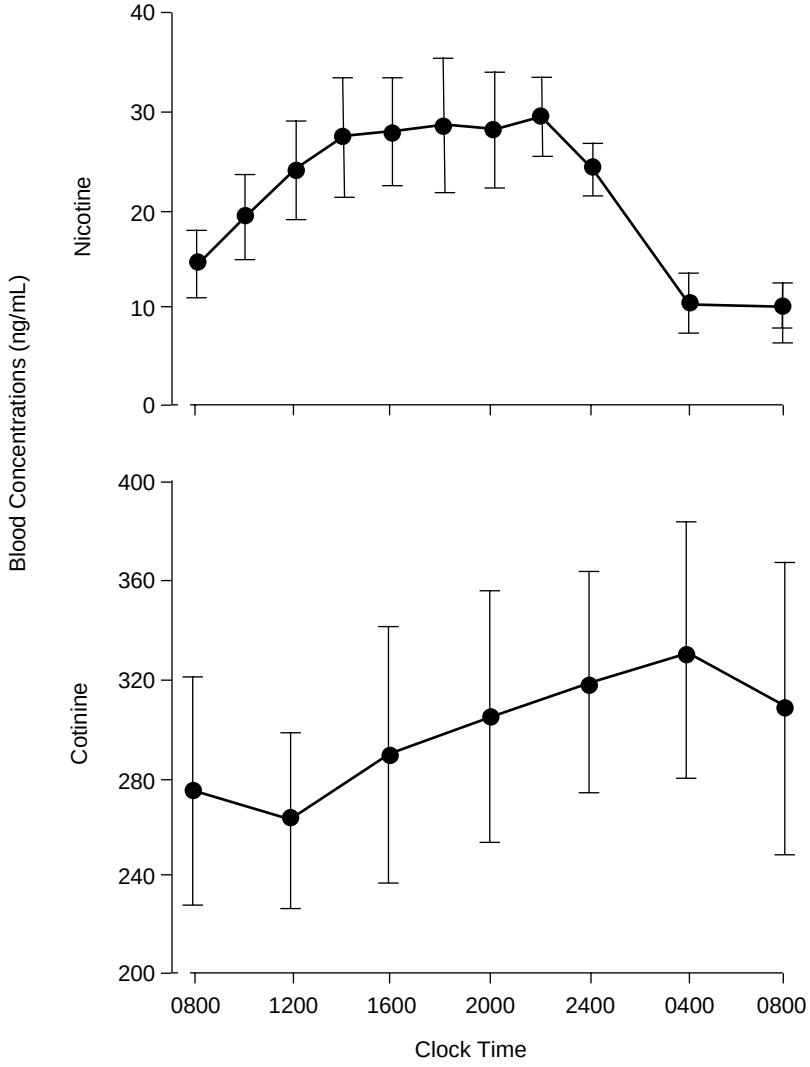


FIGURE 9-4 Circadian blood concentrations of nicotine and cotinine during unrestricted smoking.

NOTE: Data are mean ± SE for eight subjects.
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now been established, albeit in few laboratories. These encompass sensitive and specific methodologies, such as tandem mass spectrometry (Byrd et al., 1994). These tools will afford a more comprehensive approach to investigating genetic (e.g., nAchR or CYP2A6 polymorphisms; McKinney et al., 2000; Nakajima et al., 1996) and environmental factors (e.g., CYP2A6 induction or repression by alcohol or other drugs; Niemela et al., 2000), which might contribute to interindividual variability in nicotine pharmacokinetics. For example, they will include the integration of assessment of nitrosamines formed from nicotine into long-term studies of the safety of NRT.

Excretion

Nicotine is excreted by both glomerular filtration and tubular secretion. Acidification of urine greatly increases its renal clearance, which impedes tubular reabsorption by ionizing the nicotine (Benowitz and Jacob, 1999). Urinary excretion of cotinine is less influenced by pH since it is more basic. However, renal clearance of both compounds is influenced highly by urinary flow rates (Benowitz and Jacob, 1999).

PHARMACODYNAMICS

Cardiovascular Effects

The factors that mediate the effects of nicotine are complex, confounded as they are in the cardiovascular system by direct and reflex effects, acute effects and long-term desensitization, and secondary effects due to sympathoadrenal activation. Acute delivery of nicotine in a cigarette results in a transient tachycardia, cutaneous vasoconstriction, and a rise in blood pressure (Cryer et al, 1976). By contrast, desensitization of vascular or central receptors by nicotine may contribute to the lower blood pressure observed in chronic smokers (Charlton and While, 1995).

The mechanisms involved in mediating the adverse effects of cigarette smoking and of smokeless tobacco on the cardiovascular system are poorly understood, but are thought to include induction of an adverse lipoprotein profile (Allen et al., 1994), induction of a chronic inflammatory response (Strandberg and Tilvis, 2000) including oxidative tissue injury (Morrow et al., 1995; Patrignani et al., 2000; Reilly et al., 1996; Traber et al., 2000), activation of platelets and other hemostatic variables (Benowitz et al., 1993; Ludviksdottir et al., 1999; Whiss et al., 2000), and impairment of endothelial function (Raitakari et al., 2000). Following the introduction of NRT, there was considerable concern about the cardiovascular safety of this intervention, especially in patients with preexisting cardiovascular disease. However, NRT has been shown to be effective, without an apparent cardiovascular hazard, not only in the general

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population (Benowitz and Gourlay, 1997), but also in patients with established coronary vascular disease (Greenland et al., 1998; Joseph et al., 1996; Nitenberg and Antony, 1999). Controlled studies have demonstrated that switching from cigarette smoking to NRT is associated with amelioration of the lipoprotein and hemostatic profiles (Allen et al., 1994; Ludviksdottir et al., 1999; Winther and Fornitz, 1999) and a reduction in platelet activation (Nowak et al., 1987).

Although evidence of a clinical cardiovascular hazard of NRT has yet to emerge, several observations suggest that aspects of the cardiovascular effects of nicotine merit further research. For example, cigarette smoking impairs endothelial function (Celermajer et al., 1993; Raitakari et al., 1999), which appears to be a surrogate marker of future clinical vascular disease (Dugi and Rader, 2000). Interestingly, nicotine has been reported to impair flow mediated brachial arterial endothelial function (Chalon et al., 2000) and bradykinin stimulated endothelial function in dorsal hand veins of volunteers (Sabha et al., 2000). On the other hand, short term administration of nicotine gum did not alter the coronary constrictor response to the cold pressor test—reflective of the effects of sympathadrenal activation—in patients with established coronary artery disease (Nitenberg and Antony, 1999). Although exposure of mice deficient in apoenzyme E (Apol E) to cigarette smoke accelerates atherogenesis (Gairola and Daugherty, 1999), there have been no analogous studies of nicotine and no studies of atherosclerotic plaque progression in individuals receiving long-term NRT.

Switching to NRT in the short term does not appear to correct the systemic markers of inflammation in cigarette smokers (Nilssen et al., 1996), and there are conflicting reports of the direct effects of nicotine on free radical generation in vitro (Gouaze et al., 1998; Guatura et al., 2000; Wetscher et al, 1995). Interestingly, many cigarette smokers also drink alcohol (Swahn and Hammig, 2000), and alcohol is a potent prooxidant in humans (Meagher and FitzGerald, 2000). While ethanol increases the clearance of nicotine, the acute hemodynamic effects of ethanol and nicotine are additive (Soderpalm et al., 2000), perhaps reflecting a common mechanism. However, there are no reports of the effects of NRT on contemporary markers of oxidative stress or a comprehensive assessment of its effects on markers of inflammation.

Central Effects

General Effects

Nicotine is a CNS stimulant. Paradoxically, it is perceived to be relaxing in stressful situations and to enhance gating of relevant stimuli. The smoker does not react as much as the nonsmoker to external distrac-

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tions—hence its use by those trying to relax or concentrate. Stress increases the smoker's nicotine consumption. An increase in respiratory rate and heart rate has been observed with NRT. Sleeplessness has also been reported in patients using NRT (Gourlay et al., 1999). Nicotine overdose is remarkably difficult to achieve with NRT (Labelle and Boulay, 1999), however, it occasionally complicates the use of nicotine-containing insecticides. In these cases, central symptoms—initially tremors, nausea, vomiting, and possibly convulsions—give way to signs of central depression and neuromuscular blockade (Saxena and Scheman, 1985).

Memory and Cognition

Although there is considerable interest in the potential effects of nicotine on cognition (Emilien et al., 2000; Waters and Sutton, 2000), this has not been formally evaluated in individuals receiving NRT. Activation of nAchRs containing the α_7 subunit results in Ach release and calcium activation, and both effects have been implicated in memory formation and cognition (Kem, 2000). Recent interest has been focused by co-immunoprecipitation of the amyloid A β(1-42)-fragment and the α_7nAchR from the dendtritic plaques of Alzheimer's disease (AD) lesions (Wang et al., 2000a). The β-fragment of amyloid A binds to the receptor and prevents its activation by nicotine, potentially implicating defective nAchR activation in the pathogenesis of AD. Again, although there is some evidence for a slowing of deterioration of AD in individuals who smoke (Debanne et al., 2000; Doll et al., 2000; Jarvik, 1991; Lopez-Arrieta et al., 2000; Merchant et al., 1999), along with a considerable literature relating to the use of cholinesterase inhibitors for this condition, NRT has not been formally evaluated in AD.

Addiction

The Biological Basis of Addiction. Although tobacco products contain several thousand chemicals, nicotine is considered to be the principal constituent in tobacco that leads to the persistent use of tobacco products (U.S. DHHS, 1988). However, other yet unknown constituents in tobacco may also have a role in the maintaining the use of tobacco. For example, smokers experience a reduction of monoamine oxidase (MAO) activity in the brain (Berlin et al., 1995) as a result of some constituent in smoke (Fowler et al., 1996); inhibition of MAO may result in antidepressant activity (Oxenkrug, 1999) and contribute to the high prevalence in smoking among individuals with depressive disorders. Physical addiction to nicotine is associated with euphoriant and other psychoactive effects, the development of tolerance, and the experience of withdrawal symptoms

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when the tobacco product is no longer used (U.S. DHHS, 1988). In addition, the rate of absorption and therefore the speed of delivery of nicotine to the brain also play a significant role in the addictive potential of nicotine (Henningfield and Keenan, 1993). These factors contribute to the reinforcing effects or persistent use of nicotine and also may be responsible for day-to-day regulation of nicotine levels in tobacco users.

Psychoactive and reinforcing effects from nicotine are the result of the release of a number of neurotransmitters and hormones (Benowitz, 1999; U.S. DHHS, 1988; Watkins et al., 2000). This cascade of events is associated with mood modulation, cognitive and motor performance enhancements, and weight reduction. These effects may contribute to the initiation and maintenance of tobacco use. Chronic administration of nicotine can lead to neuroadaptation. One of the effects of neuroadaptation is the development of tolerance. Adaptation occurs so that the brain can maintain a state of homeostasis despite an increased release of neurotransmitters. This process includes receptor inactivation and desensitization and an increase or upregulation in receptor number (Benowitz, 1999). The extent of these changes could vary depending on the receptor subtype and site (Watkins et al., 2000). Tolerance may lead to individuals' using more of the tobacco product or switching to higher nicotine-containing products.

Neuroadaptation may subsequently lead to withdrawal symptoms when the tobacco user is no longer exposed to the product. Withdrawal symptoms include negative affect (e.g., irritability, frustration or anger, anxiety, dysphoric or depressed mood), restlessness, difficulty in concentrating, insomnia, decreased heart rate, and increased appetite or weight (APA, 1994). These symptoms occur among regular users of cigarettes and smokeless tobacco (Hughes and Hatsukami, 1992). They are less pronounced with nicotine gum use, but this distinction blurs with prolonged use of the gum (Hughes et al., 1986b; West and Russell, 1985). Approximately 49% of self-quitting smokers and 87% of tobacco cessation program attendees meet Diagnostic and Statistical Manual of Mental Disorders (DSM) IIIR (APA, 1987, 1994) criteria for nicotine withdrawal syndrome (Hughes and Hatsukami, 1992). These withdrawal symptoms peak during the first week of abstinence and return to baseline levels by four weeks (Hughes et al., 1990a). The intensity of these symptoms is further reduced over the course of time. The only exception to this pattern is increased weight. Weight may continue to increase over six months, and a reduction may not be seen at all or only after several months of abstinence (Hughes et al., 1990a).

A major determinant of whether nicotine is likely to be addictive is the amount and speed of nicotine delivery. The route of delivery also determines the pattern of nicotine delivery (as discussed earlier). For

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example, each puff of a cigarette delivers a bolus dose of nicotine, resulting in a rapid peak, which then falls to a trough level. The time between these bolus doses allows for resensitization of brain nAchRs, so that each delivery can remain reinforcing (Benowitz, 1999). In addition, this route of administration allows the delivery of a greater number or frequency of reinforcements. Other delivery routes result in a slow and persistent absorption of nicotine. Subjective effects, the desire to use more of a drug, and the actual self-administration of a drug are functions of absorption rate (Henningfield and Keenan, 1993). Therefore, whereas cigarettes have high abuse potential, nicotine patches have lower abuse potential.

It is also important to note that addiction to nicotine is not just a biological phenomenon, but also one in which learning or conditioning has taken place. Nicotine self-administration comes under the control of stimuli that have been associated with smoking or tobacco use. These stimuli can precipitate a strong desire for nicotine, withdrawal symptoms, or drug effects. Exposure to these stimuli may lead to the same biological effect on neural substrates as observed from the direct actions of the drug (Childress et al., 1999). Furthermore, stimuli associated with tobacco use, such as the sensory aspects of smoking, can become reinforcing as well; that is, they become secondary reinforcers. In addition a tobacco user develops expectancies regarding the use and effects of the substance, leading to a psychological reliance on the drug.

The susceptibility to nicotine addiction is thus a result of both the biological effects of the drug and learning history. In addition, environmental factors (e.g., access to tobacco, restrictions on tobacco, social modeling) and genetic or organismic factors (e.g., rate of nicotine metabolism, psychiatric disorders, personality factors) may play a significant role. Specific populations might be more vulnerable to nicotine addiction. Genetic twin studies have shown heritability estimates that range from 28 to 84%, with a mean estimate of 53% (Hughes, 1986). Genetic heritability has been associated with the onset as well as the persistence of smoking (Heath et al., 1998, 1999). Examples of what is inherited may be differences in sensitivity to nicotine (Pomerleau, 1995), the rate of nicotine metabolism (Tyndale et al., 1999), or other mechanisms such as genetic polymorphisms in the dopamine transporter and subtypes of dopamine receptors (Lerman et al., 1999; Shields et al., 1998). In addition, individuals with comorbid disorders tend to have a high prevalence of smoking. For example, high prevalence of smoking is found in individuals with depressive disorders, schizophrenia, and alcohol or drug abuse disorders (Breslau, 1995; Hughes et al., 1986a). The mechanisms responsible for susceptibility to smoking may differ across disorders. The nicotine-associated release of neurotransmitters is similar to those found with antidepressants and may be responsible for the association between smoking and depression and

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for the recurrence of depressive disorders after smoking cessation. Furthermore, studies have shown a genetic linkage between smoking and depression (Kendler et al., 1993), and observations have been made that depression can predate smoking or smoking predate depression (Breslau et al., 1993, 1998). For individuals with schizophrenia, the sensory gating effects of nicotine via the α_7 nicotinic receptor may provide some symptomatic relief (Dalack et al., 1998; Freedman et al., 1997). A genetic link also seems to exist for alcohol and nicotine addiction (Hughes, 1986), along with commonality in the release of dopamine across all drugs leading perhaps to increased sensitivity to the reinforcing effects of drugs or the potential for substitution. Furthermore, nicotine can be used to offset the aversive effects of drug use (Benowitz, 1999).

Assessment of Addiction. Various measures and methods have been developed to measure dependence on a drug and its abuse or addiction potential (see Table 9-1). These measures and methods are important in examining harm reduction products since addiction to a drug is one of the determining factors associated with its harmful consequences. The addictive potential of a drug can be determined by examining the number of individuals, within the general population and among those exposed to the drug, who are regular users of the drug or are considered dependent on a drug, using specific criteria. Determination of the abuse potential of nicotine replacement agents has also relied on examining whether users of the product escalate their use over time or continue its use beyond a recommended period. However, deciphering whether this persistent

TABLE 9-1 Measures of Dependence or Addiction and Abuse Liability

Measures for Dependence or Severity of Dependence
Daily or regular smoking (cotinine level)
DSM criteria
International Diagnostic Code
Surgeon General's report, 1988
Fagerström Tolerance Questionnaire
Fagerström Nicotine Dependence Test
Methods to Assess for Addiction or Abuse Liability Surveys
Daily use or dependence among the general population
Daily use or dependence among those exposed to the drug
Escalation of drug use
Relapse rates
Laboratory models
Psychoactive or subjective effects
Drug discrimination
Conditioned place preference
Drug self-administration
Withdrawal

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medication use is a result of the desire to prevent relapse to cigarettes or an addiction to the product can be difficult. The "addictiveness" of a drug can also be determined by the extent to which relapse occurs among those individuals who have tried to stop using it. In addition, various animal and human laboratory methods have been developed to assess the abuse liability of a drug, including measurement of psychoactive or stimulus effects and determination of whether a drug is a reinforcer (positive or negative) leading to preference for a drug or drug self-administration (Bozarth, 1987; Balster, 1991; U.S. DHHS, 1988).

According to Food and Drug Administration (FDA) guidelines, abuse liability is determined by two primary factors (see deWit and Zacny, 1995). One is the likelihood of repeated use, which is determined by the drug's psychoactive, positive reinforcing effects and the extent to which it can relieve withdrawal symptoms as a result of chronic use. Repeated use may also be determined by the degree of unpleasant effects associated with drug use. The second factor is the incidence of adverse short- and long-term consequences as a result of use. Drugs with a greater number of adverse consequences are thought to be more likely to have abuse liability than those with fewer adverse effects.

Measures and Surveys of Dependence. Surveys and instruments have been used to assess the amount and frequency of use (e.g., daily use, regular use) and whether an individual is dependent on a drug based on specific diagnostic criteria. These measurement tools have been used to determine the extent to which dependence occurs within a general population and among those who have been exposed to or have experimented with the drug. In addition, these diagnostic tools for dependence have been used to determine whether dependence on nicotine is a dose-related phenomenon. Both DSM-IIIR and DSMIV (APA, 1987,1994) and the World Health Organization (WHO) International Diagnostic Code-10 (IDC-10) (WHO, 1991) are the commonly used criteria to assess for nicotine dependence. According to the DSM and the IDC-10, substance dependence, including nicotine, results in several behavioral and cognitive characteristics and physiological manifestations (see Table 9-2). The primary criteria for dependence based on these definitions include a strong desire to take the drug for periods longer than intended, problems controlling its use, use despite negative consequences or having a higher priority than other activities or obligations, tolerance, and physical withdrawal (APA, 1994; WHO, 1991). Not all criteria have to be met, nor is any one criteria critical to satisfy a diagnosis of dependence. In the 1988 Surgeon General's report *The Health Consequences of Smoking: Nicotine Addiction*, the primary criteria for drug dependence included (1) highly controlled or compulsive use of a drug, (2) psychoactive effects from the drug, and (3) drug-reinforced behavior. Additional criteria, similar to those listed in DSM-IV and IDC,

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TABLE 9-2 Criteria for Substance Dependence from DSM IV

DSM-IV	IDC-10
A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifest by three (or more) of the following, occurring at any time in the same 12-month period	
Tolerance—need increased amounts of substance to achieve desired effect, or diminished effect with continued use of same amount	Increased tolerance
Withdrawal	Sometimes, physical withdrawal
Substance often taken in larger amounts or over a longer period than intended	A strong desire to take the drug
Persistent or unsuccessful efforts to cut down or control substance use	Difficulty controlling use
Great deal of time spent in activities necessary to obtain the substance or recover from its effects	
Important social, occupational, or recreational activities given up or reduced because of substance use	Higher priority given to drug use than to other activities and obligations
Substance use continued despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance	Persisting use despite harmful consequences

SOURCE: Adapted from RCP, 2000.

were also included. The number or type of symptoms experienced varies across different drugs of abuse. The major difference between nicotine and some other drugs of abuse is the lack of intoxication in regular tobacco users that results in behavioral and cognitive disruption (U.S. DHHS, 1988). However, this makes nicotine no less an agent of addiction or dependence than other drugs (Stolerman and Jarvis, 1995). In fact, many cigarette smokers exhibit at least as many indicators of dependence as other drug users and abusers (CDC, 1995b; U.S. DHHS, 1988). Assessment of nicotine dependence using these criteria can be made by a number of diagnostic structured instruments including the Composite International Diagnostic Interview-Substance Abuse Module, the National Institute of

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Mental Health-Diagnostic Interview Schedule (NIMH-DIS), and the NIMH-DIS for children (see Colby et al., 2000, for review).

Other methods have been used to assess addiction or dependence on nicotine or tobacco products. For example, population surveys such as the National Household Survey on Drug Abuse (NHSDA) assess for symptoms of tobacco dependence and include such items as how many current tobacco users (1) reported daily use of the product, (2) have tried to cut down, (3) were unable to cut down or quit or experienced difficulty quitting, (4) felt a need for more tobacco for the same effect, (5) felt dependent, or (6) felt sick or experienced withdrawal symptoms when stopping smoking and met at least one or more of these indicators (CDC, 1995a, b; CDC, 1994). Researchers have used meeting a specified number of these symptoms as proxy measures for the DSM-IV criteria for substance dependence. In some assessments, individual items, such as experiencing withdrawal symptoms or difficulty quitting have been of particular focus as indicators of dependence (CDC, 1994, 1995a, b).

Other reports assessing nicotine dependence determine the number of smokers who meet criteria for high level nicotine dependence according to the Fagerström Tolerance Questionnaire (FTQ; Fagerström, 1978; Fagerström and Schneider, 1989) or the revised version, the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Several adolescent versions have also been developed (Prokhorov et al., 1996, 1998; Rojas et al., 1998). Although this scale is continuous, a cut-off score of 6-7 or higher has been used to separate low and high level of dependence.

Based on the measures of dependence described above, the percentage of cigarette users that report dependence on their tobacco product varies according to the population examined (e.g., total populations, daily smokers, ever smokers, and so forth) and the definition of dependence used. According to the NHSDA, a population survey of noninstitutionalized civilians 12 years and older, the proportion of respondents who reported experiencing at least one indicator of dependence was 75.2% among those individuals who used cigarettes one or more times during the 30 days preceding the survey and 90.9% among daily users (reporting daily use for ≥ 2 consecutive weeks during the 12 months preceding the survey) (CDC, 1995b). In another study, the estimated prevalence of dependence according to the DSM-IIIR criteria (APA, 1987) among Americans 15-54 years old sampled for the National Comorbidity Survey was about 24.1% (Anthony et al., 1994). The lifetime prevalence of dependence among middle-aged male ever smokers in Japan was 42, 26, and 32% according to IDC-10, DSM-IIR, and DSM-IV criteria, respectively (Kawakami et al., 1998). In another study, very high rates were observed with 90% of a general sample of middle-aged male smokers meeting

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DSM-III criteria for dependence (Hughes et al., 1987). Kandel and associates (1997) used the indicators listed in the NHSDA (see above) including items assessing for frequency and quantity of use and problems related to use in order to diagnose nicotine dependence. The criteria for diagnosis were based on the DSM-IV method in which smokers must experience three or more of seven indicators of dependence. The findings showed that while 8.6% of the general population 12 years and older met criteria for nicotine dependence, 28% of those who had used tobacco products in the past year experienced nicotine dependence. A few studies have also been conducted with adolescents. The study conducted by Kandel and associates (1997) using the NHSDA examined the prevalence of nicotine dependence by age. They observed that about 19.9% of adolescents who smoked any cigarette met criteria for nicotine dependence, compared to rates ranging from 26.4 to 32.7% among smokers between the ages of 18 and 49 years and 23.7% among those 50 and older. In a study conducted in New Zealand, about 20% of a general sample of 18-year-olds were dependent on tobacco and more than half (56.4%) of the sample who smoked daily met DSM-IIIR criteria for nicotine dependence.

In another survey that used the FTQ with a score of 7 or more (indicative of a high level of dependence, not dependence per se), only 19% of Japanese male ever-smokers age 35 and older met this criteria (Kawakami et al., 1998), but 36% of U.S. males did (Hughes et al., 1987). Among adolescent smokers, the prevalence of high level of dependence according to the FTND or FTQ has also been wide-ranging. Many of the studies assessed prevalence of high level of dependence in special populations of adolescents. The highest percentage of adolescents with a score of 7 or more on the FTQ was observed among a heavy-smoking group who participated in a nicotine patch trial, with an observed rate of 68% (Smith et al., 1996). The lowest rate was 20% using a modified FTQ with a cutoff score of 7 or higher, which was observed in vocational technical high school student smokers (Prokhorov et al., 1996). This proportion was lower than the 50% rate that the investigators observed among adult smokers.

An indicator of the addiction potential of a drug is the development of daily or regular use or dependence among those who have been exposed to it. There is strong evidence to show that a significant number who are exposed to cigarettes may become daily smokers or dependent on them. Among high school students participating in the 1997 Youth Risk Behavior Survey (YRBS), of the 70.2% who tried cigarette smoking, 35.8% went on to smoke daily. This rate of escalation from trying cigarette smoking to regular use of tobacco is similar to the 33-50% observed in other studies (U.S. DHHS, 1994). The development of dependence among those who tried tobacco products is similarly high. In one population-

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based study of adult smokers, about 31.9% of those who tried tobacco became dependent on it based on the DSM-III criteria (Anthony et al., 1994). In another study of young adults aged 21-30, of the 74% who had smoked tobacco at least once, 27% developed DSM-IIIR criteria for tobacco dependence (Breslau et al., 1993). Similar data are not available for smokeless tobacco users. Existing data are limited to the number of individuals who report having used smokeless tobacco in the past month versus the number who report lifetime use of smokeless tobacco; this method of calculation represents about 18% for smokeless tobacco users. This figure is compared to 37% for cigarette smokers using a similar method of calculation (U.S. DHHS, 2000).

Relapse rates among those who tried to quit have been considered another indicator of dependence on or addiction to a drug. Relapse is high among a general population of smokers who have tried to quit smoking, with only 2.5% being able to sustain abstinence for a year (CDC, 1994). One study showed that among self-quitters, about two-thirds reported smoking within two days postquit (Hughes et al., 1992). The rate of relapse among a population of smokers who have undergone clinical treatment tends to be about 75%, with a significant number of these relapses occurring within the first few weeks. These rates and patterns of relapse are similar to those observed with smokeless tobacco (Hatsukami and Severson, 1999) and other drugs of abuse (Hunt and Matarazzo, 1973; Maddux and Desmond, 1986; Wallace, 1989). High rates of relapse are also observed among youth that smoke. Based on results from the YRBS, among high school students who smoked daily, 72.9% had ever tried to quit smoking and only 13.5% were former smokers (CDC, 1998).

Most research on the dependence on nicotine replacement products has examined the persistence of use or escalation of use over time. No data are available on the prevalence of daily use in the general population or on dependence on these products according to diagnostic criteria for dependence or FTND scores. The rate of persistent use of nicotine replacement products among smokers enrolled in clinical trials who were assigned these products is much lower than the rate of persistent use of cigarettes, ranging from 9% for nicotine gum to 18% for nicotine nasal spray (Hughes, 1998). With nicotine nasal spray the rates of persistent use are higher, and there is evidence to show that a small number escalate the amount of use over time (deWit and Zacny, 1995). In general, addiction to these products is significantly less than addiction to cigarettes due to the relatively slow absorption of nicotine, the side effects that sometimes results from use, and the cost per unit of purchase.

In summary, research shows that nicotine delivered via cigarettes and smokeless tobacco is likely to lead to a high prevalence of use and dependence. One third to one-half of individuals who experiment with

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cigarette products are likely to become regular users and dependent on them. No data are available on the initiation of nicotine replacement product use among tobacco-naïve individuals or rates of diagnosable dependence, although these rates are likely to be low (Shiffman et al., 1998). The number of new NRT users among those attempting to quit was approximately 10% per year prior to over-the-counter (OTC) nicotine replacement products and 26% per year after OTC availability (Shiffman et al., 1998). Therefore, increased availability has led to increased use of these products among smokers, however, the rate of use still remains quite low. Furthermore, among smokers who use nicotine replacement products, persistent use tends to be low. Future research endeavors should concentrate on developing uniform methods and measures for assessing nicotine dependence so comparisons can be made across products and studies. The present measures are limited to assessing the extent of dependence and limited by being designed to diagnose other drugs of abuse and not specifically to diagnose nicotine dependence. In addition, as new products evolve, rates of initiation, regular use or persistent use and dependence, or progression to dependence as a result of experimentation should be assessed.

Models of Addiction. Several methods have been developed using clinical and animal models to determine the addiction potential or abuse liability of a drug. These include models of self-administration, drug discrimination, and conditioned drug placement. Models to examine withdrawal have also been developed. For humans, subjective responses to drugs can also be determined, although these responses may not necessarily be associated with actual drug-taking behavior.

When a drug is reinforcing, it is more likely to be self-administered or preferred compared to a control drug that has no abuse potential. The subject is exposed to a drug, typically, at varying doses and then required to choose between this particular drug and a control drug or an alternative reinforcer (e.g., sucrose for animals, money for humans), or between different doses of the drug.

- In *self-administration models*, the animal is required to perform a particular maneuver, such as lever pressing, to obtain the drug, which is typically administered intravenously. This lever pressing could be based on a fixed ratio (a specific number of responses are required prior to drug delivery), a progressive ratio (more responses are required after each drug delivery), or an interval schedule (a certain time interval is necessary before drug delivery), or a combination of these. Scheduled reinforcement in response to environmental stimuli associated with drug administration are called second-order schedules (Goldberg et al., 1981). Drugs can be made

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available for a fixed amount of time or throughout the day. Drugs that are reinforcing prompt the subject to work more or pay a higher cost for them than for the control; reinforcing drugs also lead to a greater persistent responding for them even when they are no longer available (Henningfield et al., 1991). Typically the dose-response curve is U-shaped (Risner and Goldberg, 1983; Rose and Corrigall, 1997) with low and high doses resulting in reduced drug self-administration. Low doses may produce limited or undetectable effects and high doses may produce adverse effects.

- *Drug discrimination models* involve training the subject to discriminate the stimulus properties of drug A from drug B. A third drug may be introduced, and the animal or human subject is asked to decide whether the drug is more like drug A or drug B (Bigelow and Preston, 1989; Preston, 1991). Subjects can also be trained to discriminate among several sets of drugs or different doses of a drug. This model allows determination of the mechanism of action of a drug. For example, if one wanted to determine whether an opioid has μ agonist or κ agonist activity, an experiment can be developed in which the subject is trained to discriminate between drugs that are known to have each of these activities. After this period of training, the drug in question is introduced and the subject has to indicate whether the drug is more like drug A (e.g., a μ agonist) or drug B (a κ agonist). This model can be also used to determine whether a drug has the stimulus properties of a particular pharmacological class of drugs that are abused. A similar method is used in a *drug preference procedure*, in which subjects are exposed to drug A and drug B, and are required to self-administer each of these drugs during separate experimental sessions. After the drug exposure or sampling period, subjects are then asked to choose between drugs A and B, to determine their preference for one drug or another (de Wit, 1991). Drug A or B can be two different doses of a drug, different types of drugs, or an active and placebo drug.
- The *conditioned place preference model* also is used to determine the abuse liability of a drug. Animals are trained that the drug is available only in a particular place (e.g., a specific chamber). Then a determination is made of how frequently the animal is willing to go to this place. If it is chosen significantly more frequently than the other place which is associated with a control drug or no drug administration, the experimental drug may have abuse potential (Bozarth, 1987).
- *Drug withdrawal models* have typically involved observing signs and symptoms during a period of abstinence after repeated admin-

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istration of a drug (U.S. DHHS, 1988; Hughes et al., 1990; Malin et al., 1992). These withdrawal symptoms can be precipitated by antagonist drugs or allowed to occur naturally. Although the occurrence of withdrawal signs and symptoms does not necessarily indicate that that the drug will be abused, it may be one indicator of the potential for abuse.

- Finally, among humans, *subjective responses* to drugs can be determined (Jasinski and Henningfield, 1989; Fischman and Foltin, 1991; Jaffe and Jaffe, 1989). Subjects can be asked to indicate the intensity of experiencing different subjective effects, such as the degree of euphoria, liking of a drug, "high," desire for a drug, or "head rush." Comparisons can be made across different drugs and across doses within a particular drug. Subjects can also be asked to rate the effects of a drug using various standardized measures that have been developed to assess a drug profile (e.g., stimulant-like effects, depressant effects) such as the Addiction Research Inventory (Haertzen et al., 1963).

Self-administration paradigms have been used to demonstrate that a wide range of species (monkeys, mice, dogs, and rats) exhibit preference for administering nicotine over a control vehicle (Henningfield and Goldberg, 1983; RCP, 2000; Rose and Corrigall, 1997; Swedberg et al., 1990; U.S. DHHS, 1988). Studies have shown that these animals are willing to lever-press several hundred times in order to receive an injection of nicotine (Goldberg et al., 1981; Risner and Goldberg, 1983). However, unlike other drugs such as cocaine, the range of environmental conditions under which nicotine serves as a reinforcer is more restricted (Henningfield and Goldberg, 1983). In laboratory studies, human smokers have also been found to lever-press for intravenous doses of nicotine (Henningfield and Goldberg, 1983) as well as to self-administer greater number of doses of nicotine nasal spray (Perkins et al., 1997) and nicotine gum (Hughes et al., 1990b) compared to the respective placebo conditions. Clinical trials for the nicotine spray (Sutherland et al., 1992) and gum (Hughes et al., 1991) have also observed greater self-administration of active compared to placebo doses. Most human studies, however, have focused on assessing smoking behavior, looking at various indices of exposure, including number of cigarettes, number of puffs, puff volume, puff duration, inhalation duration, and intercigarette interval as well as biochemical indices of exposure such as cotinine or nicotine concentrations. Smoking behavior has been examined in response to changes in dose of cigarettes, preloading with nicotine or administering nicotinic antagonists and other drugs that may affect the reinforcing effects of nicotine (U.S. DHHS, 1988). Self-administration of nicotine is dose related in

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both humans and animals, although there is lesser dose-dependency than other drugs in animals, and the curve is somewhat flat for humans (Corrigall, 1999). Nonetheless, reduced nicotine self-administration in humans is observed with nicotine preloading and compensation with changing nicotine doses in cigarettes. Speed of nicotine delivery also plays a role in the extent to which nicotine is self-administered. Rapid bolus injections of nicotine result in greater self-administration than a slow infusion (Wakasa et al., 1995). Self-administration can be blocked by mecamylamine, a nonspecific nAchR antagonist or by dopamine receptor antagonists (see earlier discussion of the biological basis of addiction). Self-administration can be facilitated not only by the dosing characteristics of cigarettes or nicotine but also by the sensory characteristics of cigarettes (Henningfield and Goldberg, 1983; Rose and Corrigall, 1997).

Smokers tend to report dose-related subjective effects such as drug liking, drug strength, head rush, and feeling dizzy or aroused as a result of inhaled, buccal (smokeless tobacco), intravenous, or nasal spray nicotine administration (Fant et al., 1999; Henningfield et al., 1985; Jones et al., 1999; Perkins et al., 1994a, 1994b). Smokers who have a history of drug dependence exhibit a similar dose-related increase in "liking" and other subjective responses for intravenously administered nicotine as observed for cocaine, amphetamine, morphine, pentobarbitol, and heroin (Jasinski et al., 1984; Jones et al., 1999; Keenan et al., 1994). Findings from another study also revealed that intravenous nicotine was misidentified as cocaine or amphetamine by the study participants who had histories of drug use (Henningfield et al., 1985; Jones et al., 1999). Subjective responses to nicotine gum, patch, spray and inhaler have been less pronounced than responses to cigarettes or intravenous nicotine (deWit and Zacny, 1995; Henningfield and Keenan, 1993; Schuh et al., 1997).

The occurrence of withdrawal symptoms after cessation of continuous nicotine infusion in rodents has been demonstrated (Malin et al., 1992). In humans, withdrawal symptoms upon cigarette smoking cessation has also been well established (Hughes et al., 1990a). However, fewer studies have been conducted with other tobacco products or nicotine replacement agents. Cessation of smokeless tobacco use generally produces less intense withdrawal symptoms than cessation of cigarette smoking (Hatsukami et al., 1987; Keenan et al., 1989). However, in a population of smokeless tobacco users enrolled in clinical trials, the severity and number of withdrawal symptoms from smokeless tobacco were comparable to those experienced by cigarette smokers who were trying to quit (Hatsukami et al., 2000). Nicotine gum withdrawal symptoms also tend to be significantly less intense in number and severity than cigarette withdrawal symptoms (Hatsukami et al., 1991, 1993, 1995), and higher doses of gum produce greater withdrawal than lower doses of gum (Hatsukami

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et al., 1991). On the other hand, among those who have used the product for a prolonged period, nicotine gum may be comparable to cigarettes in the number of withdrawal symptoms experienced (Hughes et al., 1986b; West and Russell, 1985).

In summary, various laboratory studies have observed that nicotine is self-administered, produces psychoactive effects, and produces withdrawal symptoms. The route of delivery can determine the extent to which nicotine-containing products can produce these effects and lead to addiction, with cigarettes showing the highest potential for addiction.

Future studies on new products should routinely measure the abuse potential of a drug by using the various methods that have been described. Furthermore, these paradigms could be considered to test medications focused at reducing frequency of tobaccco use.

Gastrointestinal Tract

Nicotine exerts its effects on the gastrointestinal (GI) tract mainly via the activation of parasympathetic ganglia. Generally, it increases tone and contractility, and nausea, vomiting, and diarrhea can result from an overdose. However, GI irritation, other than mild nausea, rarely complicates NRT (Wong et al., 1999). Salivation evoked by cigarette smoking also rarely accompanies the doses used in NRT. Nicotine slows gastric emptying and reduces gastric and pancreatic secretions.

Given the association of smokeless tobacco with oral cancer (Schildt et al., 1998; Winn, 1997), there was initial concern that this might pose a risk with NRT. Follow-up studies of intermediate duration do not substantiate this concern (Wallstrom et al, 1999). In recent years, the observation that ulcerative colitis appears to be ameliorated in smokers has prompted the evaluation of NRT for this condition and controlled studies support its efficacy (Guslandi, 1999; Sandborn, 1999) and a delivery system permitting controlled release of nicotine in the colon has been developed.

Other Effects of Nicotine

There is much speculation about the existence of gender-specific effects of nicotine and their implications for NRT strategies. There is some evidence of differences in the pharmacodynamic effects of nicotine between genders and of an influence of timing in the menstrual cycle on the response to NRT and the success of attempts to quit (Pomerlau et al., 1991; Gritz et al., 1996). Women appear to have more pronounced withdrawal symptoms during the late luteal phase of the menstrual cycle, and it has been suggested that fear of weight gain, confidence in the ability to quit,

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and readiness to quit smoking might be differentially related to gender. Maternal smoking has adverse effects on the fetus, including the risk of spontaneous abortion, abruptio placentae, reduced weight at birth, and deformities (Haustein, 1999). In animal models, maternal consumption of nicotine results in hyperactivity in the neonate (Tizabi et al., 2000). Maternal smoking has been associated with sudden infant death syndrome and appears to result in an intellectual deficit, apparent in children at least as old as 6-7 years of age (Frydman, 1996).

Chronic smokers tend to have lower blood pressure than nonsmokers (Charlton and While, 1995). Maternal smoking has been associated with a reduced incidence of preeclampsia, but the mechanism is unclear (Lain et al., 1999). Nicotine does cross the placental barrier unchanged and maternal passive smoking raises nicotine levels in breast milk and in suckling infants. No linkage of nicotine consumption to birth deformities has been established; however, its contribution to the other effects of smoking during pregnancy is less clear (Haustein, 1999). For example, nicotine inhibits placental aromatase, reduces uteroplacental blood flow, and may adversely affect endothelial function in animal models (Torok et al., 2000). Presently, the experience with short-term NRT has not been associated with reports of adverse effects on fetal outcome, however; the number of individuals evaluated in this setting has been small.

Cigarette smoking is associated with lower body weight and quitting is associated with weight gain. Involvement in a weight control program amplifies the efficacy of NRT (Danielsson et al., 1999). Although the mechanisms are likely to be complex, nicotine is of some substantial relevance to this effect of smoking. Aside from its stimulatory effect on basal metabolic rate, nicotine reduces the synthesis of neuropeptide Y (NPY) in the arcuate neurons which project into the paraventricular nucleus (PVN). Injection of NPY into the PVN results in hyperphagia and obesity in rats (Frankish et al., 1995). Smoking is associated with insulin resistance, which improves after cessation (Kong et al., 2000). Elevated leptin levels have been related to weight loss in smokers, and levels appear to correlate with the degree of insulin resistance (Assali et al., 1999). Crossover studies in volunteers suggest that plasma leptin levels correlate with changes in insulin sensitivity and that intermediate levels are found in subjects on NRT (Oeser et al., 1999).

Nicotine has diverse effects on other hormonal systems in the brain that are presently poorly understood. For example, chronic nicotine administration stimulates mediobasohypothalamic tyrosine hydroxylase and suppresses pro-opiomelanocortin mRNAs. Suppression of forebrain β-endorphins may be relevant to maintaining nicotine self-administration (Rasmussen, 1998). Similarly, smoking is extremely prevalent among schizophrenics and may modulate the response to certain antipsychotics,

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such as clozapine (McEvoy et al., 1999). It has been speculated that this behavioral response may represent an attempt at self-medication, and some evidence for a disease-related abnormality in central nAchR sensory gating in schizophrenia has begun to emerge (Breese et al., 2000; Dalack et al., 1998).

Much less information is available concerning the effects of nicotine on other systems. Examples of potentially important observations include impairment of the immune response (Sopori et al., 1998), adverse effects on bone formation (Fung et al., 1999), and testicular hypogonadism (Kavitharaj and Vijayammal, 1999; Reddy et al., 1998), all observed with nicotine in model systems. The relevance of these observations, if any, to the doses of nicotine achieved in humans during NRT is unknown and should be evaluated.

Finally, cigarette smoking may result in drug interactions. While polycyclic hydrocarbons in cigarette smoke induce CYP isozymes of potential relevance to carcinogenesis, nicotine itself can induce CYP2E1, CYP2A1/2A2, and CYP2B1/2B2 in animal studies. Cutaneous vasoconstriction due to nicotine can delay the absorption of transdermal and subcutaneously administered medication, including insulin and heparin, and the stimulant effects of nicotine can diminish the analgesic effects of some opioids and the sedative effects of benzodiazapines (Zevin and Benowitz, 1999). Cigarette smoking reduces the hypotensive response to β-blockers (Fox et al., 1984), but the contribution of nicotine to this effect is unknown. Smoking reduces portal blood flow velocity and volume in humans and may modulate the disposition of drugs subject to hepatic metabolism (Rapaccini et al., 1996).

RESEARCH AGENDA

NRT has proven an effective strategy in the cessation of cigarette smoking that is remarkably well tolerated at least in the short to medium term. Although the experience is much more limited, NRT also holds promise as a strategy for reducing the number of cigarettes smoked by those who cannot or will not quit.

Both of these observations prompt considerations for future research. Thus, for those who quit smoking but continue to take NRT indefinitely, are there reasons to be concerned? First, nicotine can be addictive and although the daily exposure may be lower on NRT than when the individual was smoking, continued use implies psychological dependence, if not physical addiction. It is arguable whether this should be a concern, given the marked reduction of risk compared to smoking. However, it would seem reasonable to include surveillance of the dependence potential and various methods to determine abuse liability of various nicotine

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products. Furthermore, the implications of long-term nicotine intake for such factors as the safety of drug and alcohol consumption, progression of incidental diseases, impact of aging on cognitive and other physiological functions, and susceptibility to other forms of addictive behavior are largely unknown. For example, observations suggesting that nicotine impairs endothelial function, a property it shares with cigarette smoking, raise concerns about its effect on atherogenesis during long-term usage. Such an effect may take many years to emerge and highlights the importance of continued postmarketing surveillance of NRT. This is also true of carcinogenesis. For example, nicotine may be metabolized to nitrosamines (e.g. nicotine-derived nitroketone) with carcinogenic potential (Hecht, 2001; Hoffman et al., 1991). However, the methodology to assess their formation is just emerging, and the concentration-effect relationships and individual patterns of susceptibility are far from established. Studies of long term nicotine administration on surrogate variables that more closely resemble the mechanism under consideration (e.g., imaging of plaque progression) and attendant studies in animal models seems timely. Increasingly, the application of genomic and proteomic approaches is likely to clarify the differential effects of smoking and NRT on the expression and translation of genes related to the development of smoking-related diseases. Finally, the picture of nicotine's effect on inflammation and the immune response is confused and limited. More research is needed to clarify its effects on cytokine generation, the formation of nitric oxide and eicosanoids and oxidative injury. Research should continue to explore other potential therapeutic efficacies of NRT, including its use in ulcerative colitis, analgesia, weight reduction, Parkinson's disease, and cognitive disorders associated with aging and schizophrenia. Broadly speaking, the experience with long-term experience with nicotine via Swedish snus is reassuring with respect to safety, but formal evaluations of such risk from long-term use under controlled conditions have been scant (Idris et al., 1998; Raw and Macneil, 1990).

Continued use of NRT in conjunction with ongoing, albeit reduced, smoking prompts additional questions. For example, the constituents of cigarette smoke that mediate tissue injury are largely unknown, and it is also unknown if modulating the coincident nicotine level might influence their absorption, metabolic disposition, mechanism of action, or elimination. Design of such studies will rely on the development of more refined and tractable methodology to investigate the in vivo kinetics and dynamics of other constituents of cigarette smoke and their interactions with nicotine.

Finally, although ethnicity already seems relevant, other factors that determine interindividual differences in nicotine efficacy, safety, and addictive potential remain largely unexplored. Particular attention might be

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paid to genetic variation in proteins relevant to nicotine pharmacokinetics and dynamics and their interaction with environmental variables. As with other drugs, one anticipates increasing individualization of nicotine dosage and/or delivery when given as a therapeutic agent. Insight into the interaction of genetic and environmental factors that influence initiation (Gynther et al., 1999; Heath et al., 1999) of cigarette smoking, latency until the practice becomes habitual (Stallings et al., 1999), and the quantity then smoked (Koopmans, 1999) has been increasing. Clarification of how these factors interact is also likely to afford insights of value in predicting the individual likelihood of response to the use of NRT as a strategy for quitting or reducing tobacco exposure.

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10

Tobacco Smoke and Toxicology

PHYSICAL AND CHEMICAL CHARACTERISTICS OF TOBACCO SMOKE

Tobacco smoke is a complex mixture of toxicants and the chemical properties change—rapidly in some cases—as smoke ages. Toxicants measured at one point in time may not be what the smoker actually experiences. It is estimated that there are more than 2,000 chemical constituents of tobacco. Almost twice that number results when tobacco is burned incompletely during smoking. Three kinds of smoke can be described, each differing in terms of toxicant concentration, size of particles, effects of temperature, and a host of other characteristics. Mainstream smoke (MS) is what emerges from the "mouth" or butt end of a puffed cigarette. Sidestream smoke (SS) is what arises from the lit end of a cigarette, mostly between puffs. Environmental tobacco smoke (ETS), smoke present in air, consists of exhaled mainstream smoke and sidestream smoke.

Smoking machines are used to analyze mainstream smoke. A set of parameters has been agreed on by various international organizations. These parameters are 35-cm^3 puff volume, 2-second puff duration, once per minute puff interval, and smoking to a butt length of 23 mm for nonfiltered or 3 mm above the filter overlap for filter-tipped cigarettes. The "yields" of toxicants in the MS are frequently reported by the standard-setting organization. The two most well known organizations are the U.S. Federal Trade Commission (FTC) and the International Organization of Standardization (ISO). The controversy regarding the standard

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parameters and reporting of values is covered in other chapters of this report.

Mainstream smoke is pulled through the mouth end of the cigarette and then through a "Cambridge filter pad." Aerosol particles in the smoke larger than 1 μm in diameter are trapped with 99% efficiency. The material is referred to as cigarette smoke condensate or total particulate matter (TPM). "Tar" is the weight of TPM minus nicotine and water. The material that passes through the filter pad is the gas or vapor phase of cigarette smoke. In general, the vapor phase consists predominantly of compounds with a molecular weight <60 and the particulate phase consists of compounds with a molecular weight >200.

The yields of MS increase with successive puffs as the cigarette is machine-smoked due to the decrease in filtration provided by the cigarette rod itself. However, smoking behavior studies coupled with yield measurements suggest that yields remain consistent from first puff to last when assessed under real-life smoking conditions.

When tobacco is heated, moisture and volatile material are distilled, and combustion leads to the generation of volatile gases and the residual, carbonized char. Char reacts with oxygen in the air during puffing and smoldering, producing volatile gases (carbon dioxide, carbon monoxide, and water) and the inorganic material known as ash.

The highest temperature reached during the burning of tobacco is approximately 800˚C in the center of the burning zone during smolder. During puff, a solid-phase temperature of approximately 910˚C is reached at the burning zone periphery, while the gas temperatures are lower. They vary between 600 and 700˚C as the puff progresses. After the puff ends, solid-phase temperatures rapidly cool to approximately 600˚C. This greatly influences particle formation, particle size, and toxicant formation. These temperatures contrast with that achieved with a newly marketed cigarette-like device, Eclipse, that combusts differently than conventional cigarettes and aerosolizes nicotine and glycerin.

The chemical nature of MS changes as smoke ages. The burning zone generates a highly concentrated vapor that is drawn down the cigarette to form mainstream smoke. The vapor cools quickly (in milliseconds) due to diluting air. Less volatile compounds quickly condense, mostly in airborne state. A combination of physical size and concentration affects both thermal and mechanical properties, which influence the number of particles in smoke. Droplets of less than about 0.1 μm will attach to the tobacco through which they pass or to other particles, which continue on into MS. Particles with sizes around 1 μm are "filtered" out by depositing onto the tobacco surface.

MS is a highly concentrated aerosol mixture. Smoke particles are liquid, consisting of approximately 20% water by volume. The particles vary

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from less than 0.1 to 1.0-μm diameter. The small size and high concentration promote rapid coagulation, leading to decreased concentration and increased size of the resulting particles within less than a second. The size of particles also increases due to absorption of water, which is relevant for human smoking because of the high relative humidity of the human respiratory tract.

Sidestream smoke particles are smaller than MS particles initially. However, the aging of SS over a few minutes leads to an increase in particle size of ETS due to coagulation of particles and removal of smaller particles that attach to surfaces in the environment. Particle size in smoke is important, because it influences where within the respiratory tract a toxicant is deposited. Smaller particles, in general, deposit further down into the lungs.

Inhaled particles of the size found in tobacco smoke would be predicted to deposit mainly in the alveolar region of the lung. However, cigarette smoke-induced tumors are more prevalent in the bronchial region, suggesting that smoke particles deposit higher up in the respiratory tract than would be predicted from the initial particle size. (Recent increases of adenocarcinomas in lower airways of smokers are hypothesized to be due to so-called smoking compensation of low-yield products. Smokers of these products inhale more deeply to increase their nicotine dose.) Mucociliary clearance of inhaled particles up the respiratory tract may also increase the dose of particles to the upper airways. More importantly, the cloud-like nature of MS (see below) and the increased size of smoke particles on aging are responsible for this finding. Specific factors influencing the site of deposition in airways include coagulation of fresh smoke particles, absorption of water in the humid respiratory tract, human breathing patterns, aerodynamic interactions between nearby particles, electrostatic charge, and vapor deposition on airway walls (Dendo et al., 1998). Theoretical models of particle deposition predict that MS particles would have approximately 20% deposition in the respiratory tract. Measurements in humans suggest that deposition is actually much higher, from 50 to 95% (Phalen, 2000).

The explanation for this high deposition rate is that cigarette smoke is so dense, that it acts as a cloud. Clouds are high concentrations of aerosol particles surrounded by relatively clean air. They behave as entities that are much larger than the individual components. In depositing, the cloud behaves as if it were a much larger particle, with an aerodynamic diameter of approximately 6 or 7 μm. This particle size (see Figure 10-1) results in high total deposition in the respiratory tract, with especially high deposition in the tracheobronchial region.

Deposition in the respiratory tract is also influenced by the size of the person. Smaller individuals have greater tracheobronchial and less

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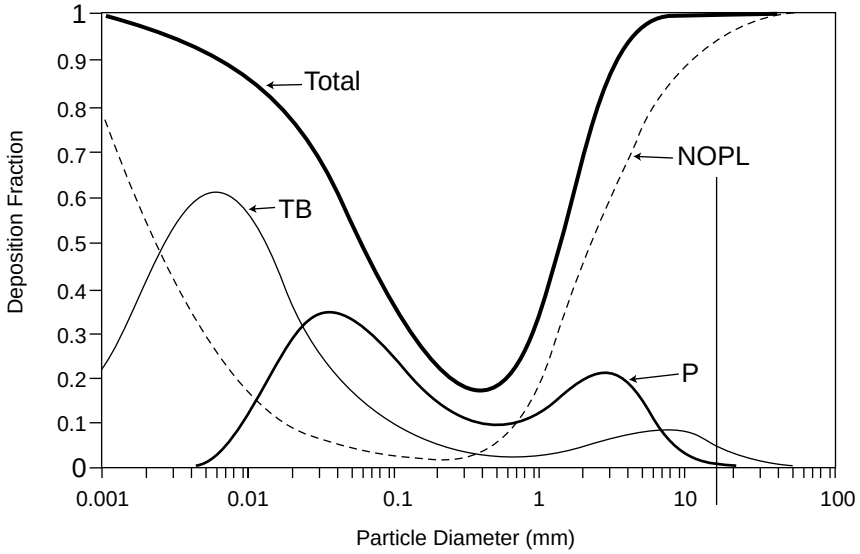


FIGURE 10-1 Aerosol deposition curves.

NOTE: applies to the Reference Man; NOPL=nasal oral pharyngeal laryngeal regions; TB=tracheobronchial region.
SOURCE: Adapted from National Council on Radiation Protection and Measurements report #125, 1997, with permission from the National Council on Radiation Protection and Measurements.

pulmonary deposition. Smaller individuals also have greater minute ventilation normalized for body weight, which is especially important for SS. This is hypothesized to be one reason infants might be more vulnerable to ETS. Importantly the small airway diameter of infants leads to high disposition in the upper airways, where it can be an irritant (Phalen, 2000).

Whole MS consists (by weight) of mostly air (nitrogen N_2, oxygen O_2, argon). The vapor phase constitutes approximately 20% by weight of the smoke, with the particulate phase accounting for approximately 5%.

The majority of cigarettes sold today have filters to remove portions of the smoke. Cellulose acetate filters are used almost exclusively in the United States, whereas charcoal filters are popular in Japan (Norman, 1999). Cellulose acetate filters remove some of the particulate phase of the smoke but have little influence on the vapor phase. The efficiency of particle removal depends on particle size and is minimal at the number-average particle size found in cigarette smoke (about 0.3 μm diameter). In

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general, cellulose acetate or paper filters remove tar and nicotine particles in this size range with an efficiency of 40–50%. Charcoal filters influence the retention of vapor-phase components and are made by adding up to 60 mg of activated charcoal in a segment of the cellulose acetate filter. Factors that influence the retention of vapor-phase compounds include the amount of charcoal used, the activity of the charcoal (based on surface area and pore volume), and the smoke velocity through the segment. Low-molecular-weight compounds with low boiling points (less than 150°C), which are not retained by the cellulose acetate filters, are partially removed by the charcoal filters. Removal efficiencies vary with the compound but are reported to be from 30 to 90%. As an example, benzene may be removed at an efficiency of 67%. Vented filters are designed to improve filter efficiency by decreased smoke flow through and increased residence time in the filter. However, vent holes can readily be covered by the fingers of the smoker, who may be inclined to do this in order to get the maximum amount of nicotine during smoking.

Under similar smoking conditions, filtered cigarettes will have lower MS yield relative to nonfiltered analogues. SS yields will not vary much, since they are reflective of tobacco weight burned during smolder. In general, more tobacco is consumed during smolder than during puffing. However, SS generally contains more alkaline and neutral compounds. SS smoke contains less or equal amounts of acids, phenols, and phytosterols than MS. Differences are due to temperature and mechanisms of chemical transfer (release) from the unburned tobacco. The approximate chemical composition of MS is given in Table 10-1. The relative concentration of specific constituents in MS versus SS tobacco smoke is shown in Table 10-2.

The pH of cigarette smoke influences the degree of protonation of the active addictive chemical, nicotine. The free-base form of nicotine is favored at a higher pH (more basic) and is more rapidly absorbed into the bloodstream than the mono- or diprotonated salt forms of nicotine that exist at lower pH (more acidic). Tobacco blends with a high sugar content produce a more acidic smoke; a basic cigarette smoke can be achieved by addition of ammonia.

TOXICITY OF TOBACCO SMOKE

The health effects of tobacco smoke in humans are well known from both clinical and epidemiological studies; such information is summarized in later chapters of this report. Animal studies of the toxicity of tobacco smoke are reviewed in the present section. The purpose of this review of animal models of tobacco smoke toxicity is to determine the potential usefulness of such models for assessing the toxicity of new and

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TABLE 10-1 Approximate Chemical Composition of Whole Mainstream Smoke

Constituent	% by Weight	
Air		
N_2	62	75.9
O_2	13	
Ar	0.9	
Vapor Phase		
Water	1.3	19.6
CO_2	12.5	
CO	4	
H_2	0.1	
CH_4	0.3	
Hydrocarbons	0.6	
Aldehydes	0.3	
Ketones	0.2	
Nitriles	0.1	
Heterocyclics	0.03	
Methanol	0.03	
Organic acids	0.02	
Esters	0.01	
Other compounds	0.1	
Particulate Phase		
Water	0.8	4.5
Alkanes	0.2	
Terpenoids	0.2	
Phenols	0.2	
Esters	0.2	
Nicotine	0.3	
Other alkaloids	0.1	
Alcohols	0.3	
Carbonyls	0.5	
Organic acids	0.6	
Leaf pigments	0.2	
Other compounds	0.9	

NOTE: Ar=Argon; CH_4=methane; CO=carbon monoxide; CO_2=carbon dioxide; H_2=hydrogen; N_2=nitrogen; O_2=oxygen.
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TABLE 10-2 Some Typical SS/MS Yield Ratios for Plain Cigarettes

Substance	MS Yield	SS/MS
Small Molecules		
Carbonyl sulfide	18-42 µg	0.03-0.1
HCN	160-500 µg	0.06-0.5
CO	10-23 mg	2.5-4.7
Hydrazine	20-43 µg	3
Methane	600-1000 µg	3.1-4.8
Acetylene	20-40 µg	0.8-2.5
Nitrogen oxides	100-600 µg	4-13
CO_2	20-50 mg	8-11
H_2O (gas phase)	3-14 mg	24-30
NH_3	50-130 µg	40-170
N_2 (generated)	<10 µg	>270
Neutral Heteroatom Organics		
Acetonitrile	50-130 µg	40-170
Benzonitrile	5-6 µg	7-10
Acetamide	70-100 µg	0.8-1.7
Methyl chloride	150-600 µg	1.7-3.3
Aldehydes, Ketones, Alcohols		
Acetaldehyde	0.5-1.2 mg	1.4
Propionaldehyde	175-250 µg	2.4-2.8
Acetone	100-250 µg	2-5
Acrolein	60-100 µg	8-15
2-Butanone	~30 µg	2.9-4.3
2-Furaldehyde	15-43 µg	4.9-7.4
Furfuryl alcohol	18-65 µg	3.0-4.8
Cyclotene[a]	3-5 µg	6-10
Pyranone[b]	13-150 µg	0.1-1.2
Phytosterols		
β-Sitosterol	59 µg	0.5
Campesterol	43 µg	0.6
Cholesterol	22 µg	0.9
Phenols		
Phenol	60-140 µg	1.6-3.0
Cresols (o-,m-,p-)	11-37 µg	1.0-1.4
Catechol	100-360 µg	0.6-0.9
Hydroquinone	110-300 µg	0.7-1.0
Acids		
Formic acid	210-490 µg	1.4-1.6
Acetic acid	270-810 µg	1.9-3.9
3-Methylvaleric acid	20-60 µg	0.8-1.5

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TABLE 10-2 Continued

Substance	MS Yield	SS/MS
Lactic acid	60-170 µg	0.5-0.7
Benzoic acid	14-28 µg	0.7-1.0
Phenylacetic acid	11-38 µg	0.6-0.8
Succinic acid	70-140 µg	0.4-0.6
Glycolic acid	40-130 µg	0.6-1.0
Amines, Pyridines, Alkaloids		
Methylamine	12-29 µg	4.2-6.4
n-Propylamine	1.6-3.4 µg	2.8-3.8
n-Butylamine	0.5-1.5 µg	2.2-4.0
Aniline	360 ng	30
Pyridine	16-46 µg	6.5-20
3-Ethenylpyridine	11-30 µg	20-40
Methylpyrazine	2-5 µg	3-4
Pyrrole	16-23 µg	9-14
Nicotine	0.8-2.3 mg	2.6-3.3
Myomine	13-33 µg	4.0-7.5
Nicotyrine	4-40 µg	5-14
Anatabine	2-20 µg	0.1-0.5
2,3′-Bipyridyl	16-22 µg	2-3
Aza-arenes		
Quinoline	0.5-2.0 µg	8-11
Isoquinoline	1.6-2.0 µg	2.5-5
Benzo[h]quinoline	10 ng	10
Indole	16-38 µg	2.1-3.4
Hydrocarbons		
Isoprene	330-1100 µg	13-19
Benzene	36-68 µg	5-10
Toluene	100-200 µg	6-8
Limonene	15-50 µg	4-12
Neophytadiene	66-230 µg	1-2
Polynuclear Aromatic Hydrocarbons		
Naphthalene	2.6 µg	17
Pyrene	45-140 µg	2-11
Benzo[a]pyrene	9-40 µg	2-20
Anthracene	24 ng	30
Phenanthrene	77 ng	2-30
Fluoranthene	60-150 ng	11
Nitrosamines[c]		
N-Nitrosodimethylamine	10-40 ng	10-50
N-Nitrosodiethylamine	nd-25 ng	3-35
N-Nitrosopyrrolidine	6-30 ng	6-30

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TABLE 10-2 Continued

Substance	MS Yield	SS/MS
N-Nitrosodiethanolamine	0-70 ng	1.2
N′-Nitrosonomicotine	0.2-3 µg	0.5-3
NNK[d]	0.1-1 µg	1-4
N′-Nitrosoanatabine	0.3-5 µg	0.3-1
Inorganic Constituents		
Cadmium	100 ng	4-7
Nickel	20-80 ng	0.2-30
Zinc	60 ng	0.2-7

NOTE: CO=carbon monoxide; CO_2=carbon dioxide; HCN=hydrogen cyanide; H_2O=water; N_2=nitrogen; nd=not detected; NH_3=ammonia; NNK=nitrosonornicotine ketone.

[a]Hydroxy-3-methyl-2-cyclopentanone.
[b]5m6-Dihydro-3,5-dihydroxy-2-methyl-4H-pyran-4-one.
[c]Much of the data in the literature on the smoke levels of volatile and tobacco-specific nitrosamines may be in error, due to artifact formation on the Cambridge pad part of the smoke collection procedure (Caldwell and Conner, 1990).
[d]Nitrosonornicotine ketone or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

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existing products that claim to reduce harm from tobacco use. The possibilities and the limits of using animals to test for toxic effects related to tobacco use are discussed. The major adverse tobacco smoke-induced health effects that require evaluation because of their prominence in humans are pulmonary inflammation, induction of lung cancer, chronic obstructive pulmonary disease (COPD), cardiovascular disease, reproductive and developmental effects, and the suppression of the immune system.

In Vitro Toxicity Tests

Toxicity tests that can be performed on cell systems in vitro have the advantage of being done rapidly and with relatively low cost. Such tests can be used to screen for general toxic properties of a chemical or a chemical mixture, such as the cytotoxicity of the material or its ability to alter the genetic material, DNA. The cytotoxicity of a compound can be predictive of its ability to induce inflammation; the genotoxicity of a compound suggests its potential to induce cancer. The limitation of such tests is that the results are based on the response of single cell types and do not

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include the influence of the whole-body system on the response. Nevertheless, such tests can be valuable in excluding products from further development if they either are extremely cytotoxic or have a high potential for producing mutations in DNA. Cellular screening assays should include benchmark materials of known cytotoxic or genotoxic potential (based on both in vitro and in vivo studies) for comparison to the test material and to allow better interpretation of the results.

Cytotoxicity Tests

Cytotoxicity tests (Balls and Clothier, 1991) are based on either primary cultures or established cell lines from the target organ of interest. Dye exclusion or the release of cytoplasmic enzymes is used to measure damage to cell membranes. In dye exclusion tests, the ability of cells to exclude extracellular dyes such as trypan blue or neutral red is measured. Release of the cytoplasmic enzyme lactate dehydrogenase (LDH) is commonly measured as an indicator of cell membrane damage. For specific purposes, the release of other enzymes, such as the hydrolytic enzymes of pulmonary macrophages, can be useful. The exclusion of the dye, neutral red, and the release of LDH have been recently used to compare the cytotoxicity of smoke condensates from standard cigarettes and a new tobacco-related PREP for which harm reduction was claimed (Eclipse Expert Panel, 2000)

Genotoxicity Tests

Several in vitro tests designed to assay for the mutagenic potential of a chemical or mixture were recently reviewed in an International Workshop on Genotoxicity Test Procedures (Lovell et al., 2000). Perhaps the most commonly used screening tool is the *Salmonella typhimurium* bacterial mutagenicity assay or Ames test (Ames et al., 1987). In addition to assays for point mutations, there are assays of clastogenic DNA damage as indicated by chromosomal aberrations, sister chromatid exchanges (SCEs), micronuclei formation (Hayashi et al., 2000), or single strand breaks via the Comet assay (Tice et al., 2000). Assays for specific chemical adducts to DNA can be used as a measure of dosimetry and, in a few cases, as predictors of adverse effects (Phillips et al., 2000). Measures of oxidized bases in DNA can be used to assay for oxidative stress (Cadet et al., 1998). In recent comparative potency studies comparing the genotoxicity of smoke condensates from standard and new tobacco-related PREP, a battery of in vitro assays included the Ames test, SCEs, and chromosomal aberrations (Eclipse Expert Panel, 2000).

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In Vivo Toxicity Tests

Animals do not smoke cigarettes in the same manner as humans, and much effort has been expended in the past in animal studies to mimic human exposures to intermittent puffs of smoke. It is impractical to replicate all of the parameters of human smoking in animals. One problem is that rodents tend to hold their breath during puffs of irritating tobacco smoke and thus avoid receiving a high dose of smoke (Kendrick et al., 1976). Studies were conducted comparing three modes of exposure of rats to cigarette smoke: nose-only intermittent, nose-only continuous, and whole-body continuous (Chen et al., 1995; Mauderly et al., 1989). Plasma nicotine was higher by a factor of 3 in whole-body exposed rats compared to nose-only exposed rats. This suggests that dermal absorption and grooming as well as inhalation contributed to the dose of nicotine received in rats exposed in the whole-body mode. Urinary cotinine was not higher in the whole-body exposed group compared to the nose-only intermittent exposure group but was higher by a factor of 1.5 compared to the nose-only continuous exposure group. This study demonstrated few significant differences in either smoke characteristics or biological effects among the three exposure modes. The biological effects thought to be related to chemical carcinogenesis (cell transformation, chromosomal damage, DNA adducts) and chronic lung disease (cell proliferation, inflammation, respiratory function) were similar for all groups. Whole-body exposures were less labor intensive and less stressful to the rats (based on body weights) and avoided the reduction in breathing known to occur during puff-by-puff exposures. Thus, whole-body exposures may be useful as a method to achieve dosing of tobacco smoke in small laboratory test animals.

ASSESSMENT OF POTENTIAL EXPOSURE REDUCTION PRODUCTS

Lung Cancer

Animals have not proven to be good models for the type of lung tumors induced by cigarette smoke in humans. Rodents tend to develop peripherally arising lung adenomas rather than centrally arising bronchial tumors when exposed to chemicals. Exposure of animals to tobacco smoke has not often produced an excess of lung tumors of any type. In 1986, the International Agency for Research on Cancer (IARC, 1986) critically reviewed animal studies on tobacco smoke; out of four rat studies judged to be adequate for analysis, only one yielded unequivocal evidence for tobacco smoke as a respiratory tract carcinogen. One problem

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may be that rats build up carboxyhemoglobin faster than humans when exposed to the same level of carbon monoxide (CO) (Guerin et al., 1974; Silbaugh and Horvath, 1982). This results in their not being able to tolerate the level of exposure to cigarette smoke that humans can. Other factors undoubtedly contribute to this species difference in response to cigarette smoke. However, rodent models can be used to test the ability of tobacco products to cause alterations in DNA, and recent studies (discussed below) indicate that the A/J strain of mouse shows promise as a model for in vivo carcinogenesis induced by tobacco smoke.

Short-term exposure of rodents followed by analysis of DNA isolated from the lungs for DNA modifications, such as oxidative damage or methylation, can determine the ability of the product to damage DNA in vivo. Aberrant methylation of DNA can be used as a marker for early stages of oncogenesis in both rats and humans (Belinsky et al., 1998; Nuovo et al., 1999; Swafford et al., 1997). Oxidative damage to DNA is used to monitor oxidative stress (Halliwell, 1998; Loft et al., 1998).

The A/J mouse strain, which is sensitive to induction of lung adenomas, has been used in a series of studies by Witschi to test for the carcinogenic potential of tobacco smoke and the effectiveness of chemopreventive measures (Witschi et al., 1997a, 1999, 2000). The A/J mice exposed to 87 mg/m^3 of environmental tobacco smoke for five months and allowed to recover for four months had a statistically significant elevation in number of lung tumors (Witschi et al., 1997a). The same strain of mice exposed similarly to filtered and unfiltered tobacco smoke suggested that the particulate phase was not required for carcinogenicity (Witschi et al., 1997b). In a chemoprevention study, acetylsalicylic acid, an agent known to protect against nicotine-derived N-nitrosaminoketone (NNK)-induced tumors in the same strain of mice, had no protective effect against tobacco smoke (Witschi et al., 1999). A second chemoprevention study indicated that a diet containing myoinisitol-dexamethasone was effective in preventing tobacco smoke-induced lung tumors but that agents known to protect against NNK-or polycyclic aromatic hydrocarbon (PAH)-induced tumors did not protect against tobacco smoke (Witschi et al., 2000).

The committee concludes that these studies indicate that removal from tobacco smoke of single classes of carcinogens, such as nitrosamines or PAHs, may not be protective against the induction of lung tumors by smoke. These studies also suggest that the A/J mouse, used in "stop-start" studies, shows promise as an animal model of value in screening for the potential of tobacco products to induce lung tumors. Future studies should determine if the model is robust enough to be repeated in other laboratories. In recent comparative potency studies for a newly developed tobacco-related PREP, the potency for smoke condensates to induce

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cancer was evaluated in 30-week dermal tumor-promotion studies in mice (Eclipse Expert Panel, 2000). Such skin painting studies provide information for hazard identification.

Chronic Obstructive Pulmonary Disease

An early response to any inhaled toxicant is pulmonary inflammation, which if persistent may lead to more severe alterations in the structure and function of the lung. Animal models can readily be used to detect and quantitate the pulmonary inflammatory response to inhaled compounds or mixtures. Analysis of bronchoalveolar lavage (BAL) fluid for cellular and biochemical indicators of inflammation has become a common tool for quantitation of the pulmonary inflammatory response of rodents to inhaled toxicants (Henderson, 1989), including tobacco smoke (Mauderly et al., 1989; Sjostrand and Rylander, 1997; Subramaniam et al., 1996). The differential cell count and the functioning of cells obtained by the BAL technique can be used to classify the type of inflammatory response. The biochemical content of BAL fluid can be used to detect the release of various cytokines and alterations in the pulmonary surfactant.

Chronic obstructive pulmonary disease in the form of either emphysema, bronchitis, or both is a well-recognized sequela of cigarette smoking (Vial, 1986). Harm reduction strategies must take into account the degree to which this type of chronic lung disease is reduced in new products. Animals models to study the degree of COPD induced by the use of new products have been suggested by the work of March et al. (1999a). F344 rats exposed to cigarette smoke over a two-week period showed enhanced pulmonary epithelial cell replication and alterations in axial airway mucosubstances—changes consistent with the development of chronic bronchitis (March et al., 1999a). Both B6C3F1 mice and F344 rats exposed to cigarette smoke over a longer period (7–13 months) were found to develop morphological evidence of emphysema. Mice developed more pronounced signs of emphysema than rats, and the condition progressed with time in mice (March et al., 1999b). In earlier studies, rats exposed for three months to sidestream smoke were reported to have emphysematous changes in the lung (Escolar et al., 1995). Comparative potency studies for a newly developed tobacco-related PREP made use of 90-day inhalation studies in hamsters and rats to test for inflammation as well as epithelial hyperplasia and metaplasia (Eclipse Expert Panel, 2000).

The committee concludes that these studies indicate there are animal models that show promise for use in screening for development of COPD-like symptoms from the inhalation of new or existing tobacco products.

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Cardiovascular Disease

Cockerels and rabbits are two animal models that have been used to test for the cardiovascular effects of tobacco smoke. Penn and coworkers (1993, 1994) found that 16-week exposure of cockerels to tobacco smoke (2-3 mg/m^3) increased the size of arteriosclerotic plaques in the aorta. Rabbits fed a cholesterol-rich diet and exposed for 10 weeks to 4 and 33 mg/m^3 showed a dose-dependent increase in the size of arteriosclerotic lesions in the aorta and pulmonary artery, as well as increased stickiness of platelets (Zhu et al., 1994). C57BL/6 mice have also been used to test for the effect of inhaled pollutants on the induction of atherosclerosis and enhancement of arterial fatty deposits in animals fed a high-fat diet (Lewis et al., 1999).

The committee concludes that such studies suggest animal models can be used to detect the potential for tobacco products to enhance the development of atherosclerosis.

Immune System Dysfunction

Smoking-related changes in the peripheral immune system in humans include elevated white blood cell counts, increased cytotoxic or suppressor and decreased inducer or helper T-cell numbers, slightly suppressed T-lymphocyte activity, significantly decreased natural killer (NK) cell activity, lowered circulating immunoglobulin titers (except for IgE, which is elevated), and increased susceptibility to infection. Similar effects have been observed in animals (Johnson et al., 1990; McAllister-Sistilli et al., 1998; Sopori et al., 1994), suggesting that animal models can be used to test for harm reduction to the immune system from use of new tobacco products or nicotine delivery devices. The major areas of interest are reduced host resistance to infections and tumors, suppression of the cellular and humoral immune system, and interference with macrophage cell function.

The effect of tobacco smoke on the immune system of humans and rodents depends on the duration and level of exposure. In general, short-term, low-level exposures do not affect the immune system or may be stimulatory, whereas longer-term exposures (six months or more) or high levels of exposure are immunosuppressive.

The committee concludes that this finding indicates that long-term animal studies are required to evaluate adverse effects of tobacco products on the immune system.

Animals exposed to cigarette smoke for extended periods are more susceptible than naïve animals to tumor and infectious agent challenge. Mice exposed to cigarette smoke for six months or longer were more

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susceptible to intratracheally instilled Lewis lung or TKL5 tumor cells in terms of increased tumor growth, metastases, and early death than unexposed mice (Chalmer et al., 1975; Thomas et al., 1974b). Such changes are not observed in mice exposed to cigarette smoke for short periods of time (days). Chronic exposure of mice to cigarette smoke results in increased susceptibility to infectious agents such as murine sarcoma virus (Thomas et al., 1974a) and influenza virus (Mackenzie et al., 1976; Mackenzie and Flower, 1979).

Cellular immunity, as evaluated by phytohemagglutinin (PHA)-induced lymphoproliferative response or development of tumor-specific cytotoxic T cells, was initially increased but, on continued exposure, greatly decreased in mice exposed to cigarette smoke (Chalmer et al., 1975; Holt et al., 1975; Thomas et al., 1973). Lymphocytes from mice exposed chronically to tobacco smoke have a decreased response to the mitogen PHA and release factors that inhibit the cytotoxic activity of NK cells against tumor cells. T-cell suppression may be due to defective antigen processing or antibody production.

The humoral immune response is also suppressed by chronic exposure of mice to tobacco smoke, while acute exposures may stimulate the humoral response. The primary and secondary antibody production by lymphocytes in the lung, lymph nodes, and spleen of mice exposed to tobacco smoke for longer than 26 weeks and challenged by inoculation with sheep erythrocytes was decreased (Thomas et al., 1975).

Laboratory test animals can be used to demonstrate the ability of cigarette smoke to slow the mucociliary clearance of particles from the lung and to alter the function of pulmonary macrophages. This effect has been observed in humans (Bohning et al., 1982; Cohen et al., 1979) and animals (Mauderly et al., 1989). In the latter study, rats exposed for eight weeks to cigarette smoke were exposed one time to cerium^{144} dioxide particles. Smoking increased the half-time of the short-term clearance of these particles by 63% and long-term clearance twofold. The slowing of clearance of inhaled particles is an adverse health effect that should be considered in studies of tobacco product toxicity.

Alveolar macrophages from rats exposed to tobacco smoke for six months have a decreased ability to phagocytize *S. tuphylocoesus aureus* (Drath et al., 1979; Huber et al., 1980). Alveolar macrophages from rats exposed to tobacco smoke for 36 days or longer had an increased ability to release reactive oxygen species, a property dependent on the particulate faction of the smoke and not the gases. Clearance of *Pseudomonas aeruginosa* from rodents exposed to cigarette smoke for 36 weeks was slower than in controls (Holt and Keast, 1977). The decreased ability to clear particles, including pathogens, and the increased release of reactive

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oxygen species contribute to enhancement of inflammatory processes in the lung.

Reproductive and Developmental Effects

There are several reports that exposure of pregnant rats to either sidestream or mainstream tobacco smoke results in decreased birthweight of the pups (Leichter, 1989; Rajini et al., 1994; Reznik and Marquard, 1980; Witschi et al., 1994). Thus, animal models are capable of detecting tobacco smoke-induced growth retardation in utero. Rat models have also been used to demonstrate the adverse effects of maternal tobacco smoke exposure on lung maturation in utero (Lichtenbeld and Vidic, 1989), leading to an increase interstitial volume in the lung parenchyma. Another study demonstrated that postnatal rats exposed to tobacco smoke had reduced proliferation of their bronchiolar epithelial cells accompanied by increased levels of cytochrome P-450 enzymes (Ji et al., 1994). Studies in rodents have shown that rat pups exposed in utero to tobacco smoke have altered composition of pulmonary surfactant (Subramaniam et al., 1999).

The committee concludes that such studies indicate the potential usefulness of animal models to detect the interference of tobacco smoke products on airway epithelial cell development.

SYNERGISTIC EFFECTS WITH OTHER POLLUTANTS

Occupational exposures to materials such as asbestos or radon daughters have proven to have a synergistic interaction with tobacco smoke leading to greatly increased production of lung tumors in exposed workers who also smoke. Although rats are not good models for detecting the induction of lung tumors from cigarette smoke alone, rats exposed to both cigarette smoke and plutonium oxide particles clearly revealed the synergistic effects of cigarette smoke on the induction of lung tumors in combined exposures (Finch et al., 1998). In the past, it has not been customary for regulatory agencies to require testing for synergistic effects of a new product with other substances.

The committee concludes that in the case of tobacco smoke, for which several synergisms are known, it would be wise to consider adding such a test to the standard regimen.

MOLECULAR BIOLOGY TESTING TOOLS

Recent advances in the area of molecular biology hold promise as future tools for toxicity screening. The technology for producing transgenic mice allows one to gain gene functions, while the development of

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knockout mice allows one to delete gene functions (Arbeit and Hirose, 1999). At present these tools are better suited for mechanistic studies than for screening purposes, but in the future, genetically altered animals may become the standards for testing for specific types of toxicity, just as genetically altered *Salmonella* bacteria have become standards for testing the mutagenic potential of xenobiotics.

DNA microarray chips, which consist of an array of thousands of specific cDNA sequences or genes on a chip, allow one to detect and quantitate messenger RNAs that are the transcription products of the specific cDNA samples on the surface of the chips. Thus, if one knows the specific genes that are upregulated in association with the onset of a disease process, one could theoretically use the microarray technique to detect some of the earliest indicators that a disease process has begun (Nuwaysir et al., 1999). This type of tool should be invaluable in developing rapid screens for early indicators of developing disease in exposed animals (or for clinical purposes in humans) in contrast to the long time frame required to detect indicators of established disease in laboratory animals. The field is developing rapidly, and some microarrays designed to detect squamous cell carcinomas of the lung have already been reported (Wang et al., 2000). Future research will be required to determine which genes are upregulated at different times during the progression of specific diseases so that microchip arrays can be designed as accurate and specific preclinical indicators of developing disease.

SMOKELESS TOBACCO TOXICITY

Smokeless tobacco products, traditionally, are differentiated into snuff and chewing tobacco; are not combusted but exert their effects by direct mucosal contact and consequent entry of toxicants into the bloodstream. Snuff is typically a finely ground tobacco product that is used orally or nasally. Snuff is manufactured in a variety of forms including moist, dry, and fine cut (Connolly et al., 1986). The oral tobacco form that is chewed or simply kept in the mouth is generally known as chewing tobacco. Chewing tobacco is also produced in different forms including plug, loose-leaf, and twist varieties (Connolly et al., 1986). (See Chapter 4 for a more in-depth description of smokeless tobacco products and use statistics.)

Smokeless tobacco products are composed primarily of fire or air-cured dark tobacco (Wahlberg and Ringberger, 1999). The tobacco then undergoes an extended aging process that involves heating or fermentation depending on the product. During production, various additives are used for the desired flavor and aroma. The chemical composition of smokeless tobacco products varies due to differences in tobacco composition

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and cut, additives, and curing or processing conditions. The differences are also found among countries for similar reasons. In Sweden, for example, moist snuff (snus) has a lower level of tobacco-specific nitrosamines (TSNAs) due to processing differences and lack of fermentation compared to snuff in other countries. Generally, the TSNA levels in both U.S. and Swedish products have decreased over the last decade secondary to changes in processing methods, and TSNA levels in certain U.S. brands of snuff have approached the Swedish variety (Ahlborn et al., 1997; Wahlberg and Ringberger, 1999).

The exact chemical composition of smokeless tobacco, as in tobacco smoke, is difficult to assess. The main target of exposure in the smokeless tobacco user is the oral cavity and the upper aerodigestive tract. The lower digestive tract, however, is exposed at a certain level because of the swallowing of snuff particles within saliva. Common carcinogens found in smokeless tobacco include TSNAs, PAHs (especially benzo[*a*]pyrene [BaP]), and polonium -210. The concentration of TSNAs in snuff ranges from 5,280 to 141,000 parts per billion (ppb), which is hundreds to thousands times higher than that allowed in other consumer and food products (Connolly et al., 1986). TSNAs are thought to be important carcinogens in humans and have been proven to be potent carcinogens in animal studies. Among the TSNAs, NNK and *N*-nitrosonornicotine (NNN) have proven to be the most important carcinogens in smokeless tobacco in Europe and North America (Hoffmann et al., 1987; Nilsson, 1998). Hecht et al (1986) showed that oral exposure to NNK and NNN in rats caused lung tumors as well as oral tumors at the site of exposure. A snuff user (10 grams of snuff per day) is exposed to 24-46 µg of TSNAs per day compared to a pack per day smoker who is exposed to, on average, 16.2 µg of nitrosamines (Hoffmann et al., 1995). Snuff use also exposes the user to trace amounts of lead, cadmium, and selenium (Hoffmann et al., 1987).

Dark tobacco has a high level of nicotine, with 3.5-4.0% reported in certain brands (Wahlberg and Ringberger, 1999). In general the nicotine content per dose of smokeless tobacco product is higher than that of cigarettes, but the maximum serum nicotine levels are similar among all tobacco users (Benowitz, 1997). While there are interindividual differences in nicotine absorption and metabolism, nicotine is absorbed more gradually from smokeless tobacco than from smoking, and blood concentration persists over a longer period of time and even overnight (NIH Consensus Report, 1986). Overall, smokeless tobacco users are exposed to a greater amount of nicotine because of continued slow absorption of nicotine up to an hour after the tobacco is taken out of the mouth as well as the more alkaline pH, causing nicotine to be present in its unprotonated form contributing to better absorption (Benowitz et al., 1988; Hoffmann and Djordjevic, 1997).

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Long-term smokeless tobacco use has been linked to oropharyngeal cancer (IARC, 1985; Mattson and Winn, 1989). The evidence has been more convincing for snuff than for chewing tobacco. As outlined in the 1986, National Institute of Health (NIH) Consensus Development Conference on the Health Implications of Smokeless Tobacco, case reports and controlled studies have consistently reported tumor growth in the location of smokeless tobacco contact with mucosa or skin, resulting in a risk of oral cancer up to 4.2 times that of nontobacco users as reported in one influential study (Winn et al., 1981). The most common type of cancer attributable to smokeless tobacco is oral squamous cell carcinoma, but verrucous carcinoma has also been reported (Connolly et al., 1986). In contrast, recent epidemiological studies from Sweden have failed to confirm a link between Swedish snus use and cancer (Lewin et al., 1998; Schildt et al., 1998). In a large population-based study looking at risk factors for squamous cancer of the head and neck, Lewin et al. (1998) found no increased risk with the use of Swedish snuff.

Results of animal studies were initially mixed regarding the effects of oral, subcutaneous, or topical administration of smokeless tobacco in rodents (Main and Lecavalier, 1988; Pershagen, 1996). More recently, however, as noted in a review of the health hazards of moist snuff by Ahlborn et al., (1997), there as been increased experimental support for the carcinogenicity of snuff. Surgically formed canals in the lips of rodents into which snuff and snuff extracts are placed have been used to more closely model the human practice of snuff dipping (Hoffmann and Djordjevic, 1997). Studies in rats and hamsters have shown a higher incidence of malignancy when there was exposure to both tobacco and herpes simplex type 1 virus or a cancer initiator (Ahlborn et al., 1997; Connolly et al., 1986). There has been inconclusive evidence linking snuff use to a variety of other cancers including prostate, pancreas, bladder, stomach, and kidney (IARC, 1985; Nilsson, 1998; Winn, 1997).

Smokeless Tobacco Research Recommendations

In terms of smokeless tobacco use as a strategy for harm reduction, more research is needed to investigate further some of the contradictory findings regarding the risk of oral cancer and cardiovascular disease. Swedish snus (lower TSNA and nicotine levels than American brands) should be evaluated as a possible harm reduction product since two recent epidemiological studies have suggested that it does not increase the risk of oral cancer and has favorable cardiovascular risk outcomes. More investigations into the cellular toxicity and genotoxic potential of smokeless tobacco extracts are needed. Smokeless tobacco may be a valid substitute for cigarette smoking but would pose specific risks in certain groups

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including pregnant women, those with inflammatory bowel disease, and those with established cardiovascular disease. Also, the population risks include concomitant smoking and adolescent use of smokeless tobacco as a gateway to cigarette smoking.

The same types of animal studies used to evaluate the toxicity of inhaled tobacco smoke could be done to evaluate the toxicity of smokeless tobacco products, such as Swedish snus or snuff, with a change in emphasis to the oral route of delivery. Based on known adverse health effects in humans, animal tests would be needed to evaluate the potential for smokeless tobacco to cause chronic inflammation or cancer in tissues of the oral cavity. Toxicokinetic studies would be required to determine other potential target organs for extracts of smokeless tobacco. Examples of in vitro studies include reports showing that smokeless tobacco causes pro-inflammatory changes in cultured endothelial cells (Furie et al., 2000) and activates the complement cascade, suggesting an inflammatory potential (Chang et al., 1998). Animal studies have been used to evaluate the potential of smokeless tobacco to induce oral cancer, as reviewed by Grasso and Mann (1998).

Thus, the committee concludes that preclinical toxicity testing should be of value for assessing the potential adverse health effects from use of smokeless tobacco.

GENERAL RESEARCH AGENDA AND RECOMMENDATIONS

Toxicology studies, both in vitro and in vivo, provide the opportunity to evaluate the potential harm reduction offered by potential reduced-exposure products (PREPs). The comparative potency of the PREP can be determined in a series of preclinical studies that include both the PREP and the standard tobacco product that can be replaced by the PREP, particularly tobacco-related PREPs (Figure 10-2). Such tests have recently been reported for a new cigarette-like product (Eclipse Expert Panel, 2000). The preclinical tests should include in vitro tests in both animal and human cells to determine the cytotoxicity and the genotoxicity of the tobacco product to which humans will be exposed. Such a test must include dose-response studies to determine the amount of the exposure material required to cause toxicity. Next, studies should be conducted in vivo in the best animal models available to determine the comparative potency of the PREP versus the standard product in producing: (1) pulmonary inflammation, (2) COPD, (3) cardiovascular disease, (4) reproductive toxicology, and (5) pulmonary neoplasms. If these preclinical studies indicate that the PREP is less potent than the standard tobacco product, clinical studies should be conducted to determine acute toxic effects, the toxicokinetic properties, or the adverse effects of the PREP in humans. The determination

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	In Vitro Studies		In Vivo Studies	Clinical Studies In Humans	Epidemio-logical Studies
	Animal Cells	Human Cells	Animals	Acute Effects	Chronic Effects
Standard Tobacco Product	✓	✓	✓	✓	✓
Modified Tobacco Product	✓	✓	✓	✓	?

FIGURE 10-2 Preclinical studies for standard and new tobacco products.

of human health effects from chronic use of the new product can only be inferred from comparisons of the results of comparative tests in the old and the new product, but cannot be determined directly. Thus the testing approach will allow the rejection of risk reduction claims for products that are as toxic or more toxic in preclinical tests compared to products already on the market; however, only after long-term use of the product by many people could it be determined if the chronic toxicity of the new product is less than that of the standard product.

Based on the above information, it is clear that preclinical toxicity testing in vitro and in vivo can be done to assess the potential health effects of new products before they are released for human use. It is beyond the scope of the committee's task to recommend the specific set of toxicity tests that should be done on new or existing tobacco products. The committee recommends that a panel of experts be convened to determine the specific set of toxicity tests and details of the testing regimens. Details to be considered include species and strains of test animals, duration of tests, end points of interest, dose-response considerations, biomarkers of dosimetry and response, and standard comparison products to be tested as positive and negative controls.

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11

Exposure and Biomarker Assessment in Humans

The evaluation of potential reduced-exposure agents (PREPs) has to be defined in the context of the outcome of interest (e.g., individual or population reduction in risk and disease type) and compared to an appropriate baseline (i.e., nonsmokers, former smokers, current smokers in the context of host susceptibility and previous level of smoke exposure). Tobacco exposure can be measured in the aggregate at the level of the entire population (e.g., through the measurement of tobacco sales or reported consumption in population-based surveys) and related to disease incidence or change in mortality rates. These methodologies are considered descriptive epidemiological tools that are useful in generating hypotheses and/or validating public health strategies, marketing programs, and so forth. Exposure can also be measured at the level of the individual through biomarker measurements. This type of assessment within epidemiological studies can be used for hypothesis generation or testing. A range of methodologies and assays can be used for assessing exposure, as well as a range of assays for assessing host susceptibilities to exposure.

The evaluation of a PREP can include four components: (1) external exposure measurements, (2) internal exposure measurements, (3) biomarkers estimating the biologically effective dose (Perera, 1987), and (4) biomarkers of potential harm (see Figure 11-1). The definitions of each are provided in Table 11-1 and explained further herein. There have been different definitions of types of exposure assessments used previously, but more recent understandings of biomarker uses and limitations, as

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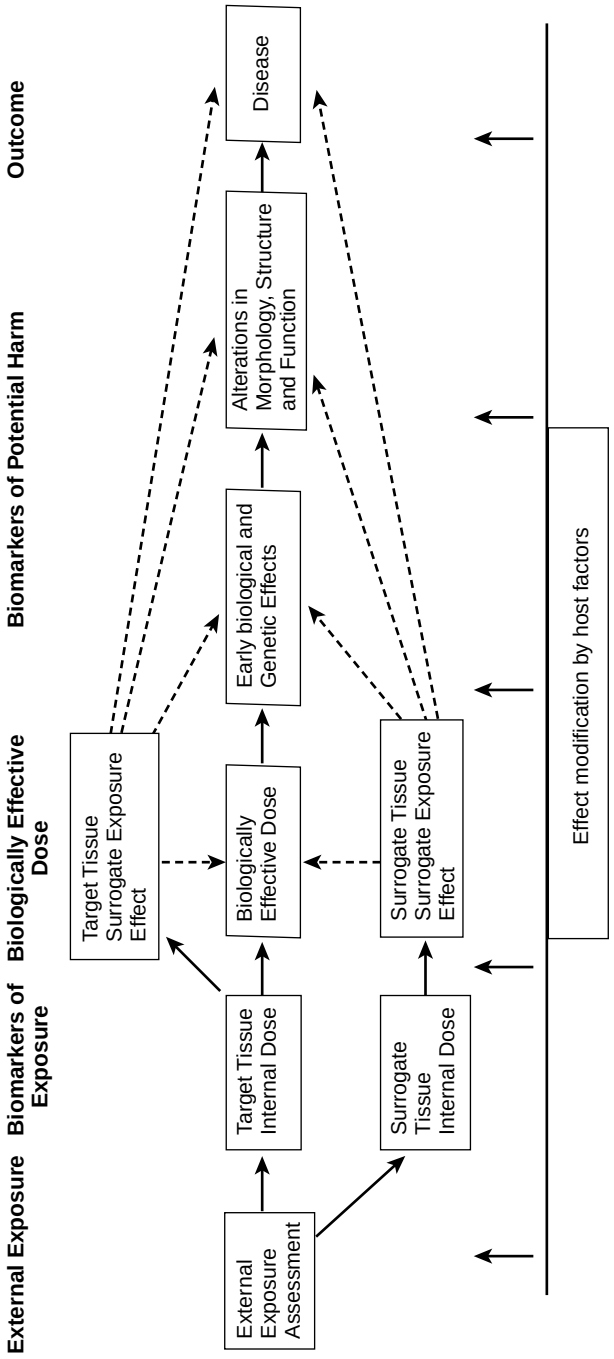


FIGURE 11-1 Assessing potential harm reduction products.

NOTE: Dashed lines indicate hypothetical indirect relationship. Solid lines indicate mechanistic direct relationship.
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TABLE 11-1 Exposure and Biomarker Assessment Definitions

Exposure or Biomarker Assessment[a]	Definition
External exposure marker	A tobacco constituent or product that may reach or is at the portal of entry to the body
Biomarker of exposure	A tobacco constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose
Biologically Effective Dose (BED)	The amount that a tobacco constituent or metabolite binds to or alters a macromolecule; estimates of the BED might be performed in surrogate tissues
Biomarker of potential harm	A measurement of an effect due to exposure; these include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm; also includes "preclinical changes"

[a]Categories and definitions reflect concept that the critical exposure is at the level of a biological macromolecule, so that exposure for this discussion is not limited to a measurement at the portal of entry to the body.

well as different approaches needed for PREP evaluation lead to a need for clarification and redefinition. The latter three measurements improve upon the first by quantifying exposure at the cellular level to characterize low-dose exposures or low-risk populations, providing a relative contribution of individual chemical carcinogens from complex mixtures and estimating total burden of a particular exposure where there are many sources (Vineis and Porta, 1996). In assessing PREPs through biomarkers, understanding the biological effects of a wide range of exposures will be important. Within the context of this chapter, exposure at the level of the cell and critical macromolecules is considered with greater weight, rather than the traditional view of exposure at the portal of entry into a person.

Biomarkers are intuitively more informative and better disease risk markers when measured in the target tissue through biopsies (e.g., oral mucosa, lung, bladder). However, biomarker assays are technically limited, and target tissue can be difficult to obtain, especially in nondiseased smokers. Therefore, biomarker assays have been developed for surrogate tissues and fluids (e.g., expired breath, saliva, blood, urine). While these are technically simpler to use and easier to collect, the ability to prove a

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TABLE 11-2 Measurements Used For Assessing Harm Reduction Products

Factor	Comment
Type of measurement	Types of measurements that can be used include external exposure assessment, biomarkers of exposure, biomarkers that represent the biologically effective dose, and biomarkers of potential harm. Depending on the context, the PREP, and the outcome of interest, different measurements might be more appropriate, although it is likely that a combination will be needed
Target tissue and outcome effect	Is the measurement used for detecting effects in target or surrogate tissues, and is this a measurement of pathogenesis?
Dose-response data	Measurements must have a dose-response relationship that is understood on a mechanistic basis. Biomarker should be able to demonstrate effects from exposure over the range of human experience, so that it can show exposure reduction from a PREP
Harm reduction in dose-response data	Biomarker should be able to predict a decrease in disease incidence after exposure is reduced
Specificity	Is the measurement specific for a tobacco product constituent, or does is also measure exposures from nontobacco products?
Sensitivity	Is the measurement sensitive enough to measure what it is supposed to measure in humans within the possible exposure ranges?
Validation	Are there sufficient data to show that the assay is reproducible?

predictive value for the potential harm reduction is more difficult. It should be noted that the biomarkers discussed in this chapter refer to either target or surrogate tissue or fluid assays, but that the biologically effective dose refers to the assessment of a mechanistically relevant biomarker only in the target organ.

The following factors should be considered when evaluating measurements for predicting or determining the effects of a PREP. Table 11-2 summarizes these factors and Table 11-3 provides an overview of available measures to predict the effects.

1. *Type of measurement.* Measurements are defined within four general categories—namely, external exposure, biomarkers of exposure, biomarkers estimating the biologically effective dose, and biomarkers of

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potential harm. Placing a measurement solely within one category may not be possible. The external exposure assessment category is limited to those methods that are not detected by an assay using a body fluid or part. Although some external exposure methods might be poor predictors of disease risk and hence also poor measures for assessing a new product (e.g., the Federal Trade Commission [FTC] method described below), others might be strongly associated with disease risk and might therefore be better (e.g., cigarettes per day). While some external exposure assessments might be useful for harm reduction risk assessments (e.g., smoking history), they should not be used alone in assessing harm reduction because the predictive power for disease is not sufficient without corroborative biomarker data. Biomarkers of exposure are assayed in a body fluid (including exhaled air) or tissue that measures a constituent of tobacco smoke, tobacco-related products, or metabolites, where the constituent is not bound to a biomolecule. These biomarkers include unmetabolized compounds (e.g., carbon monoxide [CO], serum nicotine, carcinogen levels in serum or internal organs), biomarkers of exposure to individual cigarettes (e.g., incremental increases in exhaled CO or serum nicotine), and metabolites in any body fluid (e.g., cotinine in serum or urine, carcinogen metabolites in urine). Biomarkers assessing the biologically effective dose are those considered mechanistically related to disease outcomes (e.g., carcinogen-DNA adducts in the target tissue). Surrogate biologically effective doses, once validated, estimate a biological effect in a target organ (e.g., hemoglobin adducts or white blood cell carcinogen-DNA adducts). These biomarkers are in theory best able to link exposure (external and internal) to disease outcomes. Biomarkers of potential harm can reflect early or late damage (e.g., loss of heterozygosity in sputum, background mutations in nondiseased tissues, reactive airway disease, arrhythmias, premalignant lesions, mutations in premalignant lesions, chromosomal aberrations in smoking-damaged epithelium, hypermethylation of genes, atherosclerosis). In this context, potential harm implies that the assay might or might not reflect actual harm and that some change in physiological function, for example, might not represent a harmful effect.

2. *Target tissue and outcome relationship.* A biomarker assay should be shown to be relevant to the outcome of interest. Besides having a mechanistic relationship to pathogenesis, data should be available to determine the predictive capacity for disease and disease reduction. This validation includes supportive evidence that the assay reflects harm reduction, such as might be done in an experimental cell culture or animal study. Assays that measure the effects in target tissue would generally have the greatest weight to support the use of a PREP. Sometimes, the target tissue effect

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TABLE 11-3 Methods for PREP Assessment

Category	Type of Measurement	Target vs. Surrogate	Examples	Strengths
External exposure	External exposure assessment	Neither	Questionnaire data, FTC yield	Inexpensi
Biomarker of exposure	Internal dose	Target tissue	Polycyclic aromatic hydrocarbon in lung tissue	Provides exposur
		Surrogate tissue	Urinary measurement of tobacco constituent or metabolite, exhaled CO, carboxyhemoglobin, urinary mutagenicity	Easily acc measur smokin host ca clearan
Biologically effective dose	Biologically effective dose	Target tissue	Carcinogen-DNA adducts in human lung tissue, exfoliated bladder cells, or oral mucosa	Reflects i exposur activati cycle co
		Surrogate tissue	Carcinogen-DNA or hemoglobin adducts; DNA adducts; lipid peroxidation	Does not greater availabl epidem
Biomarker of potential harm	Early biological and genetic effects	Target tissue	Changes in RNA or protein expression, somatic mutations, and LOH in normally or abnormally appearing tissue; change in methylation or gene control; mitochondrial mutations, mRNA expression arrays, or proteomics	Assessme leading
	Alterations in morphology, structure, or function	Target tissue	Osteoporosis, hypertension, cough, hyperplasia, dysplasia, lipids, blood coagulant pathways, mRNA expression arrays, or proteomics	Greater al with ma
	Surrogate assays	Surrogate tissue	Leukocytosis; HPRT mutations; chromosomal aberrations; circulating lymphocytes; mRNA or protein expression via microarrays in cultured blood cells	Easily acc measur smokin host ca clearan
Effect modifiers	Measures of interindividual variation	Neither	Genetic polymorphisms for genes involved in disease pathways	Reflects li high th
		Target	Enzyme induction of metabolizing enzymes	Integrated exposur exposur

NOTE: HPRT=hypoxanthine phosphoribosyltransferase; LOH=loss of heterozygosity.

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	Strengths	Limitations
	Inexpensive	Does not reflect actual internal doses
on in lung	Provides integrated measure of external exposure and smoking behavior	Expensive; may not be specific for tobacco products; does not necessarily reflect biologically effective dose; tissue may be difficult to access; may be difficult to validate as a risk marker for disease
co haled CO,	Easily accessible; provides integrated measure of external exposure and smoking behavior; metabolites reflect host capacity for metabolism and clearance	May not be specific for tobacco products; does not necessarily reflect biologically effective dose; may be difficult to validate as a risk marker for disease
uman er cells,	Reflects integrated measure of external exposure, smoking behavior, metabolic activation, DNA repair capacity, cell-cycle control, and capacity for apoptosis	Difficult to measure and validate as a disease risk marker, predictive value for disease risk is insufficiently studied, more commonly reflects internal dose to a target macromolecule rather than disease risk
in	Does not require invasive procedures, greater amount of tissue is generally available; more likely to be used in an epidemiological setting	Relationship to disease risk is not fully established
pression, in earing or gene ions,	Assessment of mechanistic pathway leading to disease	Tissue difficult to obtain; technically difficult; relationship to disease risk difficult to establish; harmful effects may already be present; bioinformatics with which to process information not yet available
ugh, , blood mics	Greater ability to identify risk for disease with marker	Tissue difficult to obtain; late effects where harm has already occurred; bioinformatics with which to process information not yet available
; rculating ein n cultured	Easily accessible; provides integrated measure of external exposure and smoking behavior; metabolites reflect host capacity for metabolism and clearance	Relationship to target organ effect is difficult to prove; specificity for tobacco product needs to be proved; bioinformatics not yet available
nes s	Reflects lifetime response to exposure; high throughput possible	Candidate gene approach will typically study many polymorphisms that are not related to disease risk
zing	Integrated assessment of how prior exposures or genetic traits affect exposures and harm	Tissue technically difficult to obtain; laboratory validation difficult

osity.

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might also be a surrogate for an effect in other tissues, and a surrogate tissue assay might reflect effects in multiple organs.

3. *Dose-response data for harm.* Assays that have a demonstrable dose-response relationship to actual disease outcomes is important for assessing a PREP and, if they do not, it should be shown to have a dose-response relationship to a biomarker of potential harm relevant to a disease pathway. The mechanistic basis for the relationship should be well understood in order to make meaningful interpretations of data used to assess a PREP. For example, assays that demonstrate a dose-response relationship between smoking and DNA damage in epithelial cells of a target organ could be useful. Methods assessing tobacco exposure as a complex mixture would have greater weight than a single component exposure.

4. *Dose-response data for harm reduction.* Assays that show a reduction in harm after reducing exposure to tobacco smoke or a tobacco product constituent would have the greatest weight, where the experimental design uses an initial dose level for a specific duration of time followed by exposure to a lower level at a later time. The intent is to simulate the effects of a person's switching from one level of exposure to another level of exposure. Importantly, the effects of the biomarker should be measurably different over the range of human exposures, so that the assessment can predictably measure the effects of exposure reduction from a PREP. Currently, there are some biomarker assays that have been assessed in former smokers or smoking cessation trials. These biomarker studies that indicate measurable decreases in effect can provide some information about the utility of markers for assessing exposure reduction. Included in this are half-life data, which must be measured and taken into account when evaluating a tobacco-related PREP. Methods assessing tobacco exposure as a complex mixture would have greater weight than a single component exposure.

5. *Specificity.* Consideration should be given to whether the effect is specific to a constituent of tobacco smoke or a tobacco product, or whether the method also measures exposure from other sources. Higher degrees of specificity are useful, although in some cases the method might be useful for assessing exposures from multiple sources other than tobacco in order to provide an understanding about relative contributions. Assays that are specific for tobacco's complex chemical mixture and those that are specific for a chemical or chemical class both have utility, but the former would have greater weight if appropriately validated, because persons are exposed simultaneously to all of the constituents. Validating assays for complex effects is more difficult because they may have less specificity for tobacco.

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6. *Sensitivity.* The assay must be sufficiently sensitive to measure what it is supposed to measure in the human tissue of interest. This is especially problematic in measuring low-level effects, for example, in assessing the effects of environmental tobacco smoke (ETS) exposure.

7. *Validation.* It is critical that biomarkers for assessing PREPs be well validated in the laboratory. Validation includes proof that the assay measures what it claims to measure and that it is reproducible. Sensitivity, specificity, and predictive value are all important to consider.

EXTERNAL EXPOSURE ASSESSMENT: THE FTC METHOD AND QUESTIONNAIRE DATA

External exposure markers attempt to measure the amount of a tobacco smoke or tobacco product constituent that may enter at a portal to the body. However, these predictors generally do so without regard to most interindividual differences in smoking behavior and cellular processes. There are several types of external exposure assessment, some of which are listed in Table 11-4.

A common way to assess potential exposure to tobacco smoke is by measuring the yield of tobacco smoke constituents. One attempt to estimate delivered doses is the method adopted by the Federal Trade Commission in 1967. It was intended to provide a standardized estimate of tar and nicotine yield by cigarette brand, simulating a cursory observation of human smoking behavior. A cigarette is inserted into a smoking machine and lit, puffs are taken through a syringe (35 ml over 2 seconds, every 60 seconds) until the cigarette is "smoked" to a fixed length. Particulates are collected on a filter and weighed. Nicotine is assayed separately. Tar is measured as total particulate matter less nicotine, other alkaloids, and water. Although the machine provides yield data that can be used to compare one cigarette to another, this information has limited usefulness for understanding human exposure because people do not smoke cigarettes as the machine does due to different smoking behaviors. Smokers also can affect cigarette filter performance by covering ventilation holes in the filter with their lips or fingers, which would increase yields in vivo. Although FTC yields might define a comparative range of actual exposures, there is a wide overlap of actual to predicted yields among types of cigarettes (i.e., low, medium, and high yields), where smokers of low-nicotine cigarettes might have higher nicotine levels than those who smoke brands with higher FTC yields (Byrd et al., 1998, 1995). Altering the FTC method to simulate puffs and times for actual smokers results in

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TABLE 11-4 External Exposure Assessment[a]

Category	Variables Used in Literature	Related to a Disease Outcome[b]	Strengths	Limitations
FTC machine method	Tar yield Nicotine yield Individual smoke constituent yield	Yes	Standardized method for yields	Little relationship to actual human experience
Subject smoking history	Cigarettes per day Years of smoking Age of initiation Recall of inhalation depth Usual type of cigarette smoked Quitting attempts Cumulative tar exposure	Yes	Inexpensive assessment; generally considered reliable, except in some circumstances listed in limitations	Recall is subject to self-perceptions of risk. Reporting is variable depending on context, such as smoking cessation program or where recall bias might exist in epidemiology studies. Known limitations for persons who are switching brands or altering smoking behavior; also not sufficiently reliable in smoking cessation studies. Thus, not sufficiently reliable in harm reduction studies
Smoking Topography	Puff duration Puffs per cigarette Interpuff interval Puff volume	No	Direct measure of inhalation exposure per cigarette. Can be used to assess effects of cigarette brand switching	Measurement performed in artificial environment

[a]References are not provided in this table but can be found in the text of this and disease-related chapters.
[b]Any report related to a disease outcome where the report is plausible but has not necessarily been replicated.

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higher exposures to tar and specific carcinogens (e.g., tobacco-specific nitrosamines and benzo[a]pyrene) (Djordjevic et al., 2000; Fischer et al., 1989; Hoffman and Hoffman, 1997). For example, using modified protocols to stimulate human smoking behavior, the medium-yield (0.9-1.2 mg nicotine per cigarette) and low-yield (0.8 mg nicotine per cigarette) cigarettes deliver similar amounts of tar per day, although by FTC method measured per cigarette yields of tar, benzo[a]pyrene (BaP), and tobacco-specific nitrosamines (TSNAs) were higher in the former (Djordjevic et al., 2000). As cigarettes with different designs are developed and marketed, an assumption that the FTC method of estimating yields will be comparable to existing products is premature.

Over the last 30 years, data from surveys have been an important tool in the assessment of tobacco exposure among individuals and the population. They have been an effective means of tracking patterns of tobacco use and the societal perceptions that ultimately influence consumption. Individual exposure can be assessed through the measurement of the number of cigarettes smoked per day, duration of smoking, types or brands of cigarettes smoked (e.g., "tar" delivery, filter type, type of tobacco, mentholation), and age at initiation (IARC, 1986; Kaufman et al., 1989; La Vecchia et al., 1990; Lubin et al., 1984; Stellman and Garfinkel, 1989; U.S. DHHS, 1988; Vutuc and Kunze, 1983; Wilcox et al., 1988; Zang and Wynder, 1992). Lifetime exposures can be estimated by calculating pack-years (average packs per day multiplied by number of years smoked) or cumulative tar exposure (Zang and Wynder, 1992). A more detailed description of the most common surveys in use is presented in Table 11-5.

Most analyses indicate that self-report validity among adults is good (Patrick et al., 1994). Certain limitations, however, are evident in this type of exposure assessment (Giovino, 1999; U.S.DHHS, 1994). First, sampling errors may occur in any study in which generalizations are made from a selected population sample. One example is the over- or underrepresentation of certain groups, especially those that exhibit significant tobacco use or have differing smoking behavior. In fact, there is a built-in exclusion in many of the major surveillance tools of various segments of the population, such as the institutionalized mentally ill, prisoners, and those in areas of inadequate telephone coverage. Errors in response must be considered including memory errors, nonresponse errors, and misclassifications and inconsistencies in reporting. The validity of self-reported responses can be influenced by many factors (Velicer et al., 1992), particularly the respondent's perception of privacy (Giovino, 1999). This is especially a concern among adolescents in the home setting and among groups that have increased pressure to abstain or to quit, including pregnant women, adolescents, and patients with heart or lung disease. One

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TABLE 11-5 Major Tobacco Use Surveys

Survey	Sponsor	Population	Size
National Health Interview Survey (NHIS)	National Center for Health Statistics, Centers for Disease Control and Prevention (CDC)	Civilian, noninstitutionalized adults over age 18; children by proxy	More than families
Behavioral Risk Factor Surveillance System (BRFSS)	CDC and individual states	Noninstitutionalized adults over age 18	
National Health and Nutrition Examination Survey (NHANES)	CDC	Age 2 and over	Approxim 40,000 p between 1994
National Household Survey on Drug Abuse (NHSDA)	National Institute on Drug Abuse and Substance Abuse and Mental Health Services Administration	Noninstitutionalized civilian population over age 12	Approxim 25,500 p in 1998
American Legacy Foundation Survey		Sixth to twelfth grade students	
Monitoring the Future Survey (previously, the National High School Senior Survey)	University of Michigan Survey Research Center	Eighth, tenth, and twelfth grade students	Approxim 50,000 s from pu private schools
Youth Risk Behavior Surveillance System (YRBSS)	CDC	Ninth to twelfth grade students	

effort to validate self-report measures and to reveal any ETS exposure can be found in the National Health and Nutrition Examination Survey (NHANES; see Table 11-5), which collects serum cotinine levels of respondents (CDC, 2000; Giovino, 1999; Giovino et al., 1995; SAMHSA, 1998).

Population surveys have limited practicality in evaluating the consequence of tobacco exposure because of the relatively long time frame required. However, in context, population assessments have been studied extensively in relation to disease outcomes and thus can be considered a

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	Size	Setting	Comments
tution- er age proxy	More than 38,000 families in 1998	Household interview with responses typed directly in laptop computer; annual	Excludes homeless not in shelters, military personnel, prisoners, hospital patients Data: cigarette, chewing tobacco, cigar, and pipe use since 1965 Oversampling of black American and Hispanic populations
zed adults		Computer-assisted telephone interviews; annual	Added smokeless tobacco use questions in 1987 State level
	Approximately 40,000 participants between 1988 and 1994	Personal interview with physical exam and blood tests; periodic	Serum cotinine measurements Oversampling of children 1-5years, adults over age 60, black Americans, and Mexican Americans
zed ion over	Approximately 25,500 participants in 1998	Household interview; self-administered through a computer; annual	State level Oversampling of black Americans, Hispanic Americans, and youth
rade		School based	Evaluates knowledge of and attitudes towards all forms of tobacco, including bidis and Kreteks
twelfth	Approximately 50,000 students from public and private high schools	Classroom based; self-administered; annual	Random sample from each senior class is followed after graduation for longitudinal data
grade		Classroom based; self-administered; biennial	Oversampling of black and Hispanic-American students. Combination of national, state, and local surveys

crude measurement of individual risk and a better measure of population risk. These surveys do provide insight into trends of tobacco product use within and across a variety of sociodemographic groups, including age, sex, race or ethnicity, educational status, and economic status. The data can be compared to morbidity and mortality registries to understand new or changing consequences of use patterns or specific products. In addition, these trends in prevalence, initiation, and cessation in turn aid in the evaluation of the effects of tobacco-related activities, policies, and interventions within the general population and its subgroups.

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Methods for assessing external exposure (e.g., number of cigarettes per day) are widely used and relatively inexpensive but do not provide an assessment of how someone smokes cigarettes and how the body responds to exposure. Thus, these measures approximate the level of actual exposure and, as described below, become less reliable in assessing exposure reduction. Smoking topography is an additional method of assessing external exposure (e.g., how much smoke enters the lung, estimated by measuring puff volume, number of puffs per cigarette, puff duration, total inhalation time, and interpuff interval) (Bridges et al., 1990; Gritz et al., 1983; Herning et al., 1983; Hofer et al., 1992; Kolonen et al., 1992b). In the laboratory, if subjects smoke their own cigarettes, then it is presumed that the measurement reflects their usual smoking behavior. A limitation of smoking topography studies is that cigarettes are typically smoked via cigarette holders, which may influence puffing behaviors and prevent vent hole blocking that might normally occur when the cigarettes are smoked without the holder. Smoking topography studies have contributed to the findings that persons who switch from high-tar and nicotine to low-tar and nicotine cigarettes increase their intake of smoke per cigarette to compensate for a lower yield of nicotine (Benowitz et al., 1986a, b). It is well established that smokers self-titrate their blood nicotine levels, such that smokers of lower-nicotine cigarettes inhale more (Benowitz et al., 1983; Benowitz et al., 1986b; Benowitz et al., 1998; Ebert et al., 1983; Gritz et al., 1983; Hill and Marquardt, 1980), and altering topography leads to differences in nicotine absorption and CO boosts (Hofer et al., 1992; Kolonen et al., 1992a). Smoking lower-nicotine delivery cigarettes increases puff volume (Battig et al., 1982; Bridges et. al., 1986; Kolonen et al., 1992b) and, to a lesser extent, puff duration (Bridges et al., 1990). Using a multiple regression model for prediction of nicotine blood levels, the best-fit model incorporates interpuff interval, number of puffs per cigarette, puff volume, puff duration, inhaled volume, and inhalation duration (Herning et al, 1983). These studies are difficult to interpret, however, because cigarette and topographic parameters are interrelated (Bridges et al., 1990; Kolonen et al., 1992a; Nemeth-Coslett and Griffiths, 1984).

Different methods have been developed for the study of exposure to environmental tobacco smoke (EPA, 1992). Stationary and personal air monitors can be used to measure total particulates or individual constituents. Some measurements, such as nicotine, are more specific for ETS. Ambient air concentrations and personal exposures to polycyclic aromatic hydrocarbons (PAHs) and other tobacco constituents can be measured, but their relationship to disease risk has not been adequately studied.

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BIOMARKERS OF EXPOSURE

Biomarkers of exposure, measured in a body fluid, tissue, or exhaled air, represent an internal dose of tobacco smoke or a tobacco product constituent that is either the parent compound or its metabolite. They are not measurements of how the constituents interact with body functions or macromolecules to cause harm. Some of these markers have been researched extensively, and they are more representative of actual human exposures to tobacco products than external measures of exposure. They are generally technically feasible and provide information about short-term (e.g., from a single cigarette) and long-term exposures. Examples are listed in Table 11-6, which gives a range of assays available but is not intended to be all inclusive. Because it has such a short half-life, carbon monoxide is best used for assessing recent exposures, although CO measurements also have been used to improve long-term exposure estimates of cigarette consumption (Law et al., 1997). The limitations of CO are that there are other sources of carbon monoxide, such as automobile exhaust and endogenous metabolism, and there is some variation with differences in physical activity, gender, and the presence of lung disease or other disease states. Nicotine blood levels are used and are helpful for assessing internal exposure primarily because it has a very short half-life. Serum, urinary, or salivary cotinine, which is a metabolite of nicotine with a longer half-life, however, has been extensively studied for confirmation of exposure in smokers, quitters, and persons exposed to ETS (Bono et al., 1996; Benowitz, 1999; Crawford et al., 1994). Cotinine levels are dependent on both the extent of formation from nicotine by cytochrome P450 (CYP) 2A6 and the rates of oxidation and glucuronidation of cotinine to 3-hydroxy-cotinine and glucuronide conjugates, respectively, which vary widely among individuals. Therefore, cotinine levels are only approximately correlated with the daily intake of nicotine. Carbon monoxide and nicotine boosts (i.e., the difference between levels before and after a single cigarette) reflect smoking topography and exposures from an individual cigarette.

Technologies exist for directly measuring internal exposure to tobacco smoke constituents in target organs through biopsies (e.g., PAHs in the lung) (Lodovici et al., 1998) and for measuring levels of metabolites of compounds (e.g., those from TSNAs in the urine) (Atawodi et al., 1998; Carmella et al., 1990, 1995). Tobacco smokers have higher levels of mutagens circulating in the body, which can be measured by using extracts of urine in the Ames *Salmonella* mutation assay (Jaffe et al., 1983; Mohtashamipur et al., 1985; Yamasaki and Ames, 1977). Levels have been found to decrease with some test cigarettes that heat, rather than burn, tobacco (Smith et al., 1996).

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TABLE 11-6 Biomarkers of Exposure[a,b]

Category	Variables Used in Literature	Dose-Response Data Available	Associated with Cessation or Half-life	Chemical Specificity	Specific to Tobacco
Nicotine-related biomarkers	Nicotine	Yes	2 hr	Yes	Yes (excep using n replacer therapy
	Nicotine boost (pre- and post-cigarette nicotine levels)	Yes	NA	Yes	Yes
	Cotinine	Yes	17 hr	Yes	Yes (excep using N
	Other nicotine metabolites	Yes	Depends on metabolite	Yes	Yes (excep using N
Minor tobacco alkaloids	Anatabine Anabasine	NDA	10-16 hr	Yes	Yes
Carbon monoxide	Exhaled CO	Yes	4-6 hr	Yes	No
	CO boost (pre- and post-cigarette levels)	Yes	NA	Yes	Yes
	Carboxyhemoglobin	Yes	Hours	Yes	No
Hydrogen cyanide	Thiocyanate	Yes	1-2 weeks	No	No

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emical ecificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
s	Yes (except when using nicotine replacement therapy [NRT])	Yes (addiction only)	Direct measure of exposure	Short half-life dependent on a person's ability to metabolize nicotine and time of sampling. Not useful with concurrent use of NRT
s	Yes	NDA	Measures exposure to single cigarette	Requires two blood draws. Short-term marker only
s	Yes (except when using NRT)	Yes (addiction only)	Well validated; can be measured easily in urine, plasma saliva, or hair. Useful for environmental tobacco smoke	Short-term marker only. At higher levels of smoking, dose-response relationship is less clear and there is wide overlap among smokers
s	Yes (except when using NRT)	NDA	Allows for assessment of nicotine metabolism	Low levels. No benefit over cotinine. Short term marker only
s	Yes	NDA	Useful when individuals are using NRT; may be precursors to nitrosamines	Short-term marker only
s	No	Yes	Easy to measure in exhaled air	Other sources exist, including endogenous processes. Short-term marker only.
s	Yes	NDA	Measures exposure to single cigarette	Short term marker only. Levels vary over the day
s	No	Yes	Measures cumulative, although short-term exposure to several cigarettes	Requires blood draw and special handling. Benefit above that for using exhaled CO not shown
o	No	NDA	Long-term marker. Can be measured in urine, saliva, and blood. Saliva easy to obtain	Many dietary sources. Dose-response curve flattens at higher smoking levels so cannot distinguish among heavy smokers

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TABLE 11-6 Continued

Category	Variables Used in Literature	Dose-Response Data Available	Associated with Cessation or Half-life	Chemical Specificity	Specific to Tobacco
Tobacco-specific nitrosamines	Urinary metabolites	Yes	45 d	Yes	Yes
Polycyclic aromatic hydrocarbons	Parent compounds	NDA	NDA	Yes	No
	Urinary 3-hydroxypyrene and 1-hydroxypyrene	Yes	NDA	Yes	No
Complex mixture assay	Urinary mutagenicity	Yes	Yes	No	No

NOTE: NA=not applicable; NDA=No data available.

The assessment of smoking exposure using nicotine or cotinine cannot be done in smokers who are concomitantly using nicotine replacement products. An alternative is to determine the levels of other tobacco alkaloids, such as anatabine or anabasine in the urine (Jacob et al., 1999).

BIOMARKERS ESTIMATING THE BIOLOGICALLY EFFECTIVE DOSE

The biologically effective dose (Perera, 1987) is the amount of a tobacco smoke or tobacco toxin that measurably binds to, or alters, a macromolecule (e.g., protein or DNA) in a cell. In some cases, the macromolecule may be a surrogate for a target molecule. The biologically effective dose represents the net effect of metabolic activation, decreased rate of detoxification, decreased repair capacity, loss of cell-cycle checkpoint control, and decreased rates of cell death. It should be noted that not all binding to, or alteration of, a macromolecule leads to an adverse health effect; so, often, what is really measured is the dose to a target macromolecule that estimates the biologically effective dose. Table 11-7 provides

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emical ecificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
s	Yes	NDA	May reflect biologically effective dose	Technically difficult to measure
s	No	Yes	Measured in organs where effect might occur	Technically difficult to obtain tissue and perform assay
s	No	NDA	Assay simple to perform	Other exposures can be substantial
o	No	NDA	May be related to in vivo mutagen exposure	Lack of specificity

[a]Selected examples; list is not all-inclusive.

[b]References are not provided in this table but can be found in the text of this and disease-related chapters.

[c]Any report related to a disease outcome associated with tobacco where the report is plausible but has not necessarily been replicated.

examples of biomarkers that estimate the biologically effective dose, but is not intended to be all inclusive.

Many tobacco-related toxins and chemical carcinogens are biologically inactive until transformed by cellular enzymes such as cytochrome-P450s into reactive intermediates. These reactive intermediates bind to macromolecules such as DNA and protein and disrupt their normal processes.

For cancer, a common assessment of the biologically effective dose is the measurement of carcinogen-DNA adduct levels. These are formed when carcinogen metabolites are alkylated to nucleotides, creating a promutagenic lesion. There are strong laboratory animal data and some human studies that indicate a relationship between tobacco smoke constituents, carcinogen–DNA adduct formation, and cancer (La and Swenberg, 1996). Laboratory animal studies have shown a correlation between cancer and increased adducts in target organs (Ashurst et. al., 1983; Nakayama et al., 1984; Pelkonen et al., 1980). In humans, tobacco smoking leads to increased adduct formation in target tissues such as the lung (Phillips et al., 1988; Schoket et al., 1998; Wiencke et al., 1995) and in

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TABLE 11-7 Biomarkers Estimating the Biologically Effective Dose[a,b]

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity
Carcinogen-DNA adducts	Nonidentified adducts/ ^{32}P-postlabeling	Yes	Yes	Yes	No
	PAH-DNA adducts	Yes	9-13 weeks (blood)	Yes	Yes
	4-Aminobiphenyl-DNA adducts	Yes	Yes	Yes	Yes
	NNK-DNA adducts	Yes	NDA	Yes	Yes
	8-hydroxydeoxy-guanosine	No	Yes	Yes	Yes
	5-(Hydroxy-methyl)uracil	No	NDA	No	Yes
	N-Nitrosamine-related-DNA adducts	NDA	26 hr (blood; O6-methyldeoxy-guanosine) and 60 hr (blood; 7-methyldeoxy-guanosine)	Yes	Yes

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Dose[a,b]

Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
Yes	No	No	Yes	Facile assay; does not require knowledge of specific adducts; blood may be surrogate for lung tissue. Adducts found in all tissues, including heart and blood vessels	Cannot identify adducts so mechanistic studies are problematic
Yes	Yes	No	Yes	Can be measured in any tissue and assays are available that are sufficiently sensitive	Low sensitivity and technical difficulties make assay use limited in large-scale studies. Diet might be greater contributor than smoking
Yes	Yes	No	NDA	Can be measured in any tissue; has some specificity for smoking if no known occupational exposure	Low sensitivity makes assay use limited in large-scale studies
Yes	Yes	Yes	NDA	Can be measured in any tissue, although methodology has low sensitivity. Highly specific for smoking	Low sensitivity makes assay use limited in large-scale studies
Yes	Yes	No	NDA	Can be measured in any tissue	Assay has large interlaboratory variation; it is easy to introduce oxidative damage into laboratory assay; low sensitivity makes assay use limited in large-scale studies
No	Yes	No	Not available	Sufficient sensitivity to use for ETS	Technically difficult
Yes	Yes	No	NDA	Can be measured in any tissue	Low sensitivity makes assay use limited in large-scale studies. Diet a common source

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TABLE 11-7 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity
Carcinogen-hemoglobin (Hgb) adducts	PAH-Hgb adducts	Yes	NDA	No	Yes
	4-Aminobiphenyl-Hgb adducts	Yes	7-9 weeks	No	Yes
Carcinogen-protein adducts	PAH–albumen adducts	Yes	NDA	No	Yes
Carcinogen-DNA adduct antibodies	Anti-BPDE serum antibodies	NDA	NDA	No	No
	Adducts	Yes	Yes	Yes	Yes
Carbon monoxide	Carboxy-hemoglobin	Yes	Yes	No	Yes
Lipid peroxidation	F2-Isoprostanes	No	Yes	No	Yes

NOTE: NA=not applicable; NDA=no data available; NNK=nitrosonornicotine ketone; BPDE=benzo(a)pyrene-diol-epoxide

surrogate tissues such as blood (Tang et al., 1995; Vineis et al., 1994; Wiencke et al., 1995). Evidence exists that carcinogen-DNA adduct levels in target and nontarget organs are modulated by interindividual differences (Badawi et al., 1995; Grinberg-Funes et al., 1994; Kato et al., 1995;

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Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
No	Yes	No	NDA	Large amount of adducts available in blood so method is facile	Surrogate assay not yet validated against target organ damage
No	Yes	No	NDA	Large amount of adducts available in blood so method is facile	Surrogate assay not yet validated against target organ damage
No	Yes	No	NDA	Large amount of adducts available in blood so method is facile	Surrogate assay not yet validated against target organ damage
No	No	NDA	NDA	May provide long-term marker of exposure	Doubtful that a dose-response relationship can be established due to complexity of immune response in individuals
Yes	Yes	No	NDA	Measured in organs where effect might occur	Technically difficult to obtain tissue and perform assay
No	Yes	No	Yes	Might also reflect a surrogate measure of biologically effective dose	Logistical problems in sample handling
No	Yes	No	NDA	Corroborative end point for oxidative damage without artifactual introduction of oxidative damage	Technically difficult

[a]Selected examples; list is not all-inclusive.

[b]References are not provided in this table but can be found in the text of this and disease-related chapters.

[c]Any report related to a disease outcome associated with tobacco where the report is plausible but has not necessarily been replicated.

Pastorelli et al., 1998; Rojas et al., 1998; Ryberg et al., 1997; Stern et al., 1993). Interestingly, in former smokers, age of initiation may influence lung adduct levels (Wiencke et al., 1999). In humans, only a few studies have investigated a link between carcinogen-DNA adducts and cancer

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risk. All data come from case-control studies of the lung and bladder, and almost all show a positive relationship (Dunn et al., 1991; Peluso et al., 1998; Tang et al., 1995; van Schooten et al., 1990). However, since no published prospective studies of tobacco smoking show a relationship of adducts to cancer, the case-control studies must be interpreted cautiously because there may be an effect due to differential metabolism or DNA repair. The utility of carcinogen-DNA adduct measurements in assessing harm reduction is suggested by studies showing that lung adduct levels are lower in persons who smoked filter cigarettes (van Schooten et al., 1990). Hemoglobin adducts, an estimate of the biologically effective dose, are higher in smokers than in nonsmokers (Bryant et al., 1987), and in those who smoke black rather than blond tobacco (Bryant et al, 1988). Snuff dipping may lead to even higher levels of some types of adduct than to smoking (Carmella et al., 1990).

A variety of assays are available to determine carcinogen–macromolecular adducts in human tissues (Farmer and Shuker, 1999; Hecht, 1999; La and Swenberg, 1996; Lee et al., 1993; Wang et al., 2000). Although DNA adduct analysis is most commonly studied in relation to carcinogenesis, adducts also have been found in atherosclerotic lesions (Izzotti et al., 1995). Assay techniques include the phosphorus-32 (^{32}P)-postlabeling assay-nucleotide chromatography (Phillips, 1997; Randerath et al., 1981), immunoassays (Lee et al., 1993), fluorescence spectroscopy (Izzotti et al., 1991), gas chromatography-mass spectroscopy (GC-MS) (Farmer and Shuker, 1999; Hecht, 1999), and electrochemical detection (Helbock et al., 1998; Park et al., 1989). Each has its strengths and limitations, and almost all are challenged by low sensitivity and/or specificity. The less specific methods, such as the ^{32}P-postlabeling assay-nucleotide chromatography, when used as originally described (Randerath et al., 1981) or with modifications (Reddy and Randerath, 1986), offer the benefit of assessing exposure to complex mixtures because multiple adducts are measured at the same time. However, because the assay does not identify the types of adducts, any interpretations of the results are limited. Chemical specificity is helpful in assessing harm reduction products when the adducts are specific for tobacco (e.g., TSNAs or 4-aminobiphenyl in the absence of occupational exposure), whereas adduct assays that determine levels from endogenous sources (e.g., oxidative damage, methylation) are more difficult to use and interpret. The study of carcinogen-DNA adducts presents other challenges in interpretation; for example, carcinogen-DNA adduct levels are higher in the heart than in the lung (Randerath et al., 1989) while cancer is rare in the former. For the future, newer adduct methods may provide increased specificity and sensitivity, along with higher throughput.

The use of target organ biomarkers can provide specific information about potentially carcinogenic effects and will best represent the biologi-

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cally effective dose. Target organs include lung for lung diseases, oral mucosa for oral cavity diseases, bladder mucosa for bladder disease, and so forth. Surrogate markers that estimate levels in target organs, such as carcinogen-DNA adducts in blood, have been partially studied, indicating that blood levels might reflect target organ levels (Mustonen and Hemminki, 1992; Mustonen et al., 1993; Tang et al., 1995; Wiencke et al., 1995), but this is not yet firmly established. Protein (Meyer and Bechtold, 1996) and hemoglobin (Wang et al., 2000) adducts also may estimate levels of exposure at the target organ and thus be surrogates. Such assays offer technological advantages because these macromolecules are more abundant in blood than DNA, but the relationship of these other macromolecular adducts to DNA levels has been insufficiently studied.

A few studies show the decline of adducts following short-term and long-term smoking cessation. Most studies will necessarily rely on blood levels, and the half-life of adducts in blood will depend on the life span of various blood cell types. In humans, the half-life for 4-aminobiphenyl-hemoglobin adducts is 7-9 weeks, which is shorter than the life span of a red blood cell (Jahnke et al., 1990). PAH-DNA adducts in white blood cells have a half-life of 9 to 13 weeks (Mooney et al., 1995). In human lungs, it was reported that adducts persist in the lungs of ex-smokers (Randerath et al., 1989), but it is not known whether this is truly persistence or the formation of new adducts from the continuing presence of tobacco constituents such as PAHs or from other exposures such as diet or air pollution (Rothman et al., 1990).

Carcinogen-DNA adduct data have essentially not been used for population risk assessments. In one example, it was considered that a doubling of PAH-DNA adduct levels would result in an additional 2,400 cancer cases per million persons (van Delft et al., 1998), but the model assumed linear dose-responses; was not adjusted for age, gender, or race; and was too simplistic.

BIOMARKERS OF POTENTIAL HARM

These biomarkers reflect changes in a cell and its macromolecules that result from tobacco. These can range from isolated changes, with or without effects on function, to events that clearly lead to illness or are symptoms of the illness (i.e., cough). Examples of biomarkers of effect are provided in Table 11-8, which gives the reader a range of assays available but is not intended to be all inclusive.

Among the most promising biomarkers of effect for assessing harm reduction claims for cancer are those that measure DNA damage or alterations of genetic function (mutations, gross chromosomal changes, DNA methylation of promoter regions, etc.). While these biomarkers are envi-

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TABLE 11-8 Biomarkers of Potential Harmful Effects[a,b]

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
Enzymatic induction	Aryl hydrocarbon hydroxylase	No	>30 d	Yes	Yes	No
	CYP1A2	No	NDA	Yes	Yes	No
	DNA repair enzymes	NDA	Yes	Yes	NA	No
	Microarray assays for mRNA expression and proteomics	NDA	NDA	Yes	NA	No
Chromosomal alterations	Chromosomal aberrations	Yes	Yes	Yes	No	No
	Micronuclei	Yes	Yes	Yes	No	No
	Sister chromatid exchanges	Yes	Yes	No	No	No
	Loss of heterozygosity	Yes	Yes	Yes	No	No
	Mutations in reporter genes (*HPRT, GPA*)	Yes	Yes	No	No	No

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
Yes	No	Yes	Indicates acquired changes in susceptibility; related to DNA-adduct levels	Technically difficult to assess in large epidemiological studies
Yes	No	Yes	Indicates acquired changes in susceptibility; related to DNA-adduct levels	Technically difficult to assess in large epidemiological studies
NA	No	NDA	Indicates acquired changes in susceptibility; provides analysis of what is likely to be critical part of carcinogenesis	Technically difficult
NA	No	NDA	Reflects integrated measure of multiple genotypes, provides complex data potentially usable for rapid identification of important risk factors	Difficult to perform; relationship to disease risk is technically difficult to prove; requires extensive laboratory validation; RNA and protein microarray assays are expensive; large-scale studies are needed; refined bioinformatic analysis required
No	No	Yes	Can be done in blood as surrogate tissue. Similar lesions observed in cancer. Can be measured in persons without cancer	Very nonspecific; relationship to target organ is not established; significant lack of specificity and wide overlap between smokers and nonsmokers
No	No	NDA	Facile assay	Lack of specificity
No	No	No	Easy to do in blood as surrogate tissue. Can be measured in persons without cancer	Very nonspecific; relationship to target organ is not established; predictivity for disease risk not established. Association with cancer in case-control studies may have case bias. Significant lack of specificity and wide overlap between smokers and nonsmokers
No	No	NDA	Similar lesions observed in cancer	Technically complex; relationship to cancer risk unknown
No	No	NDA	Facile assay in blood	Relationship to target tissue or blood unknown

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TABLE 11-8 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
	Mutational load in target genes (p53, K-ras)	NA	NDA	Yes	No	No
Mitochondrial mutations	Deletions, insertions	NDA	NDA	Yes	No	No
Epigenetic cancer effects	Whole genome methylation	NDA	NDA	Yes	No	No
	Hypermethylation of promoter regions	NDA	NDA	Yes	No	No
Lipids	Blood lipids: HDL, LDL, oxidized LDL, triglycerides	Yes	NDA	Yes	Yes	No
Cardiovascular response	Heart rate, blood pressure	No	Yes	Yes	NA	No
Thrombosis	Bleeding time	No	NDA	Yes	No	No
	Fibrinogen	NDA	NDA	Yes	Yes	No
	Prothrombin time, partial thromboplastin time, plasminogen activator inhibitor, C-reactive protein	Yes	NDA	Yes	Yes	No
	Urinary thromboxane and prostacyclins	Yes	No	No	Yes	No

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
No	No	NDA	Target gene specificity	Very difficult to do in normal tissues
No	No	NDA	Provides corroborative marker	Relationship to disease not established
No	No	No	Facile assay	Relationship to disease unknown
No	No	No	Similar lesions observed in cancers	Technically difficult; relationship to risk unknown
Yes	No	Yes	May be directly related to disease risk	Levels among heavy smokers cannot be distinguished. Wide interindividual variation. Many individuals under medication therapy. Significant confounders exist
NA	No	Yes	Easy to measure; intraindividual differences may be important for the individual	Both interindividual and intraindividual differences are significant. Substantial confounders exist, and many persons are on medications
No	No	No	Minimally invasive	Very nonspecific
Yes	No	NDA	Pathogenically related to disease	Does not distinguish levels of smoking. Nicotine might separately affect these parameters so limited use in persons using NRT
Yes	No	NDA	Leave a fingerprint at the site of their formation	
Yes	No	Yes	May be markers of platelet-vascular interactions; reflect chronic exposure	Technically difficult. Wide overlap of values due to individual differences in response

continues

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TABLE 11-8 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
	Platelet activation and survival	Yes	NDA	Yes	No	No
Blood cell parameters	White blood cell counts (i.e., lymphocytes, neutrophils, total counts)	Yes	Yes	Yes	Yes	No
	Hematocrit, hemoglobin, red blood cell mass	Yes	Yes	Yes	No	No
Bronchio-alveolar lavage response	Inflammatory cells, protein, cytokines	Yes	Yes	Yes	No	No
	Neutrophil elastase a1-antiprotease complex	Yes	Yes	Yes	No	No
	α1-antitrypsin	No	No	Yes	Yes	Yes
Inflammatory mediators of response	Leukotrienes	Yes	NDA	No	Yes	No
Pulmonary function tests	FEV1, FVC	Yes	Yes	Yes	No	No
Periodontal disease	Periodontal height	Yes	Yes	Yes	No	No
	Gum bleeding	Yes	Yes	Yes	No	No
Osteoporosis	Fractures	Yes	NDA	NA	No	No
	Bone density	NDA	NDA	Yes	No	No
Skin	Premature wrinkling	Yes	NDA	NA	No	No

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
No	No	No	Platelet activation in vivo might be pathophysiologically related to cardiac artery thrombosis	Technically difficult to use for large numbers of subjects. Significant number of confounding variables. Smoking increases platelet counts
Yes	No	Yes	Can be a surrogate marker for several processes including atherosclerosis and thrombosis	Relationship to disease uncertain, although alterations in levels are linked epidemiologically to disease. Wide interindividual and intraindividual variation and large number of confounders
No	No	No	Can reflect both cardiac and respiratory disease risk	Insensitive; wide interindividual differences
No	No	NDA	Provides different types of data with single procedure	Bronchoscopy is too invasive for large epidemiological studies
No	No	NDA	Provides different types of data with single procedure	Bronchoscopy is too invasive for large epidemiological studies
Yes	Yes	NDA	May be specific to tobacco smoke	Requires invasive test; short half-life
Yes	No	NDA	May be measured in urine, bronchioalveolar lavage, and serum	Substantial number of confounders
No	No	Yes	Widely available	Low sensitivity for mild disease. Decrease in function with aging. Large interindividual variation
No	No	Yes		
No	No	Yes		
No	No	Yes	Easily measured	Numerous confounders
No	No	Yes		
No	No	NA		Lack of specificity; involves subjective evaluation

continues

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TABLE 11-8 Continued

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco
Fetal and neonatal effects	Birth weight	Yes	Yes	Yes	No	No
Weight	Weight loss and gain	Yes	Yes	Yes	No	No

NOTE: NA=not applicable; NDA=no data available; FVC=Forced vital capacity; FEV_1=forced expiratory volume in 1 sec; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

sioned for use in developing a molecular fingerprint reflecting a particular exposure, this has not occurred for tobacco carcinogens, and measurable effects thus far are relatively nonspecific. Nonetheless, a reduction in the level of genetic damage would logically be required if a tobacco-related PREP were to be successful in reducing cancer risk, although how much reduction of genetic damage would be needed to derive a benefit in terms of disease risk is unknown. Several types of assays are available. The main limitation today is that no assays have been shown convincingly to be sufficiently predictive of cancer risk. Chromosomal damage can be measured through classical cytogenetic alterations (Bender et al., 1988; Obe et al., 1982; Ramsey et al., 1995), micronuclei formation (Thorne et al., 1998), COMET (Poli et al., 1999; Speit and Hartmann, 1999), fluorescent in situ hybridization (FISH) (Pressl et al., 1999; Ramsey et al., 1995; van Diemen et al., 1995), or polymerase chain reaction (PCR) methods assessing loss of heterozygosity (using tandem repeats or comparative genomic hybridization) (Mao et al., 1997), where the latter two methods can be used for morphologically normal-appearing cells. Mutations in reporter genes, such as hypoxanthine phosphoribosyltransferase (HPRT) (Ammenheuser et al., 1997; Hou et al., 1999; Jones et al., 1993) or glycophorin A (GPA), have been used in blood cells, but it is better to

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Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
No	No	Yes	Data collection is easy	Nonspecific; numerous confounders
No	No	Yes	Both a biomarker for metabolism and an important outcome for some people	Some people perceive weight loss as a benefit of smoking, despite significant adverse effects associated with smoking

[a]Selected examples; list is not all-inclusive.
[b]References are not provided in this table but can be found in the text of this and disease-related chapters.
[c]Any report related to a disease outcome associated with tobacco where the report is plausible but has not necessarily been replicated.

identify mutation rates for cancer genes in biopsies from target organs or in surrogate tissues, and for genes such as p53 (Greenblatt et al., 1994) or KRAS (Lehman et al., 1996; Mills et al., 1995; Scott et al., 1997; Yakubovskaya et al., 1995). Although these assays are available, current technology limits their use in large-scale epidemiological studies. The role of mitochondrial DNA lesions is receiving greater attention for cancer risk (Fliss et al., 2000), and the lesions associated with smoking might be useful (Liu et al., 1997). Among all the assays that have potential application to assessing harm reduction claims, only two studies have assessed prospectively the cancer predictive value of chromosomal aberrations (Bonassi et al., 1995; Hagmar et al., 1994), but they consisted of pooled heterogenous populations and were not focused on tobacco. Further studies are needed to indicate the value of these assays for determining harm reduction. Thus, none of these assays can be used today to allow claims of risk reduction, although in the proper setting they can suggest that such might occur.

Biomarkers of pathobiological effect include morphological markers of preneoplastic lesions (e.g., dysplasia), altered phenotypic expression of normal cellular functions (e.g., overexpression of the proto-oncogene Erb-B2), and mutations in cancer-related genes such as the p53 tumor suppressor gene. Some of these may be considered preclinical effects that are

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occurring before diagnosis. The lesions demonstrate a person's phenotype for exposure and predisposition that persist following DNA damage. Recent advances have made it possible to measure background mutations in cancer-associated genes of noncancerous tissues (Aguilar et al., 1994; Mao et al., 1997; Sidransky, 1997), which presumably are related to future cancer risk.

The study of mutations in the p53 tumor suppressor gene is uniquely suited for studying cancer etiology, exposure, and susceptibility (Harris and Hollstein, 1993), because p53 is involved in many cellular processes including maintenance of genomic stability, programmed cell death, DNA repair, and others (Attardi and Jacks, 1999; Hollstein et al., 1999; Shimoda et al., 1994; Soussi et al., 2000). The p53 gene, in particular, has a more frequent spectrum of mutations in tobacco-associated lung cancers (Bennett et al., 1999). An interactive effect of alcohol drinking and cigarette use in oral cavity and lung cancers leads to different types of p53 mutations (Ahrendt et al., 1999, 2000; Brennan et al., 1995). Interestingly, given that the p53 mutational spectrum for lung cancer is similar worldwide (Hartmann et al., 1997), it is likely that tobacco smoke is the major determinant of lung p53 mutations worldwide. Evidence for a relationship of gene-environment interactions and mutation risk in the p53 gene can be found from a Japanese study of *CYP1A1* (Kawajiri et al., 1996), where a fivefold increase in risk of p53 mutations was found for smokers with lung cancer and the "at-risk" genetic variant. This risk increased further for persons who also lacked the glutathione *S*-transferase (*GSTM1*) gene. In one study from Norway, smokers with lung cancer who lacked *GSTM1* also had more p53 mutations, especially transversions (Ryberg et al., 1994). For oropharyngeal tumors, the frequency of p53 mutations was increased for the same *CYP1A1* variant allele (Lazarus et al., 1998). An increased risk for p53 mutations in lung cancer also has been found in Japanese persons with less common variants of *CYP2E1* (Oyama et al., 1997).

Newly developed technologies allow for the detection of loss of heterozygosity (LOH) in small amounts of tissue. Losses at chromosome 3p14, 9p21, and 17p13 have been seen in the lungs of both smokers and former smokers, where the first is less frequent in former smokers than current smokers (Mao et al., 1997).

An important area that has not been well studied is the effect of tobacco toxicants on the induction of enzymes that might affect cancer risk. For example, cytochrome P-450 enzymes are induced with tobacco smoking (e.g., arylhydrocarbon hydroxylases [AHHs]) (Bartsch et al., 1995; Guengerich, 2000; McLemore et al., 1990; Nakajima et al., 1991, 1995; Rojas et al., 1992). Induction is related to greater amounts of DNA damage (Bartsch et al., 1991; Geneste et al., 1991). It remains to be tested whether a

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tobacco-related PREP can reduce AHH exposure so that other carcinogenic exposures will be less harmful. Many proteins are induced in relation to DNA damage (e.g., p53) (Bjelogrlic et al., 1994). Whether higher levels of these proteins increase or decrease the risk of disease remains unknown.

Several biomarkers can be studied in relation to cardiovascular disease risk, but none of these are specific to tobacco smoking, such as blood lipid level (Cullen et al., 1997; Freeman et al., 1993; Hellerstein et al., 1994; Ludviksdottir et al., 1999; Stubbe et al., 1982; Wald et al., 1989), which changes with cessation (Green and Harari, 1995), or urinary excretion of thromboxane A_2 metabolites (Nowak et al., 1987; Lassila et al., 1988; Rangemark et al., 1992; Wennmalm et al., 1991). F_2-Isoprostanes in blood have a dose-response relationship to smoking (Morrow et al., 1995). Tobacco smoking is associated with decreased weight (Green and Harari, 1995) and therefore modifies the relationship of weight gain to increased risk of heart disease (Fulton and Shekelle, 1997). Blood pressure has been studied but is not clearly associated with smoking (Green and Harari, 1995). Other biomarkers that have been suggested to reflect an increased cardiac disease risk include reduced platelet survival (Fuster et al., 1981). Newer imaging methods such as electron-beam computed tomography (O'Malley et al., 2000; Raggi et al., 2000) are being used to assess heart disease risk, and these methods might be used to assess the decreasing rate of formation of atherosclerosis or calcium when using a PREP.

Biomarkers of developing respiratory illness have been assessed in different ways, and several studies have specifically assessed the effects of smoking reduction separately from cessation. Symptoms, albeit late effects, such as cough, chronic phlegm production, wheezing, and shortness of breath have been used and improve with smoking cessation (Buist et al., 1976; Kanner et al., 1999). Reducing smoking, without quitting, also is associated with a reduction in symptoms (Buist et al., 1976). There are many studies that explore decrements of pulmonary function related to cigarette smoking. While such decrements occur with aging independent of smoking, further decrements are induced by smoking (Lange et al., 1989; McCarthy et al., 1976). Declines in the forced expiratory volume at 1 second (FEV_1) are associated with increased disease and mortality, including nonpulmonary diseases (James et al., 1999). The decline in pulmonary function tests slows with complete cessation (Buist et al., 1976; Kanner et al., 1999; Lange et al., 1989; McCarthy et al., 1976) and with greater than 25% reduction in the number of cigarettes smoked per day (Buist et al., 1976; Lange et al., 1989; McCarthy et al., 1976). Smoking reduction in the elderly apparently showed no effect in slowing the rate of decline (Lange et al., 1989). Bronchioalveolar lavage has been used, although it is invasive, and different types of assays can assess inflamma-

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tion, neutrophil elastase α_1-antiprotease complex, and α_1-antitrypsin (Rennard et al., 1990). Induction of these components reverses with smoking reduction (Rennard et al., 1990), and some markers such as alveolar neutrophils, neutrophil elastase α_1-antiprotease complexes, and alveolar macrophages decrease in smokers who reduce their amount of smoking when provided with nicotine replacement therapy (Rennard et al., 1990).

Several nonspecific biomarkers of effect are related to smoking, such as leukocyte count (Parry et al., 1997; Phillips et al., 1992; Sunyer et al., 1996; Wald et al., 1989), which reverses with cessation (Green and Harari, 1995; Sunyer et al., 1996) and then increases again with resumption of smoking (Sunyer et al., 1996). Levels remain increased to some extent in former smokers compared to never smokers (Parry et al., 1997). Whether these findings, however, are independent predictors of disease risk has had limited study (e.g., mortality) (James et al., 1999), and the differences that can be found may be due to disease unrelated to smoking (Wald et al., 1989). Some of these parameters are covariates (James et al., 1999). Thus, such markers would be less useful for assessing harm reduction claims but might be useful for assessing exposure reduction claims.

There are several short-term effects on the body that can be considered both from the perspective of disease and as a biomarker of effect. Examples include periodontal disease, abnormal glucose tolerance tests, and decreased birthweight of infants born to mothers who smoke. Also, changes in adult body weight can be measured in the context of harm reduction. It is well known that smoking increases metabolism and decreases appetite, while stopping smoking is associated with weight gain (O'Hara et al., 1998). This can be a very important marker of smoking effects since the consideration of weight is often a factor in persons' beginning smoking or resisting cessation.

HOST SUSCEPTIBILITY

Host susceptibility could modify the risk of tobacco-related disease and, therefore, the effects of PREPs. Host susceptibility can be influenced by genetic susceptibility, age, gender, ethnicity, health status, and so forth. These will not be discussed in detail except for genetic susceptibility, but any relevant potential modifying factor should be considered in the assessment of a PREP.

The study of genetic susceptibilities can improve the accuracy of estimates of disease associations (Khoury and Wagener, 1995). Tobacco toxicants affect people to variable degrees. It is therefore reasonable to assume that harm reduction strategies would affect people differently. There is large interindividual variation in cellular responses—for example, in metabolism and detoxification of toxicants and DNA repair. As other

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cellular responses to DNA damage are identified (e.g., cell-cycle delays, heat shock), interindividual variation in risk is likely to be discovered for these as well. Interindividual effects in cellular responses could be due to genetically determined enzyme expression, kinetics, or stability. Also, induction of enzymes from previous exposures or comorbidity also may contribute to cancer risk, and induction has a genetic component.

Susceptibility to disease from genetic variability can range from small to large, depending on the genetic penetrance. Highly-penetrant cancer susceptibility genes cause familial cancers but account for less than 1% of all cancers (Fearon, 1997). Low-penetrant genes cause common sporadic cancers and can have great public health consequences (Shields and Harris, 2000).

Genetic susceptibility can be assessed either phenotypically (measuring the resultant enzymatic function) or genotypically (determining the genetic code). Examples are provided in Table 11-9. Phenotypic assays may include determining enzymatic activity by administering probe

TABLE 11-9 Assays for Assessing Effect Modification by Heritable Traits

Assay Type	Example Used in Literature	Strengths	Limitations
Gene-based assays	Genetic polymorphisms for carcinogen metabolism and induction or DNA repair, smoking behavior	Inexpensive, simple to perform, specific gene effect when exists, high throughput available	Functional relationship of genotype to phenotype difficult to prove; disease risk for low-penetrant genes difficult to prove
Phenotypic assays	Mutagen sensitivity for DNA repair; host-reactivation assay for DNA repair; CYP450 metabolism and induction studies; RNA expression of specific genes; microarray RNA expression; proteomics	Reflects integrated measure of multiple genotypes; provides complex data potentially usable for rapid identification of important risk factors	Difficult to perform; relationship to disease risk technically difficult to prove; requires extensive laboratory validation; RNA and protein microarray assays are expensive; large-scale studies are needed; bioinformatics not available

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drugs to individuals and measuring blood levels or urinary metabolites, assessing carcinogen metabolic capacity in cultured lymphocytes, or establishing the ratios of endogenously produced substances such as estrogen metabolite ratios. One extensively studied phenotype in relation to smoking risk is AHH activity (Kellermann et al., 1973; Kouri et al., 1982). In general, it is preferable to use a gene-based assay to assess disease risk because DNA is easier to obtain and the assays are technically simpler. However, phenotypes usually represent a multigenic trait, which may not be adequately characterized by only one genetic assay. Therefore, there is a role for both gene- and phenotype-based assays in research studies and PREP assessments. Examples of frequently studied genetic polymorphisms in tobacco-related cancers that have been shown in some studies to modify smoking-related disease risk include the *N*-acetyltransferase 2 (*NAT2*) (Brockmoller et al., 1996, 1998; Henning et al., 1999), glutathione *S*-transferase M1 (*GSTM1*) (Bell et al., 1993; Brockmoller et al., 1996, 1998; Cullen et al., 1997; Jourenkova et al., 1998; Jourenkova-Mironova et al., 1999; Rebbeck, 1997), cytochrome P-450 1A1 (*CYP1A1*) genes (Bishop, 1987; Ishibe et al., 1997), glutathione *S*-transferase Pi (Ryberg et al., 1997), and others (Jourenkova-Mironova et al., 1999; Rosvold et al., 1995; Wiencke et al., 1997). These and other genetic polymorphisms are believed to affect levels of biomarkers, such as DNA adducts (Kato et al., 1995; Pastorelli et al., 1998; Ryberg et al., 1997; Yu et al., 1995).

In the general population, DNA repair capacity decreases in humans with aging (Liu et al., 1994; Wei et al., 1993), which would make this an acquired risk factor for cancer and might explain a portion of the increased cancer risk in the elderly (Simpson, 1997). Both genotyping and phenotyping assays for DNA repair or cell-cycle control that affects DNA repair might be useful in identifying individuals who might benefit from harm reduction strategies. Tobacco toxicants can affect DNA repair (Grafstrom et al., 1994), so that the effects of both tobacco toxicants and heritable capacity on DNA repair can be considered in assessing harm reduction products. It should be noted that cigarette smoking induces levels of some repair enzymes (Drin et al., 1994; Hall et al., 1993; Slupphaug et al., 1992), so caution must be used for some phenotyping assays.

Inherited susceptibilities via specific genetic polymorphisms that affect the efficiency of DNA repair (e.g., for base excision repair) have been identified recently (Mohrenweiser and Jones, 1998). Studies now being completed indicate an effect of these genetic variants on tobacco-related cancer risk (Sumida et al., 1998), some of which have functional effects on DNA repair (Lunn et al., 1999, 2000). A nonspecific DNA repair assay, which measures chromosomal aberrations in human cultured lymphocytes after an in vitro challenge with a mutagen, has shown initial promise. In this case, an increased mutagen-related aberration rate has been

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observed in persons with primary and secondary upper aerodigestive tract cancers (Cloos et al., 1996), multiple primary cancers (Cloos et al., 1994), and lung cancer (Li et al., 1996; Spitz et al., 1995; Wei et al., 1996).

Genetic susceptibilities for genes other than those involved in carcinogen metabolism and DNA repair are also being investigated (Jin et al., 1995; Sjalander et al., 1996). There has been less study of genetic susceptibilities for coronary artery disease (Gealy et al, 1999). It is likely that these genes also will play a role in modifying disease risk (see Chapter 13).

GENETIC PREDISPOSITIONS TO SMOKING ADDICTION

The greatest contributors to smoking addiction are the availability of tobacco and cultural acceptance of tobacco smoking. Genetics plays a lesser role. The tobacco smoking epidemic has occurred only over the last 50 to 70 years, and it is unlikely that human genetics have evolved in that amount of time. Nonetheless, twin studies indicate a genetic role for both smoking initiation and smoking persistence (Carmelli et al., 1992; Heath et al., 1993a, b).

People smoke in ways that will maintain a desired blood nicotine level. Nicotine in turn stimulates reward mechanisms in the brain. Presynaptic nicotinic acetylcholine receptors stimulate the secretion of dopamine into neuronal synapses. There also are effects on other pathways, such as those that involve serotonin. For dopamine, synaptic dopamine stimulates dopamine receptors; five subtypes have been identified, which are considered to be D_1- or D_2-like. Synaptic dopamine levels are governed by presynaptic release and the presynaptic dopamine transporter protein. In humans, there are different types of data supporting the link between nicotine and dopamine. Nicotine self-administration through tobacco smoking may reduce the adverse consequences of Parkinson's disease, attention deficit disorder, and schizophrenia (Bannon et al., 1995; Olincy et al., 1997; Seeman, 1995), diseases thought to be related to dopamine abnormalities. Also, smoking probably relieves depression (Gilbert and Gilbert, 1995), and the dopamine transporter inhibitor antidepressants (e.g., bupropion SR) are now used to treat nicotine addiction (Hurt et al., 1997; Jorenby et al., 1999).

The genes that code for dopamine receptors (e.g., *DRD2, DRD4*), dopamine transporter reuptake (*SL6A3*), and dopamine synthesis (e.g., dopamine hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, catechol-*O*-methyltransferase, monoamine oxidase) are polymorphic. Some of the polymorphisms result in altered protein function. Persons with higher levels of synaptic dopamine, or "more stimulation" of dopamine receptors may have less rewarding effects of nicotine and so would be

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less likely to become smokers and would more easily quit. For example, in a study of 500 smokers and nonsmokers, several candidate genes have been implicated (Lerman et al., 1998, 1999; Shields et al., 1998), whereas other studies of candidate genes have yielded null results (Lerman et al., 1997). Other investigators also have reported supporting evidence (Comings et al., 1996; Noble et al., 1994; Spitz et al., 1998). Thus, it is likely that there is a genetic contribution to smoking addiction and behavior and there may also be a genetic influence on who benefits from PREPs.

BIOMARKER ASSESSMENT FOR ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

Biomarker assessments in persons exposed to environmental tobacco smoke are problematic because exposures occur at much lower levels than in smokers, and therefore the level of detection is limiting (Benowitz, 1999). The most consistently used biomarkers are those that reflect exposures, namely cotinine (serum, plasma, or urine), rather than biologically effective doses or biomarkers of effect. Such biomarkers, for example, can show that adolescents are exposed to tobacco smoke through household smoking (Bono et al., 1996). Urinary metabolites of tobacco-specific nitrosamines also have been found in persons exposed passively to smoke (Atawodi et al, 1998; Hecht et al., 1993; Parsons et al., 1998). DNA adducts in the lung are also detected in persons who are thought to be nonsmokers (Kato et al., 1995). Children exposed to modest levels of ETS have been found to have increased concentrates of 4-aminobiohenyl adducts of PAH-albumin adducts (Tang et al., 1999). Although it may follow that proven methods to reduce harm in smokers would apply to nonsmokers with passive exposure, there are circumstances in which passive smoke exposure might be substantial (e.g., cigar smoking).

DEVELOPMENT AND VALIDATION OF BIOMARKER ASSAYS, INCLUDING QUALITY CONTROL

The use of biomarkers in assessing harm reduction can be helpful only when the assays have undergone rigorous development and validation. Reliance on insufficiently validated biomarkers becomes problematic because they are of uncertain value and so should not be used to support a claim of exposure or risk reduction. The design and development of a biomarker assay must conform to the original goals—that is, the assay should have sufficient specificity, it should be quantitatively reproducible in humans at the levels that occur when exposure reduction is achieved, and other assays should be available to corroborate the qualitative and quantitative results. Many pitfalls have already been found in

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biomarker development. There are examples of biomarker assays that are more difficult to perform at levels observed in humans compared to the use of higher-level laboratory chemical standards (e.g., immunoassays) (Santella et al., 1988). Some methodologies can artifactually affect assay results (e.g., introduction of oxidative damage) (Farmer and Shuker, 1999). In some cases, measurements of in vivo formation can be skewed by exogenous exposure to the biomarker (e.g., dietary ingestion of 3-alkyladenine) (Prevost and Shuker, 1996).

Validation of a biomarker assay includes a determination of replicability (e.g., coefficient of variation), interobserver and interlaboratory variability, intraindividual variation, and interindividual variation. These validation steps must be done using known controls that simulate human exposure levels and harm. Thus, the assay should be validated in light and heavy smokers, former smokers, and never smokers. Caution must be used in interpreting assay results in the context of certain study designs. For example, the reliability of biomarkers thought to be related to disease risk in case-control studies is problematic for markers that might be affected by disease status (differential case bias) (Wald et al., 1989).

Research laboratories providing data that can impact individual or public health should have adequate quality control and quality assurance procedures in place. The definition of adequate will depend on the population under study and the number of subjects. In clinical pathology laboratories, standards and protocols have been established by organizations such as the College of American Pathologists and the National Committee for Clinical Laboratory Standards. In a research laboratory that performs biomarkers studies assessing PREPs, there should be standards for proficiency testing, quality improvement, quality control, use of standards, methods for interpretation, specimen handling, specimen labeling, specimen processing, and reporting of results. There also should be criteria for facility and equipment maintenance.

CONCLUSIONS

The assessment of a PREP will have to consider external exposure and markers of internal exposure, estimates of the biologically effective dose, and biomarkers of potential harm. A risk reduction claim should be based on disease reduction, but time limitations mandate the use of biomarkers for both exposure and risk reduction assessments. Measurements of the number of cigarettes per day, smoking duration, estimated lifetime exposure, smoking topography, and so forth, provide an effective indicator of exposure that has been associated with risk. However, these measures may be insensitive to small changes in risk, are difficult to assess accurately over time, and have not been tested in the context of harm

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reduction. Also, because there is interindividual variation in how the body responds to these exposures, such measures might not be sufficiently accurate for new products intended to decrease exposure. The relationship of external exposure markers to disease risk might be less predictable for new products. Currently, there is sufficient evidence to show that biomarkers can provide better estimates of risk in the context of exposure, and therefore they will likely be able to provide improved assessments for harm reduction products. However, no single biomarker has been sufficiently validated and related to disease risk to be recommended as an intermediate biomarker of cancer risk. Thus, different types of biomarkers along the pathway from internal exposure to biologically effective dose, and to potential harm are needed, and additional research is necessary to identify the best combination of markers to be used. Experimental toxicity testing (in vitro and animal models) are not sufficient to support a tobacco-related PREP claim because only biomarkers can show that the PREP reduces exposure adequately enough to imply risk reduction. However, the use of intermediate biomarkers as surrogate risk factors for disease may overestimate the number of persons who actually develop disease because not all early changes in morphology or function progress to disease. On the other hand, it may underestimate if, as expected, other mechanisms are involved in the disease process that are not reflected by the biomarkers. Therefore, the implication of a potential benefit in a harm reduction strategy could also be an overestimate, but this limitation in the scientific methodology for identifying sufficiently specific biomarkers of risk requires acceptance at the current time.

Previously, the most common way in which exposure reduction has been inferred is through the use of methods that simulate human smoking behavior, such as the FTC method. Although they provide a standardized way to assess cigarettes, it is clear that these methods have limited usefulness because people smoke their cigarettes differently than the machine, with resultant differences in the types and amounts of exposure.

The use of biomarkers improves exposure assessments (e.g., characterizing low-dose exposures or low-risk populations), provides a relative contribution of individual chemical carcinogens from complex mixtures (e.g., TSNAs and PAHs in cigarette smoke), and estimates total burden of a particular exposure where there are numerous sources (e.g., BaP from air, tobacco, diet, and occupation) (Vineis and Porta, 1996). Biomarkers also can establish differences in individual susceptibilities and whether there are differences in response depending on dose. Thus, biomarkers that measure both complex exposures and single tobacco product constituents are needed and should be assessed for the range of possible human exposures and those that assess complex exposures should carry a greater weight. Also, some biomarkers should be used that are less spe-

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cific for individual tobacco constituents in order to monitor for the introduction of new hazards from tobacco-related PREPs.

Today, there remain technical limitations to the use of biomarkers. Depending on the harmful effect, surrogate assays in nontarget fluids or organs that represent effects in target organs may be easier to perform in humans because the target tissues might not be easily accessible. However, if such is the case, the relevance of the surrogate biomarker to the effect in the target organ should be demonstrated.

The use of a biomarker for harm reduction assessment should include several considerations, including where it is along the pathway from exposure to disease, its specificity and sensitivity, available harm dose-response data, available reduction in harm dose-response data, target tissue effect, and how it is validated. The need for validation cannot be overemphasized. Each biomarker should be validated for its relationship to exposure and harm and also as a laboratory assay that provides reliable and reproducible data. Separately, the way a biomarker is affected by interindividual variation in response and by behavior should also be considered.

Assessment of harm and harm reduction should be made through direct human experience, as the products are used by the general population. Most of what is known about harmful tobacco products has resulted from epidemiology, supported by in vitro studies, laboratory animal studies, and human experiments. However, while epidemiological studies can provide the most definitive data about tobacco harm and harm reduction products, the study of diseases with long latency (e.g., cancer, heart disease, chronic obstructive pulmonary disease) is problematic because such studies require many years before they provide useful data. Thus, because definitive evidence for a new risk reduction product is not available short-term markers that reflect long-term outcomes are needed. If an approach for assessing risk reduction products required only epidemiological data measuring disease outcome prior to use by the public, then an opportunity to reduce morbidity and early mortality might be missed. However, the use of intermediate markers does not replace long-term follow-up and epidemiological surveillance, but allows judgments to be made until such data are forthcoming.

Biomarkers of internal exposure, biologically effective dose, or potential harm have been validated to different degrees. It is typically easier to show a direct relationship of external exposure to biomarkers in the following order: internal exposure, biologically effective dose, and potential harm. Conversely, it is typically easier to show a direct relationship of disease outcome to biomarkers in the following order: potential harm, biologically effective dose, and internal exposure. It might be acceptable to rely on external exposure measurements for considering risk and dose-

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response, but only with substantial corroborative biomarker data. The best strategy for assessing the claims for risk reduction methods is with several markers that range from exposure to outcome, one being linked to another, and at least one with which a dose-response risk assessment can be made.

The recommendation that harm reduction products should be assessed with the use of biomarkers reflects sufficient available data to show that the public is composed of individuals with different cultural and heritable traits that affect how people use tobacco products and respond to them. To achieve the best confidence that a PREP will reduce risks for persons who cannot stop smoking, both well-validated methods for predicting risk, including external exposure indicators, and the best available biomarker assays should be used.

RESEARCH AGENDA

There are currently different methodologies for assessing PREPs, but substantial research is needed to increase confidence in the application of these methods. Although it may be possible to improve external methods for assessing exposures, such as through modification of the FTC method or improving questionnaire assessments, there is so much variability in human smoking behavior that it is believed these methods could never be much more helpful than they already are. This recommendation does not imply that questionnaires and topography instruments are not helpful in assessing smoking behavior, because they are, but it is unlikely that the methodology can be improved substantially. Indeed, clinical epidemiological studies generally have to integrate more variables for smoking behavior (e.g., accurately documenting changes in smoking, brand switching).

The development and validation of biomarkers for assessing harm reduction must be accelerated for all diseases, especially for cardiovascular and respiratory diseases because less research has been conducted compared to cancer.

The use of a biomarker for assessing harm reduction should be considered using the criteria provided in this chapter. Dose-response relationships should be established, and the biomarker should be assessed for reversibility in smoking cessation trials. In all studies of biomarker validation, consideration should be made of what nontobacco exposures, if any, would influence the biomarker study results. Also, biomarkers have to be tested and validated in different populations, to determine whether they are affected by susceptible subpopulations, and within genders, races, or ethnicities. Research efforts should focus on biomarkers that

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might be used for existing cohort studies, where disease outcome already is known. For example, markers are needed that can be used in serum or small amounts of DNA from stored samples. This is the best way to identify a relationship between exposure, a biomarker, and disease risk. Substantial research is needed to identify the relationships between biomarkers to exposure, biologically effective doses, and biomarkers of harm. Study designs that can provide these linkages are needed, and the best evidence will come from cohort studies.

Internal biomarkers of exposure such as cotinine, nicotine boosts, CO, and CO boosts provide good information about exposure, including to environmental tobacco smoke, but additional markers, such as urinary anabasine and anatabine levels, have to be developed for use in persons who are concurrently using nicotine replacement therapy. Increased efforts to measure urinary excretion of carcinogen metabolites, which are currently showing promise for use in risk assessment of active smoking and ETS, are needed. Examples include urinary excretion of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons and urinary mutagenicity, where these reflect both single and complex markers of exposure, respectively. Also, markers with longer half-lives would be useful to avoid confounding by recent changes in smoking behavior.

Biomarkers that reflect the biologically effective doses of exposure to carcinogens must be improved and validated. Newer technologies are now available that are more sensitive (e.g., mass spectroscopy) and can provide more information, and these should be applied in experimental systems and human studies that were developed long before such methods were available. For example, the determination of carcinogen-DNA adducts might be useful where small amounts of tissue are available (e.g., buccal swabs, sputum, blood).

More biomarkers of potential harm are currently being developed than any other types. This is because pathobiological pathways are well understood and newer technologies are available to explore them. However, along with better technologies will come limitations in the interpretation of new data (e.g., mRNA expression assays, proteomics). As researchers explore greater numbers of gene-smoking interactions and accumulate data for numerous genes expressed in response to exposures, it is clear that there are insufficient methods to analyze data where there are a substantial number of predictor variables. Also, some data will have to be reduced to clusters or other smaller units that are understandable in the context of biological hypotheses. Increased research is needed in methodologies to interpret these types of data, to validate the new models in the context of disease outcome.

For cancer, increased efforts are needed to assess target organ assays, such as genetic damage in lung cells in sputum and exfoliated bladder

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cells in urine, in persons years before they have a clinically detectable cancer. Given that genetic damage is only one part of the carcinogenic process, additional efforts are necessary to develop biomarkers for other pathways, such as gene silencing through hypermethylation of promoter regions. For cardiac disease, additional studies are needed to validate biomarkers of platelet function, endothelial function, endothelial thickening, and plaque formation and thrombosis. For respiratory disease, better markers are needed to assess changes in lung function that predict chronic obstructive pulmonary disease and asthma, and to assess immunological changes that will increase risk of respiratory infections.

It would be optimal to identify biomarkers that can be used to assess risk for several diseases. For example, biomarkers of oxidative damage might identify risk for cardiac disease, cancer, and respiratory illness. However, because the relationship of oxidative damage to these diseases remains mostly an unproved hypothesis, research is needed in this area.

Biomarkers will have to assess PREPs for single tobacco constituents and complex mixtures. The use of biomarkers that can assess multiple exposures from complex mixtures is critical because new tobacco-related PREPs might include compounds that are not present in existing tobacco constituents, or the ratio of exposures to individual constituents might change. A committee of experts should be convened to consider and identify those biomarkers that have the most promise and to determine what combination of biomarkers should be part of a panel for assessing PREPs.

To identify those biomarkers most useful for assessing harm reduction products, current efforts have to be focused on clinical trials that assess the effects of switching brands, using new products, and reducing daily consumption of tobacco through the concomitant use of nicotine replace therapy or other aids used for smoking cessation.

There are unique opportunities in epidemiological studies to validate biomarkers for use in assessing harm reduction strategies. Specifically, cohorts of participants in smoking cessation programs and former smokers should be established because these individuals represent the best possible reduction in the risk due to smoking. The collection of tissues and fluids from persons who have quit smoking and comparisons of persons who do and do not develop disease would be very helpful in determining which biomarkers have the most predictive value. This should be done in the context of previous smoking history to identify which persons would obtain the greatest benefit from cessation and how biomarkers might be able to identify individuals at greatest risk within these groups. Some diseases, such as cardiovascular disease, have a relatively rapid decline in risk following cessation so it would be quicker to validate cardiac disease risk factors. For cancer, the studies will take much longer. Monitoring populations that are at the highest risk of cancer, such

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as persons with resected early-stage lung cancer or bladder cancer, might be useful in this context. If a biomarker cannot predict increased risk in former smokers, it is unlikely to be useful in assessing PREPs.

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12

Cancer

Around 1950, Doll and Hill (Doll and Hill, 1950), Wynder and Graham (Wynder and Graham, 1950), and others reported the extremely high incidence of smoking in lung cancer patients. In fact, lung cancer was a rare disease before smoking (Doll and Hill, 1950). If one employs almost any method to assess causality, such as that proposed in the first Surgeon General's report on smoking (U.S. PHS, 1964) and later articulated in more detail by Sir Austin Bradford Hill (Hill, 1965), then clearly the use of tobacco products causes cancer. This conclusion comes from substantial epidemiology, laboratory animal, and in vitro studies. Tobacco smoke contains more than 100 carcinogens and mutagens, many of which are classified as carcinogens based upon human and animal studies (IARC, 1986), the latter include lung tumors in the same organs as cancers occur in humans. It is estimated that 20% of all cancers worldwide are attributable to smoking (Parkin et al., 1999).

If a regular smoker successfully quits, then the risk of cancer decreases, but the risk of cancer in former smokers does not decrease to the level of "never smokers." Thus, the concept of harm reduction by reducing exposure to tobacco carcinogens might be plausible if the exposure is significantly reduced, but the reduction in risk could not be more than that for a former smoker and would probably be less. Therefore, the most beneficial harm reduction strategy in smokers is to stop smoking.

The assessment of cancer risk from potential reduced-exposure agents (PREPs) must consider mechanisms of mutagenesis and carcinogenesis. This chapter will focus on only four types of cancer caused by cigarettes

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and tobacco-containing products, although smoking causes other cancers as well (Doll, 1996); two of these are examples of the most common cancers related to tobacco (lung and oropharyngeal), and one is an example of a cancer that occurs remotely from the site of entry of the carcinogen into the body (bladder). The fourth cancer is one in which tobacco is believed to reduce risk (endometrial). In this chapter, a mutagen is defined as a compound that causes DNA damage of any sort. A carcinogen is defined as a compound that contributes to cancer, independent of the mechanism. A tobacco constituent is any compound from a tobacco-containing product, used in an intended or unintended fashion, which results in human exposure.

MUTAGENESIS AND DNA DAMAGE

Cancers result from an accumulated amount of mutations (changes in nucleotide sequence) or gross chromosomal damage. There are several pathways to such DNA damage. Genetic damage occurs because a mutagen, or its activated metabolite, binds to or otherwise interacts with DNA. This mutagen can then cause a promutagenic lesion or in some other way perturb the genetic structure resulting in a gross chromosomal alteration (aneuploidy, break, translocation, amplification, deletion). The genetic damage follows a failure of several protective mechanisms. The first line of defense against chemical insult involves metabolizing enzymes that are intended to aid excretion of potentially damaging chemicals in the body (produced endogenously or coming from exogenous sources; Guengerich, 2000). For tobacco constituents, this "excretory" process gone wrong is a multistep pathway simplistically described as (1) entry of the mutagen into the body (i.e., oral, respiratory, and gastrointestinal mucosa) and its distribution throughout the body; followed by (2) recognition by an organ that this is a foreign substance in need of excretion (e.g., lung, liver, bladder); (3) use of enzymes for metabolic conversion of the chemical so that it can be bound to an excretory conjugate (Guengerich, 2000); (4) binding to DNA rather than an excretory conjugate; and (5) formation of a DNA adduct or a lesion that then results in DNA damage. A mutagen might be made more water soluble or able to bind an excretory conjugate (e.g., glutathione) through several chemical reactions catalyzed by cytochrome P-450 (CYP) and other enzymes, followed by conjugation catalyzed by enzymes (e.g., glutathione *S*-transferases, glucuronyl transferases, sulfuronyl transferases). Every one of these steps can influence cancer risk (Hecht, 1999a; Perera, 1997; Van Delft et al., 1998), where greater activity increases the risk of DNA damage, while greater conjugation and excretory capacity could reduce risk. Metabolic conversion and conjugate binding is a complex pathway that differs

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for different classes of mutagens, and there are redundant pathways (Anttila et al., 1992, 1993, 1995; Brennan, 1998; Grundy et al., 1998; Guengerich, 2000; Nakajima et al., 1995). Different parts of an organ such as the lung may have different capacities for activation and detoxification (Anttila et al., 1993; Bartsch et al., 1991; Geneste, 1991; Petruzzelli et al., 1989; Rojas et al., 1992; Shimada et al., 1996b). Enzymes that are responsible for metabolic activation and detoxification can be induced by exposures, which could further affect the level of subsequent DNA damage (Bartsch et al., 1995; Ciruzzi et al., 1998; Guengerich, 2000; McLemore et al., 1990; Nakajima et al., 1995). Thus, when manipulating the levels of carcinogens in tobacco products, it is important to consider how these changes might affect any of the above steps. Separately, it is well known that people have different heritable abilities for these steps, so manipulating the level of one or more tobacco product constituents might affect people differently.

If a mutagen binds to DNA, additional processes must fail before a mutagenic event occurs, and this takes place more often for some mutagens than for others. Thus, not all mutagens are human carcinogens. One form of DNA damage is a DNA adduct, which is a nucleotide with a chemically bound mutagen or some part of the mutagen. There may be some specificity for the sites of DNA adducts to occur within the genome, but adducts can form anywhere in the genome (La and Swenberg, 1996). Importantly, for the DNA adduct to contribute to the carcinogenic process, it must lead to a mutation and that mutation has to occur in a critical part of a critical gene.

Chemicals within the same class can have different capacities to form reactive intermediates and cause DNA-adduct formation in different parts of a gene. Therefore, simply altering the levels of a specific class in a harm reduction strategy might not affect the important chemical within that class, and the formation of a new adduct due to changes in chemical constituents might result in greater degrees of mutagenicity.

The chemical binding to DNA through the formation of adducts, for example, can lead to nucleotide sequence changes (insertions, deletions, or substitutions). It also can lead to gross chromosomal aberrations such as breaks, deletions, or translocations. These events occur when the mutagen causes errors during DNA replication or mitosis. However, there are protective mechanisms should any of these types of DNA damage occur and cancer develop due to the imbalance of DNA damage and DNA repair (Loeb and Loeb, 2000). Individual adducts may be repaired by excision repair pathways, while chromosomal aberrations are repaired by recombination repair pathways. In addition to DNA repair, other protective mechanisms can reduce the harmful effects of DNA damage, such as lengthening the G1 or G2 checkpoints to allow more time for DNA

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repair or triggering cell death (apoptosis). Unfortunately, some mutations might block the entry into these checkpoints or evade cell death processes. In addition to repair pathways that remove adducts, there are other control methods if these mechanisms or pathways fail. There are DNA repair enzymes that recognize and repair mismatch damage, and if this does not occur, cell death may be triggered. The combination of repair and cell turnover leads to a half-life of carcinogen-DNA adducts. To date, the effects of chemicals on these repair and control pathways, and interindividual differences in DNA repair, cell-cycle control, and cell death have only recently received some attention (Sumida et al., 1998).

The relationship between a mutagen and mutation is complex and may depend on the dose of the mutagen (La and Swenberg 1996; Van Delft et al., 1998). Low-dose exposures are often difficult to evaluate in vitro or in vivo because of mutational background rates, and extrapolation of mutation rates from high-dose to low-dose exposures depends on assumptions that may not be true (Liber et al., 1985). Mutation rates for exposures that switch from high dose to low dose and how the mutational spectra changes have not been studied.

In summary, for a tobacco constituent to cause a DNA lesion that confers a selective clonal advantage on a cell that ultimately becomes cancerous, the constituent must be absorbed and metabolically activated; it has to damage DNA, which evades repair; it has to occur in a critical part of a critical gene; and finally, the cell must evade cell death. Moreover, this has to occur in the target organ. Internal exposure can be affected by smoking behavior or storage depots in the body (e.g., adipose tissue). These pathways are important to consider for harm reduction strategies because altering the levels of different tobacco constituents or complex mixtures might affect these pathways differently, so that the net effect on carcinogenicity may not be predictable a priori, either for an individual or for the population.

CARCINOGENESIS

Carcinogenesis is a multistage process involving many different genes (Devereux et al., 1999). DNA damage is necessary, but not sufficient, to cause tumors as evidenced in experimental models (Pledger et al., 1977). One conceptual approach to understanding carcinogenesis is to consider that cancer is driven by defects in either caretaker, gatekeeper, or landscaper genes (Kinzler and Vogelstein, 1997, 1998). Caretaker genes are those responsible for maintaining genomic integrity, such as DNA repair and metabolism. Mutations or inherited variants in these genes increase the risk of mutations in other genes. Gatekeeper genes are those involved in controlling cell cycle, and replication of the genome, triggering

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apoptosis, and assisting caretaker genes in maintaining genomic integrity. Mutations in gatekeeper genes increase the risk for a cell to replicate uncontrollably and increase the likelihood of permanently establishing mutations. Landscaper genes are those that affect the external environment around the cells and thus control adjacent cells. Current data do not exist to indicate that tobacco-related harm preferentially affects any classes of genes, but an effect of tobacco carcinogens on all classes of genes is plausible and suggested by the observed complex genetic alterations in lung and other cancers.

Another way to classify cancer genes is to consider them as oncogenes or tumor suppressor genes. This classification is based on studies showing that overexpression or mutation of the former increases proliferative potential, while loss of the latter stimulates proliferative potential. For oncogenes, only one allele has to be activated, whereas for tumor suppressor genes, both alleles are usually inactivated. Thus, the former is a dominant trait, while the latter is recessive.

Oncogenes occur when proto-oncogenes, responsible for normal cellular processes, are mutated. Multiple oncogenes are involved in the pathogenesis of solid tumors including lung cancer (Fong et al., 1999; Kohno and Yokota, 1999; Rom et al., 2000). Only a few oncogenes, such as K-ras and c-MYC have been identified as playing crucial roles in the pathogenesis of several tobacco-related tumors (Reynolds et al., 1991; Rodenhuis et al., 1987; Slebos et al., 1991, 1992). However, most oncogenes remain to be discovered. The ras gene family consists of three members (K, N, and H). They are membrane-bound proteins that bind to guanosine 5′-triphosphate (GTP) when activated, and to guanosine 5-diphosphate (GDP) when inactivated. Activation sends a signal to the nucleus, via a cascade of kinases, that eventually results in the activation of transcription factors. Activating ras mutations occur at codons 12, 13, and 61 and result in loss of intrinsic guanosine triphosphates (GTPase) activity, locking in the activated form (Bos, 1988); experimental studies support the role of tobacco carcinogens that affect ras in lung cancers (Ronai et al., 1993). It has been reported that ras mutations are present usually only in smoke-related lung cancers (Gealy et al., 1999; Slebos et al., 1991). Such mutations also can be observed in smokers without lung cancer, suggesting that they can be early markers of smoking-related damage (Lehman et al., 1996; Slebos et al., 1991; Scott et al., 1997; Yakubovskaya et al., 1995).

Tumor suppressor genes in tobacco-related cancers include p53 (also known as TP53), $p16^{INK4A}$ (p16), retinoblastoma (RB), and fragile histidine triad (FHIT) genes. A frequent method of inactivation of one allele of recessive oncogenes is by allelic deletion (i.e., loss of DNA material on one of the alleles). Often, this deletion is extensive and involves not only the gene of interest, but adjacent genes as well. The p53 gene is a tumor

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suppressor gene, and mutations of this gene may represent the most common genetic abnormality discovered to date in tumors, being present in about 50% of human carcinomas (Hollstein et al., 1996). It plays a central role in the balance between gene transcription, cell proliferation, and apoptosis. DNA damage results in the induction of genes upstream of p53 (Oren, 1999), which then stimulates p53 induction and stability through posttranslational modifications. This in turn affects *p21*, *MDM2*, *GADD45*, *BAX*, and other genes responsible for DNA repair, and delay of the cell cycle to allow additional time for DNA repair, or triggers cell death when DNA repair is not possible. The (p16) gene is located on chromosome 9p, and its protein plays a crucial role (along with the retinoblastoma gene product and the cyclins) in regulating the cell cycle. It is inactivated in many smoking-related cancers including non-small-cell lung, head and neck, and pancreatic cancer and squamous carcinomas of the esophagus (Geradts et al., 1999; Liu et al., 1995; Lydiatt et al., 1995), and occasionally bladder tumors (Orlow et al., 1999). Inactivation occurs by many mechanisms including hemizygous or homozygous deletions, point mutations, or aberrant methylation of the promoter region. The latter is an example of tobacco smoke constituents affecting genetic function without causing a mutation (i.e., an epigenetic change; Belinsky et al., 1998). The FHIT gene is a putative tumor suppressor gene located on chromosome 3p14 (Sozzi et al., 1998a, b). Inactivation of the gene product has been described in many tumors including lung, head and neck, and esophagus.

It might be possible to consider mutations in different genes as "molecular fingerprints" of causation by tobacco smoke for an individual. This could be helpful in considering the effects of different types of tobacco products and changes in tobacco constituents over time. It might also be possible to identify which tumors in an individual were caused by tobacco versus some other agent. However, no such "fingerprints" have been identified for tobacco smoking, although some types of lesions occur more frequently (Kondo et al., 1996). This may be due to the numerous carcinogens in tobacco, which cause many types of DNA damage. New microarray technologies will provide sequence data for many genes, RNA expression profiles or protein expression profiles that—with sufficient bioinformatic support—a characteristic profile could enable tobacco effects to be discerned.

Tobacco smoke exposes the entire respiratory and upper gastrointestinal mucosa to carcinogens, whereas smokeless tobacco exposes only the oral cavity and the gastrointestinal mucosa. Thus, these entire "fields" are at risk for the development of preneoplastic and neoplastic lesions (Slaughter et al., 1953; Strong et al., 1984). A field effect for cancer has been demonstrated on a molecular basis, where different molecular

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lesions were found in persons with multiple synchronous lesions (Sozzi et al., 1995).

TOBACCO MUTAGENS AND CARCINOGENS

The use of tobacco products, as they are intended to be used, results in exposure to more than 100 mutagens and carcinogens (Hoffman and Hoffman,1997; Zaridze et al., 1991) that have different potencies and effects. Mainstream smoke consists of particulate and vapor phases. Although carcinogens have been identified in both the vapor and the particulate phase, the latter shows more overall carcinogenic activity. The particulate phase contains more than 3,500 compounds, of which at least 55 have been identified as possible human carcinogens (Hoffman and Hoffman, 1997). The vapor phase contains more than 500 compounds (Hoffman and Hoffman, 1997). A list of some of these constituents is provided in Table 12-1, which is not all inclusive.

Tobacco mutagens and carcinogens have different potencies and target organ specificities. A recent critical review summarizing data for tobacco constituents proposed that tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs) are classes of compounds that most affect human cancer risk (Hecht, 1999b). Although this may be true, it is currently difficult to prove in human cancer, especially because these exposures are mixed with others. Other compounds also are likely to be important. The existing data are not sufficient to determine whether some compounds are clearly more carcinogenic in humans than others when delivered through the use of tobacco products, and whether there is a synergistic effect of coexposure. Therefore, the assessment of a harm reduction strategy for cancer must consider these constituents individually and as part of a complex mixture since the former can provide mechanistic information but only the latter can be used to fully understand the effect of PREPs on carcinogenesis.

Tobacco and tobacco products have changed over time, with resultant differences in predicted exposure using the Federal Trade Commission (FTC) method for the measurement of "tar" and "nicotine" (Hoffman and Hoffman, 1997). It is known that the FTC method for estimating tar exposure underestimates actual human exposure because it does not sufficiently mimic human smoking behavior (Hoffman and Hoffman, 1997). Specifically, using a protocol that mimics actual human smoking behavior shows that the FTC method substantially underestimates the exposure to TSNAs and benzo[a]pyrene [BaP] (Djordjevic et al., 2000). While smokers of low-nicotine cigarettes have somewhat lower delivered levels of BaP and TSNAs, the daily amount of tar delivered is similar (Djordjevic et

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TABLE 12-1 List of Selected Tobacco Mutagens and Carcinogens[a]

Constituent Class	Phase	IARC Evaluation	Examples
N-Nitrosamines	Particulate	Sufficient in animals	Tobacco-specific nitrosamines (NNK, NNN), dimethylnitrosamine, diethylnitrosamine
Polycyclic aromatic hydrocarbons	Particulate	Probable in humans	Benzo[a]pyrene, benzo[a]anthracene, benzo[b]fluoranthene, 5-methylchrysene
Arylamines	Particulate	Sufficient in humans	4-Aminobiphenyl, 2-toluidine, 2-naphthylamine
Heterocyclic amines	Particulate	Probable in humans	2-Amino-3-methylimidazo[4,5-[b]quinolone (IQ)
Organic solvents	Vapor	Sufficient in humans	Benzene, methanol, toluene, styrene
Aldehydes	Vapor	Limited in humans	Acetaldehyde, formaldehyde
Volatile organic compounds	Vapor	Probable	1,3-Butadiene, isoprene
Inorganic compounds	Particulate	Sufficient in humans	Arsenic, nickel, chromium, polonium-210

[a]This list is intended to provide a conceptual overview of the complexity of tobacco product exposures. It is not all inclusive, but is included to allow the reader to understand the number of considerations that must be made in assessing PREPs.

[b]International Agency for Research on Cancer: The classifications here refer to evaluations of the compound from any exposure, not just tobacco. Not all chemicals within the class are considered carcinogenic in humans. There is no consideration in this table of delivered dose or route of exposure.

NOTE: NNK=nitrosonornicotine ketone; NNN=N-nitrosonornicotine.

al., 2000). Therefore, in this report so-called tar yields do not imply actual tar exposure.

Although it is important to understand the differences in risks by chemical class, in order to assess PREPs, it must be realized that affecting the exposure to one compound or class might not account for similar proportional decreases of other compounds, and we do not know if removing one compound or even a whole class will reduce unless other classes of compounds are also decreased. Further, the study of mixtures

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(i.e., the real-life scenario of simultaneous exposure to many chemicals and classes) has received insufficient attention, and exposure to tobacco constituents as complex mixtures would provide the most compelling evidence for prediction of a successful PREP. Cigarette smoke condensate is mutagenic in bacterial and human cell lines (Matsukura et al., 1991) and can cause a malignant transformation in human bronchial epithelial cells (Klein-Szanto et al., 1992). Whole smoke, which is also mutagenic, can be used as well (Bombick et al., 1997). Both the vapor phase of environmental tobacco smoke (ETS) and unfiltered ETS exposure causes lung cancer in laboratory animals (Witschi et al., 1997a). There is some evidence to suggest that the mutational spectra of a complex mixture reflects mostly that of the dominant chemicals in the mixture (DeMarini, 1998), although experimental animal studies of DNA adducts from benzo[a]pyrene and coal tars indicate that total adduct levels are not related to BaP content alone (Goldstein et al., 1998), suggesting that studying single chemicals is not sufficient to represent the effects of complex mixtures. Further, various polycyclic aromatic hydrocarbons cause different hotspots in p53 (Smith et al., 2000), and different dose levels of complex mixtures might have additive or synergistic effects (Hecht et al., 1999; Poirier and Beland, 1992). Thus, more studies are needed to determine the best approaches to assess the mutagenicity and carcinogenicity of complex mixtures (Guengerich, 2000).

Several constituents of tobacco are considered likely agents of human carcinogenesis. Some of these are reviewed here to highlight the considerations needed in considering harm reduction strategies.

People are commonly exposed to PAHs through tobacco products, diet, occupation, and consumption of fossil fuels (i.e., burning coal or wood). These compounds are formed from the incomplete combustion of tobacco leaves, and many types of PAHs are present in tobacco smoke as a complex mixture. Parent PAHs can be detected in human lung tissue (Lodovici et al., 1998; Seto et al., 1993). It is estimated that smokers are exposed to 2-5μg of PAHs per day per pack of cigarettes, and our diet provides PAHs of 3μg per day (Hoffman and Hoffman, 1997; Lioy and Greenberg, 1990; Waldman et al., 1991). As a class, they are mutagenic and carcinogenic in organs of laboratory animals (including the lung) and humans (Hoffman and Hoffman, 1997; IARC, 1986; Van Delft et al., 1998). PAHs have different potencies, which are thought to be related to metabolic activation of a compound that leads to either a bay region diol-epoxide (potent), or a fjord region diol-epoxide (nonpotent) compound. PAHs are metabolically activated in humans through *CYP1A1*, *CYP1B1*, and *CYP3A4* (Kim et al., 1998; Shimada et al., 1996a). They are conjugated for excretion by glutathione *S*-transferases, sulfuronyl transferases, and glucuronyl transferases (Robertson et al., 1988), and the lack of such

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activity increases mutagenic potential (Romert et al., 1989). In laboratory animals treated with benzo[a]pyrene, the half-life of DNA adducts following a single dose is 15 days in the liver, 17 days in peripheral blood lymphocytes, and 22 days in lung (Ross et al., 1990). In humans, there is more than a hundredfold variation in the resultant capacity for DNA-adduct formation (Harris et al., 1974) due to variation in induction and activity for these activating and detoxifying enzymes. PAH-related DNA adducts have been demonstrated in human lung (Kato et al., 1995), while the presence of hemoglobin and albumin adducts also shows that these compounds circulate in human blood (Day et al., 1990; Kriek et al., 1998). In vitro studies indicate that PAHs can cause the same types of p53 mutations observed in human tumors (Denissenko et al., 1996; Smith et al., 2000). DNA damage from PAHs is repaired by both excision and recombination pathways, and while there is clearly interindividual variation in the DNA repair capacity of these pathways, such variation have received little attention for PAHs (Xu et al., 1998).

Tobacco products and smoke contain *N*-nitrosamines (Brunneman et al., 1996; Fischer et al., 1989b, 1990; Tricker et al., 1991), which are among the most potent rodent carcinogens (Lewis et al., 1997). Some of the *N*-nitrosamines in tobacco smoke are specific for tobacco, whereas others are the same types formed from dietary exposures. *N*-nitrosamines cause cancer in more than 40 animal species, and there is target organ specificity, including for TSNAs and lung tumors (Lewis et al., 1997; Rivenson et al., 1989), where there is a biphasic response in experimental animals indicating both a high affinity response at lower exposure levels and a saturation effect at higher levels (Belinsky et al., 1990; Pledger et al., 1977). Experimental animal studies also show that higher doses of exposure cause tumors in less time, suggesting that intensity and duration are equally important (La and Swenberg, 1996; Lewis et al., 1997). Mutations in K-ras have been found in lung tumors of experimentally exposed animals (Chen et al., 1993). TSNAs can transform human bronchial epithelial cells (Klein-Szanto et al., 1992). The same type of adducts that occur from TSNAs in experimental animals also have been detected in humans, including in lung tissue (Hecht et al., 1994). Different types of tobacco have different TSNA yields (Brunnemann et al., 1996). In humans, metabolites of TSNAs are found in urine (Carmella et al., 1993, 1995; Hecht et al., 1994), and adducts are detected in blood, so TSNAs circulate through the body, including in persons who are passively exposed (Atawodi et al., 1998; Hecht et al., 1993; Parsons et al., 1998). The elimination half-life of several TSNAs through the urine is estimated to be 40-45 days (Hecht et al., 1999). There is no mutational specificity for *N*-nitrosamines in several genes studied to date, although there is a propensity for G→A (guanine to adenine) transitions in experimental models (Chen et al., 1993; Ronai et al., 1993;

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Tiano et al., 1994). *N*-nitrosamines undergo metabolic activation by human cytochrome P-450s located in the lung, buccal mucosa, and other tissues (e.g., CYP2E1 and CYP2A6; Hecht, 1998; Patten et al., 1997; Smith et al., 1995, 1992). Ethanol induces CYP2E1 which may have implications for oropharyngeal and esophageal cancer (Garro et al., 1981; Ma et al. 1991). Cigarette smoking and exposure to other tobacco products increase endogenous nitrosation, so that there are additional exposures to nitroso compounds (Nair et al., 1996). The metabolic activation of TSNAs and other tobacco *N*-nitrosamines leads to the formation of DNA adducts in target tissues or is associated with specific cancers (Chang et al., 1990; La and Swenberg, 1996; Liu et al., 1993; Nesnow et al., 1994; Tiano et al., 1993; Yang et al., 1990; Zhang et al., 1991). TSNAs form three different classes of DNA adducts (Hecht, 1999a). The first involves methylation of different nucleotides, which also are formed by other *N*-nitrosamines, and some of these adducts are more promutagenic than others (O^6-methylguanine more readily causes mutations than N^7-methylguanine), and there are different repair enzymes for each. The O^6-methylguanine is repaired by O^6-alkyl-alkyltransferase. The activity of this enzyme varies among people and can be reduced in smokers, because once methylated it becomes inactive (Liu et al., 1997). Other classes of adducts formed by TSNAs, which are bulky (Atawodi et al., 1998; Hecht, 1999a), are probably repaired by nucleotide excision and recombination repair, similar to PAHs. The activity of these repair pathways also varies widely among individuals. Different tobacco products contain widely differing amounts of TSNAs (Fischer et al., 1989b). Snuff use can lead to higher levels of TSNAs than smoking (Hecht et al., 1994), and changing smoking patterns can result in higher delivery of TSNAs (Fischer et al. 1989a). For example, Swedish snuff products contain substantially fewer TSNAs than snuff sold in the United States. Lower-tar and nicotine cigarettes result in greater exposure to TSNAs than high-tar and nicotine cigarettes (Brunnemann et al., 1996; Hoffman and Hoffman, 1997). The third type of DNA adducts formed from TSNAs is related to oxidative damage (Hecht, 1999a).

Aromatic amines are another class of compounds present in tobacco smoke; these consist of aryl amines and heterocyclic amines. The latter are not reviewed here. There are substantial data to implicate aryl amines and their metabolism in human carcinogenesis (Vineis and Pirastu, 1997), especially bladder cancer in occupationally exposed cohorts (e.g., dye workers; Cartwright et al., 1982). In experimental animals, 4-aminobiphenyl (4-ABP) adduct levels increase in both liver and bladder tissues, but the rise in the bladder as a target organ is substantial and correlated with tumor incidence (Poirier and Beland, 1992). Saturation pathways might occur in female mice at lower doses than male mice, and saturation effects at higher levels of smoking have been reported in

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humans (Dallinga et al., 1998). Aromatic amines are thought to contribute to bladder carcinogenesis in smokers too, so this is an example of a tobacco carcinogen that affects an organ distant to the route of entry. Aromatic amines are initially activated by CYP1A2, which ultimately leads to the formation of nitreunium ion that then forms a DNA adduct. *N-Acetyltransferases* (NAT1 and NAT2) play an activating or detoxifying role, depending on the arylamine (Windmill et al., 1997). These compounds are metabolically activated in the liver and transported to the kidney. Upon excretion in the urine, the bladder mucosa can further activate and detoxify the conjugates. Both NAT1 and NAT2 are present in the bladder mucosa (Badawi et al., 1995; Kloth et al., 1994). Aromatic amine biomarker studies have generally focused on hemoglobin rather than DNA adducts. Levels are higher in smokers than nonsmokers, and different types of tobacco can lead to higher adduct levels (Bryant et al., 1988; Carmella et al., 1990; Dallinga et al., 1998). Different types of adducts also have been detected in urinary bladder (Badawi et al., 1996; Bryant et al., 1988; Carmella et al., 1990; Kadlubar, 1994).

Both the gaseous and the particulate phases of cigarette smoke contain free radicals (e.g., nitric oxides in the gaseous phase) that induce oxidative damage (Hoffman and Hoffman, 1997; Pryor et al., 1998). Many components of cigarette smoke can individually cause oxidative damage (Leanderson and Tagesson, 1990). Nitric oxides may act synergistically with the particulate phase to induce DNA breaks. Although free radicals cause DNA damage in experimental systems and are suspected to be involved in carcinogenesis (Floyd, 1990), a direct relationship to human carcinogenesis has been suspected but not proven (Loft and Poulsen, 1996; Marnett, 2000; Poulsen et al., 1998). It is difficult to measure free radicals and oxidative damage in humans from tobacco smoke or any other source (endogenous or exogenous), because it is impossible to distinguish free radical sources and biomarker methods can artifactually induce oxidative damage (Loft and Poulsen, 1996; Marnett, 2000). Among the most common methods is to measure 8-oxodeoxyguanosine, one of the most abundant products of oxidative damage and can be seen in human lung (Inoue et al., 1998), using high-performance liquid chromatography (HPLC) and electrochemical detection (Helbock et al., 1998; Loft and Poulsen, 1996; Park et al., 1989). Levels are generally higher in leucocytes and in the urine of smokers compared to nonsmokers (Asami et al., 1996; Loft et al., 1992). In a comparison of 100 smokers in a smoking cessation program and 82 smokers who were not quitting, the cessation group lowered urinary excretion levels of 8-oxodeoxyguanosine by 21%, while there was no effect in smokers (Prieme et al., 1998). While levels of 8-oxoguanine are elevated in smokers, so is the capacity to repair these lesions (Asami et al., 1996; Hall, 1993). Separately, free F2-isoprostanes, a marker of lipid

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peroxidation, were measured in the plasma of ten smokers and ten nonsmokers. Levels were higher in smokers than in nonsmokers and decreased with abstinence (Morrow et al., 1995).

Other constituents of tobacco smoke can also play a role in human carcinogenesis. For example, although 1,3-butadiene is present in cigarette smoke at "low" levels, it is considered a potent carcinogen in experimental animal studies that specifically affects the lung (Huff et al., 1985; Melnick and Huff, 1992; Owen et al., 1987). Heterocyclic amines, are emerging as an important human carcinogen, which are formed from the pyrolysis of creatines (Knize et al., 1999). These compounds are found in smoke, and the removal of proteins from tobacco before making cigarette smoke condensate substantially reduces mutagenicity (Clapp et al., 1999).

Although it is conceivable that some harm reduction strategies might decrease exposures to PAHs, TSNAs, or aromatic amines, singly or combined, the assessment of real benefit must consider the effects of altering these carcinogens in the context of the complex exposures resulting from tobacco products (Krewski and Thomas, 1992). Thus, it is critical that PREP assessment include consideration of complex mixtures. Assays are available that can do this, as reviewed in Chapter 10. Separately, decreasing one or more tobacco constituents might not affect cancer risk if other compounds such as 1,3-butadiene, benzene, aldehydes, and acrolein are not affected, or the risks from additives or fibers might be comparatively more important. There are insufficient data to currently conclude that overall cancer rates would decrease proportionally to the reduction of a carcinogen, because although one type of cancer might decrease, others might increase. Alternatively, the substitution of one lung carcinogen for another might not allow for a sufficient benefit from harm reduction strategies.

SCIENTIFIC METHODS FOR ASSESSING HARM REDUCTION STRATEGIES

The actual exposure to tobacco mutagens is dependent on the type of cigarette and how it is smoked. Over time, manufactured cigarettes and consumer choices have changed substantially. Prior to the 1950s, most manufactured cigarettes did not have filters, but more than half of all cigarettes had filters by the beginning of the 1960s (Cummings, 1984). Although filtered cigarettes were available earlier, about the time of the first Surgeon General's report in 1964, many people began switching to filtered cigarettes (Hoffman and Hoffman, 1997; Stellman and Garfinkel, 1986). Today, more than 98% of cigarettes have filters (NCI, 1996). The so-called tar content also has declined since the 1950s, from about 37 mg to less than 15 mg. (Cummings, 1984; Hoffman and Hoffman, 1997). Most

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studies published through the 1980s included subjects who probably had smoked nonfiltered cigarettes in their lifetime, and this could make smoking studies from that time more difficult to interpret.

The introduction of low-tar and nicotine cigarettes was conceptualized to make cigarettes "safer," but currently available scientific data suggest that potential benefits may not have been realized for some or most persons (see discussion of lung cancer). In actuality, many persons who smoke low-tar and nicotine cigarettes compensate for lower nicotine delivery by smoking more (Benowitz et al., 1983, 1986b, 1998; Ebert et al., 1983; Gritz et al., 1983). Levels of TSNAs and benzo[a]pyrene in tobacco smoke can be similar for low- and high-tar cigarettes when people oversmoke their cigarettes (Djordjevic et al., 1995, 1997). It is unknown, however, what happens to carcinogenic biologically effective doses. While switching results in a higher peak nicotine level per cigarette, there is a lesser proportional reduction in urinary mutagenicity (Benowitz et al., 1986a, b; Sorsa et al., 1984). In one study, sister chromatid exchange levels, which have not been validated as a surrogate marker for the harm, do not change when persons switch from high- to low-tar cigarettes (Djordjevic et al., 1997), but the relation of this marker to short-term and long-term exposures, half-lives, and other factors that might confound such studies is not known.

Smokers have learned to block filter ventilation holes, with concomitant increase in tar exposure of more than tenfold compared to the standard FTC method (Kozlowski et al., 1982). Blocking can occur with the fingers, lips, or tape, and can be intentional or unintentional.

To consider the value of a harm reduction strategy, one must consider the effects on cancer risk of the targeted reduction in exposure and then place these risks in the context of reducing exposures by any means. This process can be used for individual constituents of exposure or in the aggregate. Through this process, several predictive models should be developed that are based on adequate scientific data, not speculation. The methods listed below are used if the proposed reduction in exposure is for carcinogens. Importantly, an assessment of a PREP can only be made in the context of risk due to conventional tobacco products. Following a risk assessment model typically used by regulatory agencies, the following three steps are proposed:

1. Cancer linkage assessment (linking exposure to cancer)

Causality assessment. Does the compound targeted for reduced exposure cause cancer, and what do we know about the biological mechanisms for that compound? The criteria proposed in the first Surgeon General's report on smoking and health (U.S. Public Health Service, 1964),

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and later extended by Sir Austin Bradford Hill, or their equivalents, proposed by others, should be applied, using experimental data and human experience.

Dose-response assessment. What is the dose-response relationship between targeted carcinogens and cancer risk? Where is the risk to persons from environmental tobacco smoke within the shape of the dose-response curve? What is the optimal way to consider dose?

Causality in context assessment. How do the risks of harmful effects from the targeted compounds compare with other carcinogens in tobacco smoke? Are there data to indicate how these compounds can affect risks for former smokers or persons with ETS.

Individual susceptibility and attributable risk assessment. Are there individual susceptibilities (e.g., age, gender, race, heritable traits, prior tobacco exposure) that can modify the carcinogenic risks of these targeted compounds, and what is the frequency of these traits in different smoker populations?

2. Cancer reduction assessment (decreasing exposure to reduce cancer risk from a higher base line level)

Reduction in carcinogenicity assessment. What is the experimental evidence that reducing exposure will reverse or halt carcinogenic processes that have already begun?

Decreasing dose-response assessment. What happens to cancer risk if doses are reduced, and how much does exposure have to be reduced to result in a meaningful benefit? A model should be developed that predicts the cancer risk or rate over time for the consistent use of the harm reduction method. This model will include several scenarios in which different categories of smoking (current smoking, lifetime smoking, and age at initiation) at the time a PREP is used are studied and, for example, assume a 10, 25, 50, 75, and 90% reduction in exposure. (Response is measured by a biologically effective dose, a biomarker of potential harm, or a disease outcome, not what is measured in tobacco smoke or delivered to the oral and respiratory mucosa.)

Adverse effects of harm reduction strategies. A model should be developed that predicts the numbers of individuals who begin smoking, do not quit, or resume smoking after quitting due to the availability and knowledge of a PREP, or belief that such products are safe. For new products that contain tobacco or tobacco constituents, a dose-response model should be developed for cancer risk that indicates risk for use by "never smokers" who initiate regular use with the PREP.

Harm reduction method in context assessment. An assessment is needed of the predicted reduction in risk versus the remaining risk of other to-

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bacco constituents and consideration of new or altered tobacco constituents.

Individual susceptibility and population-attributable risk for successful harm reduction. Are there individual susceptibilities (e.g., age, gender, race, heritable traits, previous tobacco exposure) that can modify the success of a PREP (increased, decreased, or no change in risk), and what is the frequency of these traits in different smoker populations?

3. Integrated harm reduction method assessment

Final considerations. Consideration of the above models should provide a summary statement and prediction of the numbers of cancers that are avoided due to the method. If the reduction in exposure is proposed only for carcinogens, possible effects on other tobacco-related illnesses and total mortality must be considered.

The causality assessments (linkage and reduction) can be provided in the format of Sir Austin Bradford Hill (Hill, 1965), which was originally proposed in the first Surgeon General's report (U.S. PHS, 1964; Table 12-2). In the evaluation of a PREP, it must be decided which disease outcome or outcomes are to be targeted. The role for all cancers could be evaluated with this model, or perhaps only lung cancer, because the lung is the most sensitive organ to tobacco smoking. For smokeless tobacco products, oral

TABLE 12-2 Causality Assessment[a]

Criteria	Comment
Strength of association	What is magnitude of risk?
Consistency	Are there repeated observations by multiple investigators in different populations?
Specificity	Is the effect specific or are there other known causes?
Temporality	Does exposure precede effect?
Biological gradient	Is there a dose-response relation?
Biological plausibility	Is the effect predictable?
Coherence	Is the effect consistent with other scientific data?
Analogy	Do similar agents act similarly?

[a]These criteria should serve as guidelines for assessment of PREPs. They rely on human studies (and are applicable to biomarker studies) and use experimental data to provide supportive evidence. The criteria were originally published in the first Surgeon General's report and later expanded by Sir Bradford Austin-Hill.

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cancers can be used. These targeted outcomes might change because new PREPs may increase risk in non-lung or non-oral cavity cancers, or though exposures to some carcinogens decrease, the risk from other tobacco product constituents (i.e., additives, fibers) might increase.

Various scientific methods are used to assess carcinogenicity and carcinogenic risk. These appear in Table 12-3, along with their strengths and limitations. Most of these methods, however, have limited use currently for harm reduction evaluations. The assessment of carcinogenicity in the laboratory is focused on identifying potential human carcinogens, and fewer data are available for effects at different doses in ranges to which humans are exposed. Also, these studies are designed to identify risks using continuous exposures, and there are few studies that consider intermittent exposures or exposures that begin at high dose and then change

TABLE 12-3 Scientific Methods for Carcinogenicity Testing

Method	Strengths	Limitations
In vitro cell culture models	Rapid, inexpensive. Can be used to study mechanisms in human cells. Can be used to prioritize other studies	Quantitative extrapolation to human risk cannot be done, so relevance to human experience is questionable
Laboratory animal models	Provides *in vivo* experience. Dosing protocols can be modified to assess changes in PREPs. Can be used to prioritize human studies. Can be used to develop and validate biomarkers. Transgenic mice available	Quantitative extrapolation to human risk cannot be done and so the relevance to human experience is questionable. Expensive
Human experimental models	Can provide data about short-term changes in exposure and resultant effects on biomarkers. Can assess complex mixture	Best used to assess effects on exposure rather than outcome (i.e., cancer). Expensive
Epidemiology	Provides direct experience and assesses tobacco use in the context of individual susceptibilities and complex exposures. Case-control studies provide rapid data. Prospective studies provide best evidence	Use of cancer end point means long latency periods and adverse effects on many people. Expensive

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to low dose. These types of studies are likely more relevant to predicting the effects of PREPs.

The use of in vitro cell culture models and DNA-binding studies that focus on mutagenesis is attractive because they can provide toxicity data rapidly. Many models are available and have helped elucidate various mechanisms of carcinogenesis (Balmain and Harris, 2000; Taningher et al., 1990). Combinations of assays are traditionally used to better identify genotoxic compounds and to assess the genotoxic potential of different cigarettes (Bombick et al., 1997). Although in vitro models that provide positive results for genotoxic damage best predict carcinogenesis in experimental animal studies qualitatively or semiquantitatively (Taningher et al., 1990), mutagenicity in a cell culture is difficult to extrapolate to the in vivo models, whether animal or human (Rosenkranz and Klopman, 1993). Also, a negative result in cell culture systems is less reliable (Thilly, 1985; Zeiger, 1987). Mutations found in the *Salmonella* assay predicted carcinogenicity in laboratory animals with an overall accuracy of 59.5% (Lee et al., 1996). However, simple concordance analysis of predicitivity (yes or no) may not be as useful as considering predictivity in relation to mechanistic pathways (Butterworth, 1990). Some limitations for dosing in cell culture studies are related to the balance between mutation and cell survival (Thilly, 1985). The limitations for extrapolation to animal studies are described below. Thus, in vitro models might be useful for suggesting which tobacco constituents should receive the highest priority in evaluating PREPs, but they cannot be used to quantitatively support such a claim.

The use of laboratory animal models can provide an estimate of the effects of PREPs. Typically, studies used for risk assessment have followed protocols established by the National Toxicology Program to prioritize compounds for study as potential human carcinogens (Boorman et al., 1994; Fung et al., 1995; Goldstein, 1994). However, these studies use maximally tolerated doses (MTDs) over the animal's lifetime. Definition of the MTD is based on a subchronic, 90-day study, in which the highest dose that does not affect overt toxicity or growth is chosen. A consideration of the various limitations of MTDs for extrapolation to low-level exposures would lead to the conclusion that risk assessments based on MTD tumor incidences can overestimate human risk (Portier et al., 1994). In trying to understand the prediction of risk based on the MTD, there is a correlation for a dose that induces tumors at 50% of the MTD (Krewski et al., 1993) and at 50-75% of the MTD (Haseman and Lockhart, 1994), but it is unclear whether this information validates the use of the MTD or suggests that even 50% dose levels still cause significant physiological perturbations. Thus, the extrapolation of animal studies to humans remains questionable for harm reduction evaluation under these experimental designs. The use of animal studies might be rational, however, if

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the doses approximate human levels of exposure and if the experimental animal model does not possess a sufficiently different physiological response to carcinogen exposure compared to humans. Transgenic mice are now available with human genes that may screen potentially carcinogenic agents more rapidly than the two-year bioassay (Tennant et al., 1995), but multiple dosing protocols are needed (Schmezer et al., 1998). However, their use for harm reduction has not been considered previously, and doses affecting toxicity will be different than those for other animal models.

The use of experimental animal studies to predict cancer risk is more qualitative than quantitative for a number of reasons usually related to physiological differences and expanded protocols (Int. Panel, 1996; Swenberg et al., 1987). Mice and humans have many similar genetic alterations, but there are some important differences such as telomerase activity. Target organ specificity is very different under typical experimental conditions (Benigni and Pino, 1998). There are large quantitative differences in cancer risks among any organ in experimental animals. For a variety of tissue sites, including lung, liver, breast, and skin, pairs of inbred mice differ by a hundredfold in risk for tumor development. Detailed analyses of these differences using back-cross, recombinant inbred, and recombinant congenic breeding protocols have shown specific determinants for initiation, promotion, premalignant progression, and metastatic stages. There are even larger quantitative differences in cancer risk by organ among experimental animals. In most cases, susceptibility or resistance is a property of the target tissue, not of the host, for genotoxic substances such as *N*-nitrosamines. A direct relationship between in vitro experimental studies (i.e., metabolic activation of chemicals by cytochrome P-450s), in vitro mutagenicity tests, experimental animal studies, and human epidemiology has not been proven. Although there tends to be concordance among experimental studies, this is not 100% true, and extrapolation to humans is far from concordant. For the prediction of carcinogenicity in humans, the sensitivity of experimental studies is high and the specificity is very low. Some studies suggest that consideration of multiple assays yields greater productivity (Tennant and Ashby, 1991), but only if these compounds are mutagenic (Cunningham et al., 1998; Gold et al., 1993; Int. Panel, 1996; Tennant, 1993; Tennant and Ashby, 1991). Chemicals that are highly reactive toward DNA are commonly mutagenic; however, in experimental animals, 84% of tested carcinogens and 66% of noncarcinogens are mutagenic. Chemicals that are not predictive of reactivity and are nonmutagenic are carcinogenic less than 5% of the time and so animal testing of nongenotoxic chemicals is less reliable without understanding the mechanistic etiology or carcinogenesis (Cohen, 1995). Concordance among animal species for the same organ site is less

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than 50%, almost that predicted by chance (Haseman and Lockhart, 1993; Gold et al., 1992). Importantly, the actual concordance might vary between 20 and 100%, where the currently observed concordance among rats and mice might be estimated wrongly due to measurement error (Freedman et al., 1996; Haseman and Seilkop, 1992). Other studies indicate that concordance from rat to mouse occurred more commonly for chemicals that induce tumors at different sites, chemicals that induce tumors in both sexes, those that have a reduced latency, and those that increase the rates of rare tumors (Gray et al., 1995; Tennant and Spalding, 1996). Thus, if these same criteria are considered to apply in humans, it is less likely that there would be concordance for studies assessing changing levels of tobacco constituents as a way to assess PREPs. In general, the concordance between animal and human experience also is highly variable (Gold et al., 1992; Lutz, 1999; Monro, 1994), although carcinogens that are more potent in one species tend to be more potent in others, including humans. The major reason for differences in extrapolation from experimental systems to humans is that in vitro cell cultures and experimental animals from different species handle chemical exposures, DNA damage, and stress differently.

The inclusion of biomarkers in experimental animal studies with analogy to human exposures would be helpful (Guengerich, 2000). Carcinogen-DNA adduct levels correlate with tumor incidence for the target organ of these animals (Pledger et al., 1977; Ross et al., 1990). In some cases, target organ specificity is only approximate; for example, in benzo[a]pyrene-treated animals, levels are almost equal in liver and lung, but there is a higher cancer incidence in the former (Ross et al., 1990). Adducts of different classes have relatively similar potency (i.e., the number of adducts correlated with tumor induction is within one to two orders of magnitude; Otteneder and Lutz, 1999). One limitation is that adduct levels associated with tumor incidence can vary widely among species. The relative potency of carcinogens may be assessed by normalizing adduct levels for doses that induce 50% of tumors at the MTD and then considering the dose required to generate that number of adducts (Otteneder and Lutz, 1999). Adduct measurements also can estimate the occurrence of saturation pathways and where dose-response relationships become nonlinear for both adduct formation and tumor incidence. Different tumor-adduct profiles have been shown, depending on the carcinogens and the dose level (Pledger et al., 1977). Figure 12-1 summarizes different types of data for DNA-adduct levels and tumor formation (Poirier and Beland, 1992). It shows that in some cases, the relationship of adduct levels to tumor occurrence is linear, but in some cases, the slope of the effect can be different and saturation pathways occur. Thus, prediction of the effects of individual tobacco constituents in the context of other

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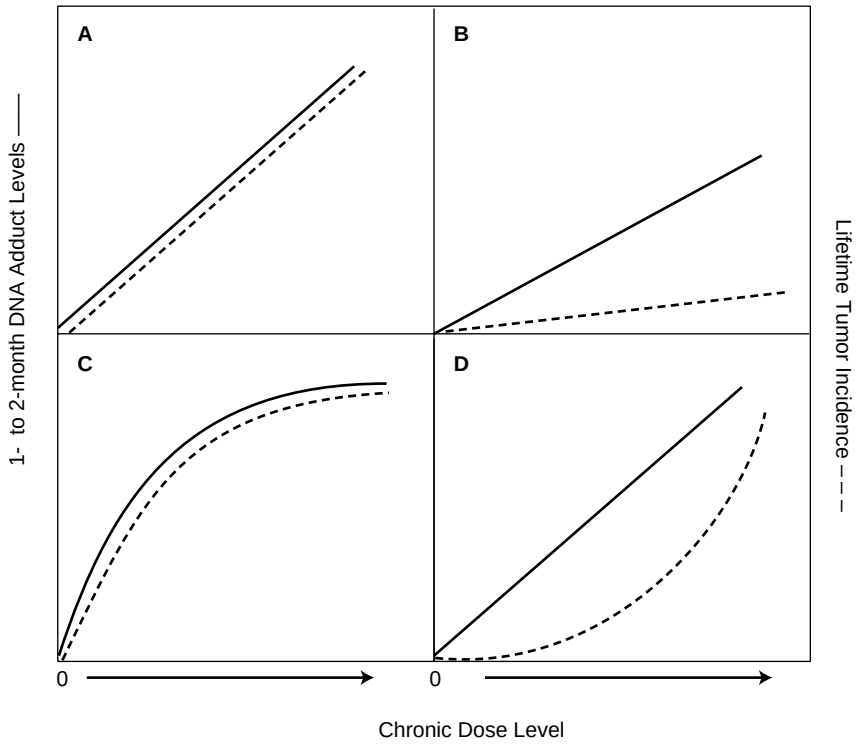


FIGURE 12-1 Lifetime tumor incidence.

NOTE: "Schematic diagrams for the different patterns of lifetime tumor incidence (—) and DNA adducts at 4-8 weeks of administration (-), observed as a function of chronic carcinogen dosing" (Poirier and Beland, 1992).
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constituents is complex. It is unknown whether the cancer effect of co-exposures is synergistic or additive, but at different dose levels, either can be observed (Poirier and Beland, 1992). Extrapolation of animal studies to humans also can be strengthened by demonstrating the same occurrence of carcinogen-DNA adducts in experimental animals and humans. Unfortunately, most studies have used only single-dose or short-term exposure (Otteneder and Lutz, 1999), so it is unknown how this relates to chronic exposure. Most of these studies also investigate levels in the experimental animal liver rather than in human target organs.

Different methods are available for assessing tobacco-related cancer risk in humans. External exposure markers attempt to predict exposure

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without regard to interindividual differences in smoking behavior and cellular processes. Biomarker assays can assess internal exposure, the biologically effective dose, and potential harm. Examples of how biomarkers might be applied to the assessment of PREPs are provided in Table 12-4. Epidemiological studies of lung cancer as the outcome would provide the best evidence for the use of a PREP. However, these studies have many pitfalls (Table 12-5), and more importantly, the assessment of a particular product would be difficult because of the short duration of use and changes in these products as technology develops, which would make it difficult to assess the risk of any individual product among all the others. (See Chapter 11 for a detailed discussion of biomarkers.)

The biologically effective dose (Perera, 1987) is the amount of a tobacco smoke or tobacco toxin that measurably binds to, or alters, a macromolecule (e.g., protein or DNA) in a cell. The biologically effective dose represents the net effect of metabolic activation, decreased rate of detoxification, decreased repair capacity, loss of cell-cycle checkpoint control, and decreased rates of cell death. It should be noted that not all binding to, or alteration of, a macromolecule leads to an adverse health effect, and so often we are really measuring the dose to a target macromolecule that estimates a biologically effective dose.

For cancer, a common assessment of the biologically effective dose is the measurement of carcinogen-DNA adduct levels (Farmer and Shuker, 1999). These are formed when carcinogen metabolites are alkylated to nucleotides, creating a promutagenic lesion. There are strong laboratory animal data and some human studies that prove a relationship between tobacco smoke constituents, carcinogen-DNA adduct formation, and cancer (Farmer and Shuker, 1999; La and Swenberg, 1996). Laboratory animal studies have shown a cancer correlation with increased adducts in target organs (Ashurst et al., 1983; Nakayama et al., 1984; Pelkonen et al., 1980). In humans, tobacco smoking leads to increased adduct formation in target tissues such as the lung (Bartsch, 1991; Phillips, 1996; Phillips et al., 1988; Schoket et al., 1998; Wiencke et al., 1995) and in surrogate tissues such as the blood (Bartsch, 1991; Hou et al., 1999; Phillips, 1996; Tang et al., 1995a; Vineis et al., 1994; Wiencke et al., 1995). Evidence exists that carcinogen-DNA adducts levels in target and nontarget organs are modulated by interindividual differences (Badawi et al., 1995; Bartsch, 1991; Grinberg-Funes et al., 1994; Kato et al., 1995; Pastorelli et al., 1998; Rojas et al., 1998; Ryberg et al., 1997; Stern et al., 1993;).

In humans, only a few studies have investigated a link between carcinogen-DNA adducts and cancer risk. All data come from case-control studies of the lung and bladder, and all show a positive relationship (Dunn et al., 1991; Peluso et al., 1998; Tang et al., 1995a; Van Schooten et al., 1990). However, since no published prospective studies shows a rela-

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TABLE 12-4 Examples of Variables Affecting the Success or Failure of PREPs

Variable	Questions
Effect on metabolic enzymes	1. Does a change in one or more tobacco constituent affect enzymatic induction or activity? 2. Does a change in enzymatic induction or activity result in a change in resultant DNA damage by the agent and, if so, by how much? 3. Does a change in enzymatic induction or activity result in a change in resultant DNA damage by other agents that are substrates in the same metabolic pathway and, if so, by how much? 4. Will people be affected differently because of interindividual differences in enzymatic induction or activity, and if so, what is the proportion of persons affected in a population (race, gender, age, etc.)? 5. Does a change in one or more tobacco constituents affect smoking behavior (e.g., absorption of nicotine, irritation, mucosal damage)?
Effect on DNA repair, cell-cycle control, and programmed cell death	1. Does a change in one or more tobacco constituents affect the induction or activity of DNA repair enzymes? 2. Does lowering exposure to one or more tobacco constituents result in less DNA damage from these constituents but also result in less time for cell-cycle arrest or less cell death, so that other carcinogens can cause more DNA damage or cell proliferation is enhanced? 3. Will individuals be affected differently because of interindividual differences in DNA repair, cell-cycle control, or programmed cell death, and if so, what is the proportion of persons affected in a population (race, gender, age, etc.)?
Effect on mutational spectra of gatekeeper and caretaker genes or tumor suppressor genes and oncogenes	1. Does a change in exposure to tobacco smoke carcinogens result in a change in the mutational spectra of one or several genes or in different RNA and protein expression profiles? 2. Do different levels of exposure result in different mutational spectra or RNA and protein expression profiles? 3. Does the mutational spectra or expression profile differ in persons who have changed their exposures compared to those who have not? 4. Does a tobacco constituent cause DNA damage through the formation of DNA adducts, free-radical damage, and/or gross chromosomal aberrations, (each of these mechanisms might affect the success of a harm reduction strategy and all might have to be considered)?

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TABLE 12-5 Competing Risk Factors, Confounders, and Sources of Error in Tobacco-Cancer Associations

Problem	Examples
Competing risk factors and confounders	Type of tobacco product
	Variability in tobacco constituents
	Duration of smoking
	Dose estimates: daily vs. cumulative, packs per day, pack-years, etc.
	Depth of inhalation
	Smoking behavior following a change in brand
	Tumor histology
	Age-related factors: starting, quitting, age at diagnosis
	ETS (duration, intensity, dose)
	Occupational exposure to carcinogens
	Air pollution
	Dietary factors: carcinogens, preventive substances
	Genetic predisposition
	Social and cultural factors
	Gender, race, or ethnicity
	Education
Study design errors	Selection bias
	Recall bias
	Information bias (especially use of proxies in interviews)
	Poor choice of control subjects
	Inadequate matching, overmatching
	Lack of control for confounders
External factors	Publication bias

tionship of adducts to cancer, the case control studies must be interpreted cautiously because they may suffer from differential metabolism or DNA repair due to case status. A variety of assays are available to determine carcinogen-macromolecular adducts in human tissues (Farmer and Shuker, 1999; Hecht, 1999a; La and Swenberg, 1996; Lee et al., 1993; Wang et al., 2000). These are reviewed in Chapter 11, along with data indicating which markers are useful for assessment in target organs.

Biomarkers of potential harm can range from isolated early changes with or without effects on function to events that clearly lead to carcinogenesis and can be observed in cancer cells. Assessing PREPs through clinical and epidemiological studies would consider this full range of effects. These studies are better focused on the earliest events that have been linked to disease, so that the adversity of disease is not a consequence. One goal has been to develop a molecular fingerprint of genetic damage that reflects a particular exposure in persons without cancer,

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although this has not happened for tobacco carcinogens, and any measurable effects are nonspecific. Nonetheless, a reduction in the level of genetic damage would logically be required if a PREP were to be successful, although the amount of reduction needed to derive a benefit in terms of disease risk is unknown. Several types of assays are available. The main limitation today is that no assays have convincingly been shown to be sufficiently predictive of cancer risk, so they can not be used singly to predict harm reduction. Chromosomal damage can be measured using classical cytogenetic methods (Obe et al., 1982), micronuclei formation (including in bronchial mucosa; Lippman et al., 1990; Schmid, 1975; Xue et al., 1992), COMET (Poli et al., 1999; Speit and Hartmann, 1999), fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR) methods assessing loss of heterozygosity (using tandem repeats or comparative genomic hybridization), where the latter two methods can be used for morphologically appearing cells. Use of mutations in reporter genes, such as HPRT (Ammenheuser et al., 1997; Bailar, 1999; Duthie et al., 1995; Hou et al., 1999; Jones et al., 1993) or glycophorin A (GPA) have been used, but it is better to identify mutation rates in cancer susceptibility genes such as p53 (Brennan et al., 1995; Ciruzzi et al., 1998; Kure et al., 1996; Yang et al., 1990) or K-ras (Gealy et al., 1999; Mills et al., 1995; Scott et al., 1997; Slebos et al., 1991; Valkonen and Kuusi, 1998; Yakubovskaya et al., 1995).

Biomarkers of potential harm that reflect later stages of carcinogenesis include morphological markers of preneoplastic lesions (e.g., dysplasia), altered phenotypic expression of normal cellular function (e.g., overexpression of the proto-oncogene Erb-B2), and mutations in cancer-related genes such as the p53 tumor suppressor gene. It is possible to measure p53 mutation rates in normal tissues (Hussain and Harris, 1999) of persons without cancer and to measure mutations in sputum for persons with cancer (Sidransky, 1997b). Although these assays are available, current technology limits their use for large-scale epidemiological studies. It also has been found that measuring loss of heterozygosity (Mao et al., 1997) or hypermethylation of genes involved in neoplasia (Belinsky et al., 1998) might be useful for assessing the effects of tobacco smoke.

The study of p53 tumor suppressor genes in tumors might be helpful in determining which tumors were related to specific etiologies. It has been reported that there is a dose-response relationship between tobacco smoking and p53 mutations in general (Kondo et al., 1996) and for G→T (guanine-to-thymine) transversions in particular (Kure et al., 1996; Takagi et al., 1998). Women have more G→T transversions than men for similar levels of smoking, even though men have p53 mutations more commonly (Kondo et al., 1996; Kure et al., 1996). In vitro studies show that BaP and other PAHs cause the same types of lesions, but in different parts of p53

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(Smith et al., 2000). An interactive effect of alcohol drinking and cigarette use in oral cavity and lung cancers leads to different types of p53 mutations (Ahrendt, 2000; Brennan et al., 1995). Interestingly, given that the p53 mutational spectrum for lung cancer is similar worldwide (Hartmann et al., 1997), tobacco smoke is likely the major determinant of lung p53 mutations worldwide.

LUNG CANCER

In this country, there were about 171,000 newly diagnosed lung cancer cases in 1999; 92.6% of these were incurable (Landis et al., 1999). Lung cancer consists of four major histological types, namely squamous cell cancer (SCC), small-cell lung cancer (SCLC), adenocarcinoma (AD), and large-cell carcinoma (LCC; Travis et al., 1995). The first two types tend to arise from the large or medium-sized bronchi ("central tumors"), while the latter two tend to develop from the small bronchi, bronchioles, and alveoli ("peripheral tumors"). There has been a shift in the prevalence of histology types over time, in which AD has been increasing relative to SCC (Charloux et al., 1997; Thun et al., 1997; Travis et al., 1995). In Connecticut from 1959 through 1991, associations between cigarette smoking and death from AD versus SCC increased nearly seventeenfold in women and nearly tenfold in men, while smoking-related lung cancer risk increased from 4.6 to 19 in men and 1.5 to 8.1 in women (Thun et al., 1997). This is presumably due to the use of lower-nicotine cigarettes, increased exposures to TSNAs, and greater depths of inhalation.

Lung cancer is preceded by a series of histopathological changes. These changes have been identified for SCC and consist of both reactive changes (hyperplasia, metaplasia) and preneoplastic changes (dysplasia, carcinoma in situ [CIS]; Auerbach et al., 1961). These histologic changes occur far less frequently in never smokers than in cigarette smokers and increase in frequency with the amount of smoking, adjusted for age (Auerbach et al., 1979). Advanced histologic changes are rarely seen in nonsmokers, but occur in 2.6% of those who smoked 1 to 19 cigarettes a day, 13.2% of those who smoked 20 to 39 per day, and 22.5% of those who smoked 40 cigarettes or more a day. Advanced bronchial preneoplastic changes (moderate to severe dysplasia and CIS) do not regress on smoking cessation, persist for many years, and possibly persist for life. Compared to men, women have a lower prevalence of high-grade preinvasive lesions in the observed airways (14% vs. 31%; odds ratio [OR]=0.18; 95% confidence interval [CI]=0.04, 0.88; Lam et al., 1999). Bronchial preneoplastic lesions are difficult to identify by routine white-light bronchoscopy but may be visualized by fluorescence bronchoscopy (Lam et al., 1998). Preneoplastic lesions preceding SCLC and AD are not well defined. AD

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has been associated with the presence of peripheral lesions known as atypical adenomatous hyperplasia (Kerr et al., 1994), while SCLC may arise directly from histologically normal or reactive epithelium (Wistuba et al., 2000).

Extensive molecular changes already are present in the bronchi of smokers before any morphological changes can be discerned (Mao, 1996; Wistuba et al., 1997). Allelic losses at chromosome regions 3p and 9p are present in about 80% of smokers, but are rarely present in those who have never smoked. Approximately one-third of the bronchial epithelium of smokers with lung cancer has sustained molecular damage (Park et al., 1999). These changes are more frequent and extensive in SCLC, intermediate in SCC, and much less frequent in AD (Wistuba et al., 2000).

Allelotyping of human lung cancers indicates multiple sites of frequent allelic (>30%; Virmani et al., 1998) loss, which may represent the sites of recessive oncogenes. Loss of heterozygosity (LOH) on chromosomes 11 and 17 occurs more frequently with increased smoking (Mao et al., 1997; Schreiber et al., 1997). A molecular technique known as comparative genomic hybridization (CGH) permits identification of genomic sites of allelic loss as well as sites of amplification. CGH studies of human lung cancers and cell lines confirm allelotyping data and indicate that multiple sites of increased copy number are present in lung cancers, including c-MYC (Levin et al., 1995; Petersen et al., 1997).

Oncogene mutation frequency in lung cancers varies with the histological type. Ras gene mutations are present in about 30% of adenocarcinomas but are relatively rare in other lung cancers (Gealy et al., 1999; Slebos and Rodenhuis, 1992). It has been reported that ras mutations are present only in smoking-related cancers and that these mutations are associated with cigarette smoking (Reynolds et al., 1987; Slebos et al., 1991). Such mutations also can be observed in persons without lung cancer, suggesting that they may be an early marker of smoking-related damage (Lehman et al., 1996; Scott et al., 1997; Slebos et al., 1991; Valkonen and Kuusi, 1998; Yakubovskaya et al., 1995). Interestingly, the K-RAS mutations are G→T transversions, typical of PAH exposure (Gealy et al., 1999; Hutchison et al., 1997; Slebos et al., 1991). LOH affecting at least one locus of the FHIT gene was observed in 80% of lung cancers in smokers, but in only 22% of cancers in nonsmokers (Sozzi et al., 1998a). These findings suggest that FHIT is a candidate molecular target of carcinogens contained in tobacco smoke. Many other molecular changes are present in lung cancers, such as the ERB-B family and MYC (Fong et al., 1999; Hecht, 1999b; Kanetsky et al., 1998; Sekido et al., 1998), but because they have not been directly linked to smoking, they are not discussed here.

Overall allelic losses (Wistuba et al., 2000) and mutations of the p53 gene (Chiba et al., 1990; D'Amico et al., 1992) are more common in SCLC

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and SCC than in AD. For p53, a positive relationship exists between lifetime cigarette consumption and the frequency of mutations (Ahrendt et al., 2000), and of G→T transversions in particular (Kondo et al., 1996), and these lesions are more common than G→A transitions. Supporting the role of PAHs in p53 mutations, benzo[a]pyrene-diol epoxide and other PAHs bind to guanine at codons 157, 248, and 273 of the p53 gene (Denissenko et al., 1996; Smith et al., 2000), which are hotspots for the G→T transversions (Denissenko et al., 1997). Never smokers who develop lung cancer have a completely different, almost random grouping of p53 mutations (Ahrendt et al., 2000; Rom et al., 2000). Alcohol consumption might further increase the frequency of p53 mutations (Ahrendt et al., 2000).

The contribution of DNA repair pathways to lung carcinogenesis has had limited study. Increased frequencies of microsatellite alterations (single shifts of nucleotides), rather than microsatellite instability (multiple shifts of multiple nucleotides), are seen in 20-30% of lung cancers (Fong et al., 1999), suggesting defective DNA repair through a mechanism similar to that seen for colon cancer and defective mismatch repair. Separately, mutations in the mitochondrial base excision repair enzyme, *OGG1* have been seen (Chevillard et al., 1998). Also reported is O^6-alkyl-alkylguanine transferase mutations (et al., 1997), which might increase susceptibility to *N*-nitrosamines.

There are nonmutational effects of smoking in lung carcinogenesis. For example, telomerase expression is very frequent in lung cancer (Fong et al., 1999), which is increased in smokers compared to nonsmokers and former smokers, suggesting that this is reversible (Xinarianos et al., 1999). Expression of gastrin-releasing peptide is seen in lung cancer in response to tobacco smoking (Shriver et al., 2000), and might contribute to bronchial epithelial cell proliferation before lung cancer develops. Some data exist to implicate nicotine as the inducer of gastrin-releasing peptide (Shriver et al., 2000). Hypermethylation of promoter regions, such as that for p16, death-associated protein kinase, glutathione *S*-transferase P1, estrogen receptors and O^6-alkyl-alkylguanine transferase have frequently been observed in lung cancer (Fong et al., 1999), and smoking in particular has been associated with an increased frequency of hypermethylation of p16 (Belinsky et al., 1998). Reactive oxygen species, produced by tobacco smoke constituents, as well as through inflammatory responses, can affect many different protein kinases and transcription factors (Minamoto et al., 1999). How these effects influence carcinogenesis is currently unknown, but perturbations in the balance between oxidative stress and response clearly affect cell survival.

Lung cancer survival after surgical resection and for more advanced stages might be affected by smoking history (Hendriks et al., 1996; Hinds

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et al., 1982; Sekine et al., 1999; Xavier, 1996), especially in the earlier years after surgical resection (Sobue et al., 1991). While women who smoke might be diagnosed at later stages because their symptoms have been ignored, the early-stage data supports a relationship between smoking history and survival of lung cancer patients. Smoking also increases the risk of lung metastases in breast cancer patients (Scanlon et al., 1995) and of second primary cancers after the diagnosis of lung cancer (Levi et al., 1999). Thus, a PREP in a person with lung cancer or breast cancer might be beneficial, in addition to reducing risks for secondary cancers.

Dose-Response for Smoking and Lung Cancer

The evaluation of a PREP would include an assessment of how the dose-response curve for smoking is altered as exposure is reduced. Today, however there are limited data on the effects of decreasing exposure short of complete cessation. When people stop smoking, their risk of lung cancer decreases over time. Thus, it is plausible that exposure reduction short of cessation may also reduce risk. One might be able to predict the effects of a particular harm reduction method by assuming that the risk for a smoker who achieves exposure reduction will drop to that of a continuous lower-level smoker. This assumption would be speculative at present and it must be evaluated through an understanding of the dose-response relationship of smoking to lung cancer. The modeling for a PREP, however, might be more complicated and analogous to intermittent exposure situations (Murdoch et al., 1992).

A dose-response relationship between cigarette smoking and lung cancer has been established in cohort studies of both men and women (Chyou et al., 1992; Doll and Peto, 1976; Engeland, 1996; Friedman et al., 1979; Nordlund et al., 1997; Shaten et al., 1997; Thun et al., 1995; Tverdal et al., 1993; Winter et al., 1985). These studies show remarkable consistency. Both daily smoking amounts and duration of smoking are important contributors to risk, although the lung cancer risk ratios for daily smoking are higher than for duration of smoking. An earlier age at initiation is a separate lung cancer risk factor (Benhamou et al., 1994; Benhamou et al., 1985; Hegmann et al., 1993; Khuder et al., 1998). Zang and Wynder had proposed to estimate cumulative tar exposure by determining all brands used for different periods of life and the quantity per day for a person, using milligram yields calculated by the FTC method (Zang and Wynder, 1992). The reported effect of how deeply someone inhales also has been associated with an increased risk (Agudo, 1994; Benhamou et al., 1994; Joly et al., 1983; Khuder et al., 1998). There is some data to indicate that smoking more cigarettes per day increases the risk for small-cell carcinoma (Weiss et al., 1977).

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The slope of a dose-response curve may provide an indication of the success of a PREP in smokers. Several groups of investigators have modeled different cohort study sets for lung cancer and have found different relationships. Using data from single studies, Armitage (1985) and Gaffney and Altshuler (1988) provided evidence that smoking risk fits either a multistage or a two-stage model for initiation and cell proliferation. Doll and Peto (1978) found that their data on British doctors fit a second-order polynomial equation for number of cigarettes per day and a quadrate equation for duration, although this was only true for smoking less than 40 cigarettes per day. Reanalysis of their data using different approaches confirmed the quadratic function where any two of three dose-dependent parameters (cigarettes per day, duration, age) were considered and the greatest predictor was cigarettes per day (Moolgavkar et al., 1989). A linear relationship was reported in Japanese men (Mizuno and Akiba, 1989), with duration identical to the estimate of Doll and Peto (1978). Puntoni and coworkers summarized data for nine different cohort studies and found that a multistage model best fit the data (R^2=0.67, which increased to 0.80 when one study was eliminated; Figure 12-2; Puntoni et al., 1995). Logit, Probit, and Weibull models also provided a good fit (all R^2=0.61), but a one-hit model provided a poor fit (R^2=0.36). As a validation step, the authors included data for passive smoking and the fit was acceptable. Importantly, these models all predict a greater slope for increasing risk at lower doses and a plateau at higher doses. The multistage model showed that risk increased to a plateau at about 20 cigarettes per day, while the Weibull model showed a decrease in the rate of increasing risk at about 5 cigarettes per day. The latter model, however, never clearly reaches a plateau so that any decrease in smoking might have some benefit. These data imply that small amounts of exposure reduction at higher levels of smoking may not be sufficient to achieve harm reduction. In contrast, Law and coworkers (1997) argued that if smoking data in cohort studies were adjusted for actual internal exposure, in their case predicted by carboxyhemoglobin levels, then the shape of the curve assumes a quadratic relationship, where the slope is higher at more than 20 cigarettes per day; these authors argue that a quadratic relationship is more biologically plausible (Figure 12-3). This data imply that the greatest effect of harm reduction would occur in smokers with the highest levels of baseline smoking. Because of these conflicting models, it is impossible at this time to conclude a lesser or greater benefit from exposure reduction at higher or lower levels of smoking. However, the argument by Law and coworkers for including an internal exposure assessment are compelling (Law et al., 1997). Therefore it is likely that the use of biomarkers would provide better estimates of dose-response relationships and harm reduction. It also should be noted that the above analyses that derive

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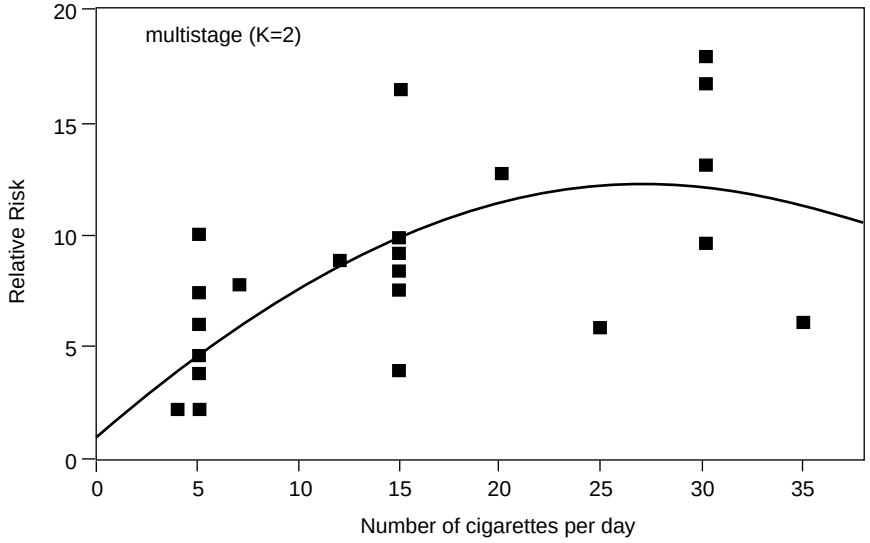


FIGURE 12-2 Relative risk verses number of cigarettes per day.

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models for dose-response relationships mostly do not consider duration of smoking. It is possible that the daily consumption of cigarettes and lung cancer risk have different relationships based on the number of years smoked (Mizuno and Akiba, 1989; Rylander et al., 1996).

The available cohort studies do not provide data that allows for modeling at smoking levels of less than ten cigarettes per day, which is important for understanding the effects of PREPs that result in low exposure levels. Models developed by Puntoni et al. (1995) for smoking less than an average of 1.4 cigarettes per day do not indicate the existence of a threshold, and there are no current data today to show where one might exist. It should be noted that thresholds are difficult to demonstrate (Purchase and Auton, 1995). Puntoni and colleagues (1995) predict an increased risk for smoking at levels as low as 0.25 cigarette per day. Depending on the model however, there are different slopes for low-dose exposures, where a Weibull model predicts a rapid rise to a relative risk (RR) greater than 2 at 0.2 cigarette per day. A multistage model, however, shows a linear response at low levels of exposure. Either model, however, indicates that the best goal for harm reduction is complete cessation because there are

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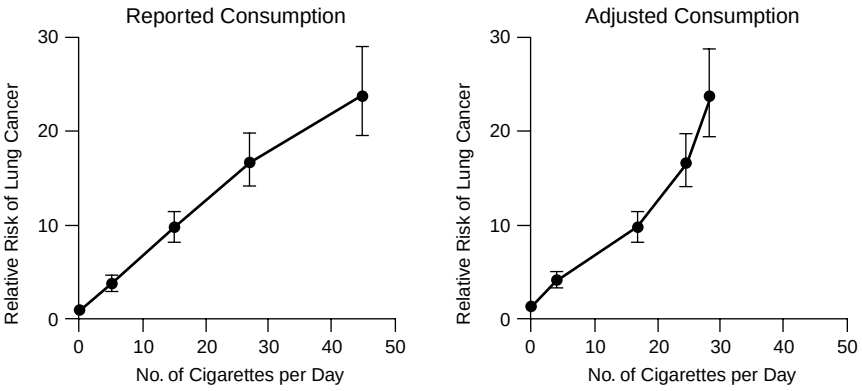


FIGURE 12-3 Relative risk of lung cancer verses number of cigarettes per day.

NOTE: Estimates (with 95% confidence limits) from the U.S. veterans study (Kahn, 1996) of lung cancer mortality in current smokers relative to that in never smokers, according to reported cigarette consumption and adjusted cigarette consumption.
SOURCE: Reprinted from Law et al. (1997) by permission of the publisher Churchill Livingstone.

risks at the lowest levels of smoking, and no safe level can be discerned from the literature. It has been estimated that ETS exposure is equivalent to approximately one cigarette per day (Vutuc, 1984), and although this seems to be a small amount, the risk will depend on duration of exposure as well. Thus while hormesis is thought to exist (Teeguarden et al., 1988), it has not been shown for tobacco exposure.

Biomarker studies have attempted to establish a dose-response relationship for smoking, but the relationship has been variable. Most studies crudely examine smokers versus nonsmokers, rather than reporting a relationship by levels of smoking. Dallinga and coworkers (Dallinga et al., 1998) determined 4-ABP-hemoglobin adducts and "total" phosphorus-32 postlabeled (^{32}P-postlabeled) DNA adducts in peripheral lymphocytes in 55 smokers. The slope of the response was greater for the "total" ^{32}P-postlabeled DNA adducts than for the 4-ABP-hemoglobin adducts in relation to cigarettes per day, and a third-order polynomial curve best fit the data. A plateau began at about 10 cigarettes per day for the former and 20 cigarettes for the latter. In this same study, so-called tar consumption per day had a similar effect. The correlation coefficients for tar were higher than for cigarettes per day, but no models were presented that would allow one to assess the relative contribution of tar versus cigarettes

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smoked per day, and topography was not considered. The data suggest that for a given level of cigarettes per day, the type of cigarette affects the adduct levels, but that at certain higher levels of cigarettes per day, there is less adduct formation per cigarette. This might be due to differences in smoking topography at higher levels of smoking or saturation of metabolic, repair, and apoptotic capacities. All of these factors probably play a role and have led to differences in adduct formation rates in hemoglobin and in lymphocytes.

A PREP would have to work by reducing exposure, but there are few data today to provide an estimate of how much reduction would have a measurable effect in disease outcome. Studies that examine switching to lower amounts of smoking are few. Benhamou and coworkers reported that compared to 1,503 controls, 1,057 lung cancer patients who reported decreasing daily cigarette use by more than 25% had a 20% reduction in risk, although this was not statistically significant (Benhamou et al., 1989). Lubin, et al. reported that reducing daily consumption by more than 50% reduced risk by about 16%, which was barely statistically significant (Lubin et al., 1984a). Thus, the data available is not sufficient to suggest how much decreased consumption must occur to show a measurable benefit. Wald and Watt (1997) reported that persons who switched from cigarettes to pipes or cigars had a higher risk of lung cancer than persons who had never smoked cigarettes. They also found that these individuals inhaled more of their cigars and pipes; so while there was a reduction in risk compared to continuous cigarette smoking, there was still a persistent effect (Wald and Watt, 1997). Graham and Levin found a sixfold increased risk in persons who switched from cigarettes to other tobacco products, compared to an 8.8-fold risk of continued cigarette use and a 2.6-fold risk for persons who had only smoked other tobacco products and continued to smoke them (Graham and Levin, 1971). This represented a 27% reduction in risk compared to continued smoking.

Lung Cancer Risk and Cigarette Type

An important question is whether smoking low-tar and nicotine cigarettes is associated with lower lung cancer risk and whether switching to such cigarettes has shown a benefit. The available data can be summarized as those that examine risk in relation to tar content or to the use of filtered cigarettes. It is important to understand that there are few differences in type of tobacco used among commercial cigarettes and that most changes in tar and nicotine delivery are achieved mainly through the use of a filter, which affects the absorption of carcinogens as well as diluting the smoke with air through ventilation holes. Thus, under similar smoking circumstances (which does not happen in humans), the amount of tar

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that would be delivered from a cigarette varies in the following order from the highest to the lowest: nonfilter, filter high tar and filter low tar. Confounding this relationship, however, is the fact that over the past 30 years, the amount of tar yield per cigarette type has also decreased.

While the studies described below indicate a lesser risk in lung cancer for low-tar and nicotine cigarettes, there are outstanding questions about smoking behavior that might affect the interpretation of epidemiological studies. While it is possible to examine risks for persons who smoke low-tar and nicotine cigarettes, the perceived decreased risk may be due to several confounding variables that have not yet been measured. For example, such individuals might be smoking these cigarettes because of a desire to quit or reduce their smoking, and so might smoke less of their cigarettes, have more quitting attempts, or underreport what they smoke. They also might have some illness (i.e., respiratory problems) that may lead them to reduce the amount they smoke. Finally, these may be individuals who have "healthier" life styles (e.g., diets that reduce lung cancer risk).

Studies Assessing Tar Content. Several large studies have suggested that higher-tar cigarettes are associated with increased lung cancer risk or that the risk is less for smokers of low-tar cigarettes compared to high-tar or mixed exposures (Benhamou et al., 1985; Kaufman et al., 1989; Lubin et al., 1984b; Stellman and Garfinkel, 1989; Vutuc and Kunze, 1983). Other studies have not shown a reduced risk due to low-tar cigarettes (Kuller et al., 1991; Lee and Garfinkel, 1981; Sidney et al., 1993; Wilcox et al., 1988). The American Cancer Society Cancer Prevention Study (CPS-1) Cohort study had a lower standardized mortality ratio (SMR) for persons who smoked lower-tar cigarettes within smoking amount categories (Stellman and Garfinkel, 1989). The SMRs increased from 841 to 1,236 in smokers using cigarettes with less than 17.6 mg for the lowest-tar category and more than 25.7 mg for the highest-tar category. The greatest proportional increase was in persons who smoked the highest number of cigarettes per day. An important limitation of this study was that no adjustment was made for smoking duration, with the claim that an age adjustment approximated this need, although models of lung cancer risk do not support this assumption (Moolgavkar et al., 1989). It also classified tar exposure based on current cigarette use, rather than usual brand smoked or switching. A hospital-based case-control study of 881 cases and 2,570 controls indicated that there was a threefold increased risk from smoking 22-28 mg tar cigarettes compared to less than 22-mg tar cigarettes, which increased to fourfold for more than 29 mg (Kaufman et al., 1989). Lubin and coworkers (1984) studied 7,804 lung cancer cases and 15,207 hospital-based controls in five different European cities. This study collected data

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for previously used cigarette brands, up to a maximum of four, and considered cigarettes per day and duration for each of those brands. So-called total tar exposure was estimated, and a statistically significant trend for increasing risk with highest-tar exposure was observed in both men and women. Compared to persons who only used low-tar brands, a person who used other brands less than 25% of the time had a risk of 1.2, using other brands more than 25% of the time led to a risk of 1.5; using high-tar brands more than 75% of the time led to a risk of 1.8; and exclusive use of high-tar brands produced risk of 1.7. By contrast in another study (Benhamou et al., 1985), the risk of mixing cigarette types was no different than exclusive use of nonfiltered or dark-tobacco cigarettes (Benhamou et al., 1994), where data were provided for smoking duration and cigarettes smoked per day, and there was no clear subgroup (high or low levels of smoking) that had a particularly higher or lower risk compared to low-tar or filtered cigarettes. In a hospital-based case-control study by Alderson and coworkers, reported switching to filtered cigarettes for either less than or more than ten years before lung cancer diagnosis did not show a statistically significant difference in difference risk (Alderson et al., 1985). The potential for increasing consumption when switching brands is important and can modify the possible benefits of presumed lower-tar exposure, as shown in a case-control study of 763 cases and 900 controls by Wilcox and coworkers, in which increasing weighted average tar yields crudely predicted increased risk until exposures were controlled for by cigarettes per day, duration, or pack-years (Wilcox et al., 1988). The Wilcox group, interestingly, concluded that there was more compensation by increasing cigarettes per day in cases compared to controls that switched to lower-tar and nicotine cigarettes. Data pooled from four cohorts failed to show a statistically significant benefit for low-tar cigarettes in terms of lung cancer risk, even among different levels of smoking (Tang et al., 1995b), as did another large cohort study (Sidney et al., 1993). Lee and Garfinkel provided a summary of lung cancer risk and type of cigarette smoked (Lee and Garfinkel, 1981) and were unable to demonstrate a significant decrease in risk based on tar content. There was some observed benefit in terms of tar content when comparing high- to low-tar cigarettes but not for medium versus high tar. Thiocyanate levels, which reflect quantity of cigarettes per day and smoking topography, are associated with increased lung cancer risk, whereas the tar yields of cigarettes were not (Kuller et al., 1991).

Case-control studies have provided evidence that black tobacco carries almost a fourfold risk higher risk tan blond tobacco (Benhamou et al., 1985, 1989; Joly et al., 1983), and a 6.6-fold higher risk in women (Agudo et al., 1994).

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In summary, while some studies suggest that there is a lower risk of lung cancer with lower-tar cigarettes, many do not, especially when risk is considered along with biomarkers in relation to smoking behavior.

Studies Assessing Filter Cigarette Use. One of the earliest reports suggesting that filtered cigarettes were less hazardous than nonfiltered cigarettes was published by Bross and Gibson, who estimated a 60% decrease in risk in 265 cases compared to 214 controls (Bross and Gibson, 1968). Lubin and coworkers (1984b) reported that nonfilter cigarette use compared to filtered cigarettes consistently gave higher RR estimates for lung cancer, no matter the history of cigarette smoking duration or cigarettes per day. Interestingly, the magnitude of the risk for cigarettes per day and years of use increased substantially more for persons using filtered compared to nonfiltered cigarettes. This suggests that decreasing cigarette use in persons using PREPs might have more easily demonstrable benefits. In other studies of filtered versus nonfiltered cigarettes, a decreased lung cancer risk of 30% was found in a French study of 1,625 lung cancer cases and 3,091 controls (Benhamou et al., 1985, 1989), a twofold lower risk in a Philadelphia study (Khuder et al., 1998), a 3.5 fold decrease in an Argentinian study (Pezzotto et al., 1993), and a fourfold decrease for women in a Spanish study (Agudo et al., 1994). Wynder and Stellman (Wynder and Stellman, 1979) reported that among 684 cases and 9,547 controls, there was a reduced risk for those who smoked nonfiltered cigarettes for ten years or more, although the results were not statistically significant. However, when they later reported data for 1,242 lung cancer cases compared to 2,300 controls and accounted for increasing smoking per day after switching to lower-tar cigarettes, they found that lung cancer risk was not reduced and even increased in the highest levels of compensation (Figure 12-4; Augustine et al., 1989). Other studies also have reported a reduced risk for filtered cigarettes (Rimington, 1981; Pathak et al., 1986), but a dose-response relationship for persons who mix their brands was harder to demonstrate (Lubin et al., 1984b; Pathak et al., 1986). Lee and Garfinkel provided a summary of lung cancer risk and type of cigarette smoked (Lee and Garfinkel, 1981) and concluded that there was about a 25% reduction in lung cancer mortality for filtered cigarettes. In this review as in others, there was no consideration of biomarkers, actual smoking consumption, or analysis for persons who switched cigarette types. Several studies do not support a decreased risk for filtered cigarettes. In a population-based case-control study, when amount of smoking was considered, there was no benefit from filtered cigarettes (Wilcox et al., 1988). Data pooled from four cohorts failed to show a statistically significant benefit for filtered cigarettes and lung cancer risk, even among different levels of smoking (Tang et al., 1995b), as did another large cohort of 79,946 members of Kaiser Permanente (RR=1.03 for men and 0.65 for women; neither

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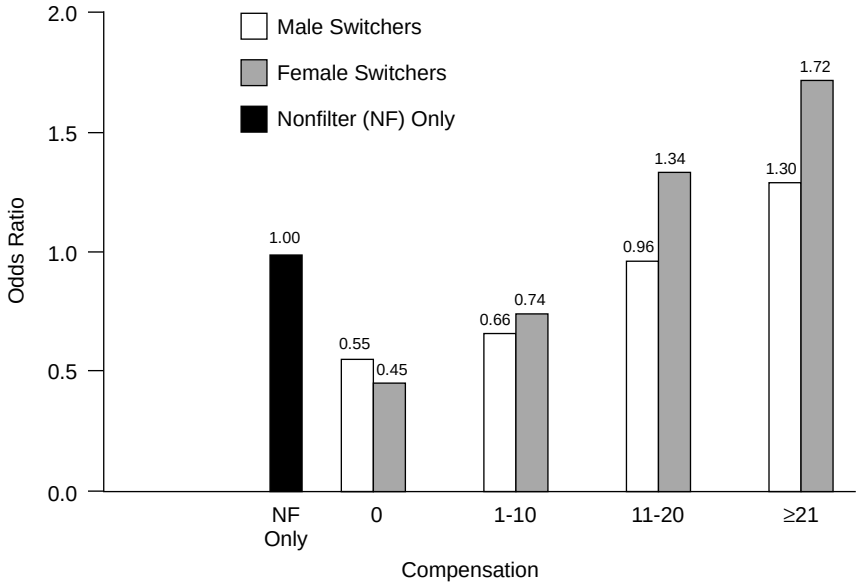


FIGURE 12-4 Risks among switchers relative to nonfilter only smokers according to difference levels of compensation.

NOTE: Compensation is the increase in cigarettes per day after switching to filter cigarettes. Computed from the result of Augutine, Harris and Wynder study (1989) and the results of the study by Wynder and Kabat, 1988.
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was statistically significant), although women who used filtered cigarettes for more than 20 years had a risk of 0.36 (95% CI=0.18, 0.75; Sidney et al., 1993).

In comparison to nonfiltered cigarettes, filtered cigarettes are more closely associated with AD rather than SCC (Pezzotto et al., 1993; Stellman et al., 1997a, b), although this was observed mostly in women smokers in another study (Lubin and Blot, 1984; Stellman, 1997a, b). Hand rolled cigarettes had an increased risk for SCC and not AD (Engeland et al., 1996). This association is thought to be due to greater depths of inhalation when the filter is in place to compensate for lower nicotine amounts, as well as increased delivery of TSNAs. Evidence for this includes self-report of frequency and depth of inhalation associated with AD rather than SCC (Lubin and Blot, 1984). When considering persons who switched from nonfiltered to filtered cigarettes, compared to lifetime nonfilter ciga-

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rette smokers, there was a decrease in risk for SCC but not AD in men and women (Stellman et al., 1997a, b).

Most of the above studies suggest that the use of filtered or low-tar cigarettes was associated with lower lung cancer risk, even though there is clearly an increased risk of all types of lung cancer with all types of cigarettes. Ecological studies also support such a conclusion when smoking rates and lung cancer mortality over time are compared and the slopes for the decline in smoking are less steep than the decline in mortality (Peto et al., 2000). However, many significant considerations that make such data difficult to interpret. These studies assess smoking at a specific point in time, which prevents the collection of useful data later in prospective studies and is subject to recall bias in case-control studies. Indeed, assessing smoking prospectively at multiple time points or considering individual smoking improves estimates (Lee, 1998; Akiba, 1994). Separately, these studies do not account for cohort effects where the public's overall lung cancer risk may have changed due to diet and lifestyle or for the possibility that persons who smoke low-tar cigarettes otherwise differ from those who smoke high-tar cigarettes. Additionally, it is important to note that these studies do not provide an assessment of what happens to persons who switch cigarette type, which is directly relevant to assessing PREPs.

Gender Differences in Lung Cancer Risk

The prevalence of smoking among women is less than among men and consequently have overall lower rates of lung cancer (Shopland et al., 1991) and preneoplastic lesions (Lam et al., 1999). However, lung cancer rates recently have been decreasing for men but not for women (Wingo et al., 1999). The rates of increase since the 1950s for lung cancer in general, and AD in particular, are higher for women than men, because women have increased the amounts of cigarettes smoked per day, start smoking earlier, and smoke different types of cigarettes (Haldorsen and Grimsrud, 1999; Levi et al., 1987; Shopland et al., 1991; Thun et al., 1997). Women more commonly have AD than SCC, even after controlling for smoking status (Ernster, 1996). Several studies have provided evidence that women have a higher risk of lung cancer for a given level of smoking. In a study of 1,108 males and 781 females with lung cancer, compared to 1,122 male and 948 female controls, women were found to have a 1.2- to 1.7-fold higher risk, which was limited to AD and SCLC cancers, rather than SCC (Zang and Wynder, 1996). These data provided similar results when examined by estimated tar yields according to the FTC method, pack-years, and recent smoking per day. Other studies have provided similar findings (Brownson et al., 1992; Cohn et al., 1996; Engeland, 1996; Lubin and

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Blot, 1984; Osann et al., 1993; Risch et al., 1993), although some have not (Doll and Peto, 1976; Halpern et al., 1993). While some might hypothesize that the difference in cancer risks between men and women are due to differing baseline nonsmoking rates (Prescott et al., 1998), this was found not to be the case using summary statistics from several large cohort studies (Risch et al., 1994). An increased risk in women is also evidenced by data showing that there is a higher risk for lung cancer in women at similar ages of initiation and the risks are the same for women who start smoking over age 25 as for men over age 20 (Hegmann et al., 1993). In a study of lung cancer risk among persons who switched from filtered to nonfiltered cigarettes, both women and men had a lower lung cancer risk if they smoked similar amounts of cigarettes per day before and after switching (Augustine et al., 1989). However, women had a greater likelihood of compensation and smoking more cigarettes, especially at lower doses. For similar levels of increased cigarettes per day, women had a much higher risk of lung cancer. There are several plausible explanations for this increased risk that bear directly on the effects of PREPs. The increased risk observed in women might be due to smoking behavior and/or biological differences. For example, women may be at higher risk because they have begun smoking in recent times with lower-tar and nicotine cigarettes (Thun et al., 1997), which can deliver greater amounts of TSNAs (Hoffman and Hoffman, 1997). There is a lack of evidence, however, showing consistent differences in greater smoking topography, but this may be because both men and women were smoking similar types of cigarettes.

Another explanation for a higher lung cancer risk in women might be related to biological differences between men and women. There might be a hormonal relationship, because women more commonly have estrogen or progesterone receptors in lung cancer (Kaiser et al., 1996). Two studies found a high abundance in both males and females, but a difference between the two could not be discerned (Canver et al., 1994; Su et al., 1996). Also, because women suffer more tobacco withdrawal symptoms during menses, they might have greater lifetime exposure (O'Hara et al., 1989). Women have higher levels of carcinogen-DNA adducts in lung tissues, even though they have the same or lower levels of smoking (Ryberg et al., 1994a), which supports the latter hypothesis. Separately, Chinese women have a higher risk of lung cancer if they have more and shorter menstrual cycles (Liao et al., 1996; Gao et al., 1987). The frequency of p53 mutations is higher in men, consistent with the greater amounts of smoking, but women more commonly have G→T transversions (Kure et al., 1996), suggesting a particular susceptibility to tobacco smoke carcinogens. Women might also be more susceptible if they have particular metabolic polymorphisms that affect carcinogen detoxification (Mollerup et

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al., 1999; Ryberg et al., 1997; Tang et al., 1998). Separately, gastrin-releasing peptide has been shown to be more highly expressed in women than men for the same level of smoking (Shriver et al., 2000). The gene for this peptide is located on the X chromosome, so a double copy might result in increased levels that in turn trigger growth stimulation. Therefore, assessment of PREPs also should consider possible effects on hormonal status and differences in the effects of individual tobacco constituents in women.

Racial and Ethnic Differences in Lung Cancer Risk

Lung cancer rates differ by race and ethnicity (U.S. DHHS, 1998). Lung cancer incidence rates are highest among African-American males (112.3 per 100,000), followed by Caucasian males (73.1 per 100,000). African-American and Caucasian females have similar rates (46.2 and 43.3 per 100,000, respectively). Asian-American males and females have relatively lower rates (52.4 and 22.5, respectively), while Hispanics have the lowest rates (38.8 and 19.6, respectively). In the United States, smoking rates differ; African Americans, Hispanics, Chinese Americans, and Hawaiians tend to smoke fewer cigarettes per day than European Americans (Le Marchand et al., 1992). In the United States, Hispanic males and females tend to smoke less than nonHispanic whites, but the risks within smoking levels are similar (Humble et al., 1985). Hawaiians have a greater risk of smoking compared to Filipinos and Caucasians living in Hawaii (Le Marchand et al., 1992). The differences in lung cancer rates within smoking categories may be due to smoking topography, types of cigarettes smoked, differences in the frequencies of heritable traits, and/or environmental, lifestyle, and dietary differences. For example, Japanese have lower rates of lung cancer than persons from other countries, which may be due to the use of tobacco with lower TSNAs, more frequent use of charcoal filters, or lifestyle differences. However, the effects of these factors on lung cancer rates are small compared to the overall increased risk for use of cigarettes.

There are some data to suggest that lung cancer risk is higher in African Americans than Caucasians for a given level of smoking (Harris et al., 1993; Schwartz and Swanson, 1997). For example, Harris et al. reported an RR of 1.8 for African Americans compared to Caucasians at the same level of tobacco consumption calculated as cumulative tar intake (Harris et al., 1993). African Americans tend to smoke menthol cigarettes, while the opposite is true for Caucasians (Cummings et al., 1987). Menthol cigarettes provide cooler smoke that helps anesthetize airways (Sant'Ambrogio et al., 1991), so smoking topography might be affected (Orani et al., 1991). The greater use of mentholated cigarettes among African Americans (Cummings et al., 1987; Wagenknecht et al., 1990) is

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associated with a higher lung cancer risk (Sidney et al., 1995), although not in other studies of menthol cigarettes (Kabat et al., 1991). In two studies the carbon monoxide (CO) boost was shown to be higher among users of menthol cigarettes (Clark et al., 1996; Jarvik et al., 1994), but not in another study that examined women (Ahijevych et al., 1996). Another mechanism for potential harm from mentholation is pyrolysis of menthol, which leads to benzo[a]pyrene production (Schmeltz and Schlotzhauer, 1968). Socioeconomic status may also contribute to racial differences in lung cancer incidence (McWhorter et al., 1989).

African Americans tend to smoke less than Caucasians (Hahn et al., 1990; Kabat et al., 1991; Royce et al., 1993; Vander Martin et al., 1990), but may be more highly nicotine dependent (Royce et al., 1993; Vander Martin et al., 1990). They also tend to smoke higher-tar and nicotine cigarettes, resulting in higher nicotine levels and greater tar yields (Hahn et al., 1990; Perez-Stable et al., 1998). This is consistent with repeated findings of higher cotinine levels in African Americans compared to Caucasians (Caraballo et al., 1998; Wagenknecht et al., 1990) and higher urinary TSNAs in African Americans (Richie et al., 1997). Even though it was recently shown that African Americans have decreased cotinine clearance, rather than different nicotine metabolism (Perez-Stable et al., 1998), there is still the possibility of higher relative carcinogen exposure. For example, this study did not consider smoking topography. There are data showing that African Americans smoke more of their cigarettes (Clark et al., 1996) and have a higher CO boost per millimeter of cigarette smoked (Ahijevych et al., 1996; Clark et al., 1996). They also have higher nicotine intake per cigarette (Perez-Stable et al., 1998).

When considering a PREP, we must consider different races within the United States and other countries, where more environmental exposures are shared. In general, within levels of smoking, the risks of lung cancer around the world are similar, with some exceptions. In China, a combined analysis of studies that appeared in the Chinese literature reportedly demonstrated a dose-response relationship for men and women (Liu, 1992). However, the slope of the dose-response relationship was less than that in Western studies and similar to that for Japan. Importantly, the attributable risk for smoking was only 57% in men and 26% in women, where 88% and 46% of male and females smoked, respectively. A substantial number of Chinese also smoked pipes of various types, and among these individuals, the risk of lung cancer was lower than among persons who smoked only cigarettes (Lubin et al., 1992). Whether this represents a method of harm reduction remains unknown since that was not specifically studied, and the lower risk might have been observed for many reasons. Caution must be used in attempting to implicate any particular factor for differences in lung cancer rates in different geographical

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areas. These differences might be due to uses of different tobacco products, smoking topography, modifying effects of tobacco (e.g., diet), or increased frequencies of genetic traits. Separately, differences in health system access, reporting methods, or diagnostic procedures also may substantially affect the accuracy of risk estimates.

In summary, there are sufficient data to show that the use of tobacco products, exposures, and outcomes can vary in different racial and ethnic groups. Thus, PREPs must be assessed in the context of the ethnicity and race of intended users.

Factors Modifying Lung Cancer Risk

Although this report focuses on the evaluation of PREPs, it also is recognized that other factors affect lung cancer risk, both positively and negatively (Lee and Forey, 1998; Lutz et al., 1999). These factors are not detailed here, but evidence follows to show that the evaluation of PREPs should consider other exposures and host susceptibilities that might affect an individual's risk related to PREPs. Many cancer risk factors covary with smoking consumption and thus can confound some studies (Thornton et al., 1994). Factors shown to modify cancer risk may include diet (Breslow et al., 2000; Grinberg-Funes et al., 1994; Mendilaharsu et al., 1998; Voorrips et al., 2000; Yong et al., 1997), vitamin use, and chemopreventive agents (Clapp et al., 1999; Omenn et al., 1996), although whether these factors actually modify cancer risk has not been conclusively demonstrated (Koo, 1997). While the latter might have sufficient impact because of dose, diet and vitamin supplementation would unlikely provide a significant benefit to proven harm reduction methods. This report does not consider these areas as potential harm reduction strategies.

Coexposures to other lung carcinogens from nonsmoking sources can lead to a multiplicative risk effect. These exposures include occupational asbestos exposure, occupational radiation exposure, radon, and therapeutic radiation exposure (Brownson et al., 1993; Carstensen et al., 1988; Inskip and Boice, 1994; Jockel et al., 1992; Moolgavkar et al., 1993; Neugut et al., 1994; Osann et al., 2000; Qiao et al., 1989; Tokarskaya et al., 1995; Torkarskaya et al., 1997). This report does not consider these coexposures in detail, but it should be recognized that they might affect the efficacy of PREPs. Prior lung disease history might increase lung cancer risk in smokers and persons exposed to tobacco smoke (Mayne et al., 1999b).

Heritable susceptibilities can affect tobacco-related cancer risks (Brockmoller et al., 1998; Shields, 2000; Shields and Harris, 2000). The use of genetic susceptibilities in the context of a given type of exposure can increase risk assessment prediction (Khoury and Wagener, 1995). Evi-

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dence for familial transmission of risks comes from analyses of lung cancer patients and their parents (Amos et al., 1999; Sellers et al., 1992a, b), although some studies have disagreed (Braun, 1994; Mayne et al., 1999a). While these types of studies tend to implicate high-penetrance genes, there also is evidence that low-penetrance genes in carcinogen metabolism can modify cancer risks, and it is likely that other types of genes will also (e.g., DNA repair, cell-cycle control, apoptosis, signal transduction). Examples of frequently studied genetic polymorphisms in tobacco-related cancers that have been shown in some studies to modify smoking-related disease risk include the glutathione *S*-transferase M1 (GSTM1; Bell et al., 1993; Brockmoller et al., 1996, 1998; Jourenkova-Mironova et al., 1998, 1999; Kihara et al., 1995; Lehman et al., 1996; Rebbeck, 1997), cytochrome P-450 1A1 (CYP1A1) genes (Ishibe et al., 1997; Kihara et al., 1995), glutathione *S*-transferase Pi (Ryberg et al., 1997), and others (Bouchardy, 1998; Jourenkova-Mironova et al., 1999; Rosvold et al., 1995; Sjalander et al., 1996; Wiencke et al., 1997). These genetic polymorphisms and others are believed to affect levels of biomarkers, such as DNA adducts (Kato et al., 1995; Pastorelli et al., 1998; Ryberg et al., 1997; Yu et al., 1995). Interestingly, in Japanese, the risk for the GSTM1 null genotypes increases with increasing levels of smoking (Kihara and Noda, 1994), but the opposite is true for CYP1A1 (Nakachi et al., 1991), indicating a saturation effect. Also, several biomarker phenotypes representing carcinogen metabolism and DNA repair have been shown to modify the effects of smoking-related risks (Li et al., 1996; Spitz et al., 1995; Wei et al., 1996). More specific evidence for a relationship between gene-environment interactions and mutations in the p53 gene can be found from Japanese studies of CYP1A1 (Kawajiri et al., 1996), where a fivefold increase in risk was found for smokers with lung cancer. This risk increased further for persons who also lacked GSTM1. In one study from Norway, smokers who lacked GSTM1 also had an increased risk of lung cancer from p53 mutations, especially transversions (Ryberg et al., 1994b).

Thus, it is important to study the differences in responses to PREPs by individual susceptibilities, in addition to gender, race, and diet, because they might increase or decrease product effectiveness in specific persons. In addition to carcinogen metabolism and DNA repair, genetic traits for other aspects of carcinogenesis and smoking behavior will undoubtedly be identified.

Former Smokers and Lung Cancer

Central to the issue of decreasing the harm from tobacco use in the general population is the evidence for lung cancer risk reduction among former smokers. The risk that is observed in former smokers can reason-

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ably be predicted to be the lowest risk achievable by a PREP. This section describes studies of persons who quit smoking cigarettes and were not reported to have switched to other tobacco products.

The risk of lung cancer in former smokers is less than in current smokers, as demonstrated by both case-control and prospective studies. Case-control studies among former smokers are numerous and most have reported statistically significant reductions in the odds ratio of lung cancer relative to smokers. Some individual studies have been limited by the use of hospital controls, lack of adequate age adjustment, reliance on proxy interviews for information about the smoking behavior of deceased cases, and lack of information on potential risk reduction variability by histological type of lung cancer. A study conducted in Germany (Pohlabeln et al., 1997) addressed many of these issues. That study compared 839 lung cancer cases with an equal number of population-based controls matched on age, gender, and region and examined ORs by years since quitting and by histological type of lung cancer. Relative to current smokers, the lung cancer ORs among former smokers were 0.97 for those who had quit 10 years ago, 0.55 for 11-20 years since quitting, and 0.25 for those who had quit more than 20 years ago. The same pattern of OR reduction was observed among all histological types. In a separate study by Muscat and Wynder (Muscat and Wynder, 1995), the frequency of AD compared with SCC after 25 years of cessation appeared more like that in those who have never smoked than in current smokers. This was true for both men and women and is in agreement with other studies (Tong et al., 1996). Other studies indicate that risk differs depending on previous smoking history and duration of abstinence (Ben-Shlomo, 1994; Graham and Levin, 1971).

One of the difficulties in obtaining reliable estimates of the reduction in lung cancer risk among former smokers in case-control studies is the variability in the ages at which people take up smoking. In the study conducted by Sobue et al. in Japan (Sobue et al., 1993), all of the male former smokers had started smoking cigarettes between the ages of 18 and 22, a far narrower range than reported in many other case-control studies. In that study, the OR reduction for lung cancer among former smokers ranged from 50 to 65%, depending on the age at smoking cessation and the age at admission, with stronger benefits accruing to men who quit at younger ages and who were diagnosed at younger ages. This study also is noteworthy because it documented a hazard reduction even among men in their seventies who had stopped smoking for just a few years: the decrease in cancer risk among male ex-smokers of this age group is significant due to the higher incidence of lung cancer among men this age than in the general population. While the greatest absolute

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reduction in risk occurred among older smokers, the greatest rate of reduction in risk occurred among younger smokers.

Alavanja et al. (1995) used case-control study data from 618 female lung cancer patients and 1,402 population-based age-matched controls to estimate the population attributable risks (PARs) of lung cancer among nonsmokers and ex-smokers. By far, the most important factor for female ex-smokers was their history of active smoking, explaining 56% of lung cancer incidence in the population of female ex-smokers and far outweighing factors such as environmental tobacco smoke (PAR=1.7), occupational risk factors (PAR=4), and family history of lung cancer (PAR=14).

Unlike case-control studies, prospective studies can directly compute the relative risk of lung cancer among former smokers, and several large cohort studies have examined this in detail. (Doll and Peto, 1976) followed 34,440 British male physicians for 20 years and observed an age-adjusted annual death rate from lung cancer of 43 per 100,000 among ex-smokers, compared to 10 in nonsmokers and 140 in men smoking cigarettes exclusively. Thus, the rate was clearly lower than that in smokers but remained higher than that of nonsmokers. Results from the American Cancer Society's CPS-II of nearly 900,000 men and women (reported by Halpern et al., 1993), demonstrated dose-response curves for the association of lung cancer mortality with years since quitting. For both men and women, the RR of lung cancer death by age 75 was <0.05 among lifelong nonsmokers compared to current smokers, while among ex-smokers who had quit in their thirties and forties, the RRs were in the range of 0.07-0.15. Even those who had quit at ages 60-64 experienced a reduction in risk of lung cancer mortality at age 75 (RR=0.45 for men, 0.49 for women). The 20-year follow-up report on mortality among 12,866 participants in the Multiple Risk Factor Intervention (MRFIT) study observed a 60% reduction in deaths from lung cancer among ex-smokers compared to men who continued to smoke (Kuller et al., 1991).

Figure 12-5 shows the reduction in the RR of death from lung cancer among former smokers compared to those who continued to smoke from the large prospective cohort study of (Halpern et al., 1993). The amount of harm reduction depends not only on the length of time since quitting but also on the person's current age. Nonetheless, while the curves for each cohort of former smokers show downward trends for fatal lung cancer, the risk ratios never reach the low level experienced by persons who have never smoked cigarettes. Quitting at an earlier age provided the greatest risk reduction. In a logistic regression model, significant independent variables included gender, education, age (β=0.085), number of cigarettes per day (β=0.025), years smoked (β=0.055), and years quitting (β depends on quit cohort). Enstrom and Heath (1999) compared lung cancer mortality among smokers and quitters in a cohort of 118,000 men and women in

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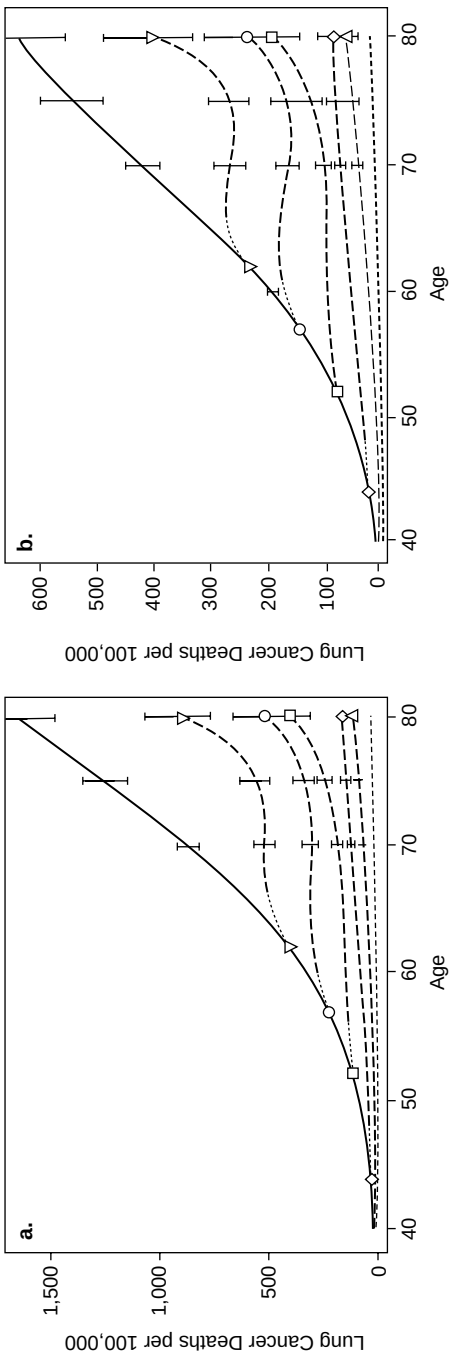


FIGURE 12-5 Lung cancer death rates of women and men.

NOTE: Figure on the left: Model estimates of lung cancer death rates by age for female current, former, and never smokers, based on smokers who started at age 18.5 and smoked 22 cigarettes/day. Estimates are plotted for current smokers (solid line), never smokers (dotted line), and former smokers (dashed lines). The five age-at-quitting cohorts are distinguished by the following symbols on the graph at the age of quitting and also at age 80: Δ 30-39, ◊ 40-49, □ 50-54, ○ 55-59, ▽ 60-64.

Figure on the right: Model estimates of lung cancer death rates by age for male current, former and never smokers, based on smokers who started at age 17.5 and smoked 26 cigarettes/day. Estimates are plotted for current smokers (solid line), never smokers (dotted line), and former smokers (dashed lines). The five age-at-quitting cohorts are distinguished by the following symbols on the graph at the age of quitting and also at age 80: Δ 30-39, ◊ 40-49, □ 50-54, ○ 55-59, ▽ 60-64.
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California born between 1900 and 1929 and traced from 1960 through 1997. Lung cancer mortality declined among ex-smokers, but never reached the rate experienced by people who had never smoked and was still twice as high after 20 years of quitting. This result is in agreement with the lung cancer mortality RR of 1.73 for people who had stopped smoking at least 15 years ago observed by Enstrom (1999) in the analysis of both National Health and Nutrition Examination Survey (NHANES I) data (N=4,900) and a large veterans study (N=284,000). Figure 12-6 shows (Enstrom, 1999) results on the RR of fatal lung cancer according to the number of years since quitting, relative to men who never smoked. Note that the RR does not decline all the way to unity but remains modestly elevated (RR=1.8) even after 15 or more years since smoking cessation. Such results (Enstrom, 1999) suggest the possibility that many former smokers are in poor health around the time of quitting, with substantial mortality with the first few years. This effect diminishes with time, and after five years the benefits become increasingly substantial among survivors. Other data show that risks of lung cancer shortly after quitting do not change much, but decrease to a 30% increased risk over nonsmokers after ten years of cessation (Graham and Levin, 1971). No data are available to suggest differences in risk by cigarette type among former smokers. Some data do not indicate a greater benefit for quitting in women

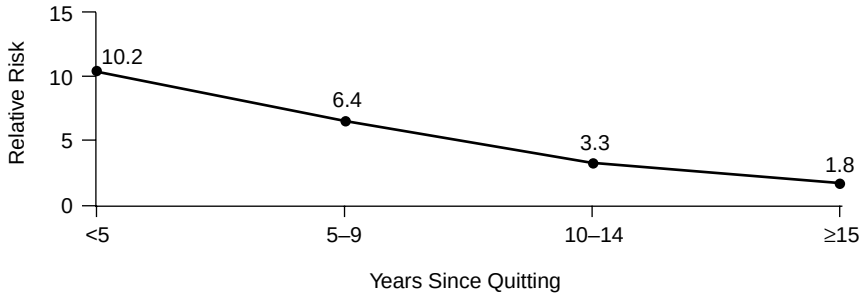


FIGURE 12-6 Relative risk of lung cancer death among former male smokers, relative to never smokers.

NOTE: Data from Enstrom's (1999) prospective cohort study of U.S. male veterans, comparing 43,559 former smokers to 59,351 men who never smoked cigarettes.
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compared to men (Halpern et al., 1993), although other studies do (Risch et al., 1993).

An overall challenge in assessing this cancer risk reduction is the question: Are quitters systematically different from current smokers and never smokers in ways that would explain the differences in cancer risks among these groups? A large, cross-sectional survey of nearly 9,000 adults in Britain (Thornton et al., 1994) attempted to answer this question by randomly sampling nonsmokers, ex-smokers, and current smokers in the population. The study collected data on a wide range of risk factors for poor overall health, including dietary, lifestyle, medical, and socioeconomic factors. Of 33 risk factors assessed, 27 were most prevalent among current smokers, and most risk factors decreased in prevalence with the amount of time since quitting. The data allowed estimation of the degree of confounding in smoking studies due to multiple risk factors and, importantly, called attention to the likely impact of these factors on epidemiological studies where weak associations are detected. In other words, the potential effects of confounding variables may be profound for weak associations between cancer and smoking variables, including those that attempt to estimate risk reductions among former smokers (where RRs have approached 1.5 or less and have been much debated). Finally, greater smoking and lower tendency to quit have been observed among socioeconomically disadvantaged groups relative to others, suggesting an increasing burden of tobacco-related cancers on persons of lower socioeconomic status. It should be noted that the MRFIT prospective trial found a higher lung cancer rate in the group with smoking cessation counseling versus usual care (Shaten et al., 1997). While this is likely due to chance alone, it may suggest that the greatest decrease in risk occurs in persons who are able to quit without counseling or that those who continue to smoke after counseling have high levels of exposure.

Many studies indicate that lung cancer mortality is increased for the first five years after quitting (Alderson et al., 1985; Enstrom, 1999; Graham and Levin, 1971; Halpern et al., 1993; Higgins and Wynder, 1988; Pohlabeln et al., 1997), which has been called the "quitting-ill" effect. It is presumed that this occurs because people who are ill are induced to quit. Although that is probably the explanation for this phenomena, it is not known if there is also some chronic induction of cytotoxicity or other mechanism in the lungs induced by tobacco smoking. When smoking ceases, this effect diminishes and allows already present neoplastic cells to replicate, so persons who would have developed lung cancer do so at a more rapid rate. This is currently speculative. The issue of biological evidence for tobacco harm among former smokers has been addressed in studies examining lung tissue biopsies. Mao et al. (1997) compared LOH at several chromosomal loci in nontumor lung tissue samples from

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smokers, ex-smokers, and nonsmokers. LOH at 3p14 was found in 88% of smokers, compared to 45% in ex-smokers (p=.01) and 20% in nonsmokers. A similar pattern of increasing levels of genetic damage in current, former, and nonsmokers has also been reported with regard to p53 mutations in bladder tumors (Djordjevic et al., 2000). Witsuba et al., on the other hand, did not detect such differences in LOH at the loci they surveyed, but ex-smokers were just as likely as current smokers to have genetic changes typical of lung tumors, and these changes persisted many years after quitting (Wistuba et al., 1997). Thus, there do appear to be irreversible sequellae of past tobacco use even among people who have abstained for many years and are not currently diagnosed as having lung cancer.

In summary, stopping smoking decreases the risk of lung cancer, and the earlier that an individual stops, the greater is the reduction in risk. Data are not sufficient to determine whether certain levels of prior smoking result in proportionately greater or lesser risk reduction, although clearly, a greater smoking history carries a greater lung cancer risk (Graham and Levin, 1971). The data supports the conclusion that after about 20 years of quitting, the risk reduction plateaus and remains slightly above never smokers. Thus, it is unlikely that a PREP would achieve a greater level of risk reduction than the level at 20 years, and at any time point before that, the risk is likely to be greater than that of someone who quit.

OROPHARYNGEAL CANCERS

Oropharyngeal cancers include cancers arising in the oral cavity, tongue, pharynx, and larynx. Almost all are squamous cell carcinomas. Their incidence is about 40,000 cases annually, of which about 12,000 will eventually die from the disease (Greenlee et al., 2000). There is a male-female ratio of about 2:1.

Preneoplastic lesions, which include keratosis, dysplasia, carcinoma in situ, and microinvasive cancer, are considered a sequential continuum (Gillis et al., 1983). Keratosis is the most common oral lesion, occurring as white (leukoplakia) or red (erythroplakia) patches, and is present in 1-10% of adults (Mao and El-Naggar, 1999). Some molecular evidence exists that premalignant lesions are the direct precursors of invasive lesions (Califano et al., 2000). Cessation of smoking does not remove the potential for progression of the disease and all patients must be followed indefinitely (Gillis et al., 1983).

The major risk factors for oropharyngeal cancers are tobacco and alcohol use. The role of smokeless tobacco is discussed below. There is a dose-response for both smoking and alcohol use; together the two agents act synergistically (Ahrens, 1991; Barasch et al., 1994; Blot et al., 1988; Hayes et al., 1999; Iribarren et al., 1999; Keller and Terris, 1965; La Vecchia

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et al., 1990; Lewin et al., 1998; Macfarlane et al., 1995; Mashberg et al., 1993; Muscat et al., 1996; Sanderson et al., 1997; Schildt et al., 1998; Schlecht et al., 1999; Takezaki et al., 1996; Talamini et al., 1998). The attributable risk for alcohol and/or tobacco use is about 75-80% for males and 52-61% for females (Blot et al., 1988; Hayes et al., 1999). There is some evidence for a weak familial association in smokers (Goldstein et al., 1994). Some studies suggest that tobacco consumption is more likely than alcohol consumption to cause precursor lesions (Jaber et al., 1999; Kulasegaram et al., 1995) and cancer (Elwood et al., 1984; Macfarlane et al., 1995). Another study reported the converse in women (Schildt et al., 1998), although this was a small study of Swedish women who may have been snuff users (see section on Smokeless Tobacco; Sanderson et al., 1997). Actual consideration of the relative carcinogenicity of the two agents depends on the level of consumption for each. Talamini and coworkers studied 60 nonsmoking drinkers and 32 nondrinking smokers and compared them to controls (Talamini et al., 1998). Depending on the amount of drinks per week, the OR reached 5.3 (95% CI=1.1, 24.8) in the nonsmokers and 7.2 (95% CI=1.1, –46) in smokers. Thus, the dose–response curves overlapped. In a pooled analysis of three studies form New York, Italy, and China, the OR for males with greater than 33 pack-years was 1.3 (95% CI=0.6, 3.1) and for females who smoked more than 18 pack-years was 4.6 (95% CI=1.9, 10.9). Three published studies that report data by gender all indicate an increased risk for women compared to men, especially at the highest levels of smoking (Blot et al., 1988; Hayes et al., 1999; Muscat et al., 1996).

Cigarette type and oropharyngeal cancer risk have not been extensively studied. Three reports have not shown a difference between filter and nonfilter cigarettes (Blot et al., 1988; Hayes et al., 1999). Hand-rolled cigarettes appear to carry greater risks than manufactured cigarettes (De Stefani et al., 1998). Only one study could be identified that examined so-called tar content for cigarettes, and a lower risk was associated with low-tar cigarettes (La Vecchia et al., 1990). Black tobacco carried about a five-fold higher risk than blond (De Stefani et al., 1998). Where studies are available, there are no differences in risk for similar levels of smoking in Caucasian Americans compared to African Americans (Blot et al., 1988; Day et al., 1993), although one study suggested that African Americans were at a lower risk, but there was no breakdown by smoking and drinking categories.

Smoking cessation changes the risk of oropharyngeal cancers. Cancer of the larynx has been found to be markedly less likely among ex-smokers than among current cigarette smokers (U.S. PHS, 1964). In a relatively large case-control study in Brazil (Schlecht et al., 1999), 784 cases of cancer of the mouth, pharynx, and larynx were compared to 1,578 noncancer controls, compared to never smokers, the ex-smokers of >20 years had an

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OR=2.0 (95% CI=1.0, -3.8) for all types combined, lower risks for mouth (OR=1.6) and pharyngeal cancer (OR=1.5), and a high risk for laryngeal cancer (OR=3.6). The benefits of quitting were greatest for cigarettes and lesser for cigars and pipes.

Excellent reviews have been published of the molecular changes present in oropharyngeal cancer (Mao and El-Nagger, 1999; Sidransky, 1997b). Many of the molecular changes in smoking-related upper aerodigestive tract tumors, including lung and oropharyngeal cancers, are similar and commence during multistage pathogenesis (Mao and El-Nagger, 1999; Sidransky, 1997b). Changes include frequent losses at chromosome arms 3p, 9p, 17p, 5q, and 8p, aneuploidy, p53 gene mutations and expression abnormalities of the TGF-b signaling pathway, activation of telomerase, downregulation of RAR-a, and inactivation of the p16 gene (Brennan et al., 1995; Field et al., 1995; Izzo et al., 1998; Picard et al., 1999). Deregulation of the cell cycle is related to the degree of tobacco exposure (Davidson et al., 1996; Gallo et al., 1995).

Oropharyngeal tissues clearly have the capacity to metabolically activate tobacco smoke carcinogens and cause DNA damage (Badawi et al., 1996; Degawa et al., 1994; Kabat et al., 1991; Liu et al., 1993; Matthias et al., 1998). Among the highest levels of CYP1A1 have been reported in these tissues compared to others (Kabat et al., 1991). NAT1, but not NAT2, activity is present, and there is some evidence that CYP2C plays an important role in these tissues. Aromatic DNA and 4-ABP adducts have been detected in laryngeal tissues; these were higher in smokers than in nonsmokers (Flamini et al., 1998; Szyfter et al., 1994). Adduct levels in oral mucosa are correlated with biopsy levels indicating that mucosa can be used as a surrogate marker (Besarati et al., 2000; Jones et al., 1993).

Several studies have indicated an increased risk of oropharyngeal cancers in those who have a heritable trait demonstrated by genetic polymorphisms, although which markers play the greatest role is not yet known (Cullen et al., 1997; Helbock et al., 1998; Henning et al., 1999; LeVois, 1997; Morita et al.,1999; Rebbeck, 1997; Sturgis et al., 1999; Sumida et al., 1998; Trizna, 1995), and there is some evidence for a greater effect in persons with lower levels of smoking (Jourenkova et al., 1998). In one study, heritable traits in carcinogen metabolism increased the frequency of p53 mutations (Lazarus et al., 1998). When cultured lymphocytes are exposed to mutagens and resultant chromosomal breaks are counted, there is a greater mutagen sensitivity in cases, especially smokers (Cheng et al., 1998; Cloos et al., 1996; Schantz et al., 1997; Spitz et al., 1993). This trait also predicts the risk of secondary cancers in persons with oropharyngeal cancer (Spitz et al., 1994). There are some data to suggest that smoking might increase mutagen sensitivity, so there might be an inductive effect in this assay (Wang et al., 2000).

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The mutational spectrum of p53 in oropharyngeal cancers is similar to that in lung (Liloglou et al., 1997), although some studies disagree (Olshan et al., 1997). Mutations occur more commonly in smokers than nonsmokers (Brennan et al., 1995; Field et al., 1994; Lazarus et al., 1996b; Liloglou et al., 1997). In a study by Brennan and coworkers, the frequency of p53 mutations for tobacco and alcohol users was higher than for either of these exposures alone (Brennan et al., 1995).

The above information suggests that assessments for oropharyngeal and lung cancer risk related to the use of potential inhaled (i.e., tobacco smoke) PREPs are similar. It can be inferred that a suggested benefit for lung cancer would also benefit oropharyngeal cancer. However, these studies cannot imply that the quantitative benefits might be similar or even measurable in persons who continue to drink alcoholic beverages because of the synergistic effect of tobacco smoking and alcohol. The study of persons with oropharyngeal neoplasms provides some opportunities because of the accessibility of tissue and the occurrence of preneoplastic lesions.

BLADDER CANCER

More than 53,000 cases of bladder cancer will occur in the United States in the year 2000, and approximately 12,000 persons will eventually die from this disease (Greenlee et al., 2000). The male-female ratio is about 2.6:1. About 70% of bladder cancers are superficial at the time of presentation (i.e., confined to the mucosa or submucosa), while the rest are deeply invasive (Soloway and Perito, 1992). Most bladder cancers in this country are transitional cell carcinomas, arising from the normal transitional epithelium after multistage progression (hyperplasia, dysplasia, carcinoma in situ, superficial invasion). However, in some parts of the world such as Egypt, where schistosome infection of the bladder is common, squamous cell carcinomas are associated with chronic inflammation and squamous metaplastic changes. The chemicals most commonly implicated in bladder cancer in humans are aromatic amines, although other compounds such as PAHs might also play a role (Ross et al., 1996; Vineis and Pirastu, 1997).

Patients with cancer of the urinary bladder often present with metachronous tumors, appearing at different times and at different sites in the bladder. This observation has been attributed to a "field defect" in the bladder that allows the independent transformation of epithelial cells at a number of sites. Analyses of clonality indicate that a number of bladder tumors can arise from the uncontrolled spread of a single transformed clonal population (Sidransky et al., 1992). The molecular pathology and development of bladder cancer have been reviewed recently (Rao et al., 1999). As with other cancers, many molecular changes have been

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described in bladder cancers, including p53 gene mutations, p16 and retinoblastoma gene silencing, LOH at various chromosomal regions, aberrant methylation, and the presence of microsatellite alterations.

Many studies have shown a dose-response effect of smoking on bladder cancer risk in both men and women (Hartge et al., 1987; Slattery et al., 1988; Vineis et al., 1983, 1984). A recent report summarized a combined analysis of 11 case-control studies (Brennan et al., 2000). The authors found a linear increasing risk of bladder cancer with increasing duration of smoking, ranging from an OR of 1.96 after 20 years of smoking (95% CI=1.48, –2.61) to 5.57 after 60 years (95% CI=4.18, –7.44). A dose-response relationship was observed between number of cigarettes smoked per day and bladder cancer up to a limit of 15-20 cigarettes per day (OR=4.50, 95% CI=3.81, –5. 33), after which no increased risk was observed. An immediate decrease in risk of bladder cancer was observed for those who gave up smoking. This decrease amounted to more than 30% after 1-4 years, (OR=0.65; 95% CI=0. 53, –0.79) and was more than 60% after 25 years of cessation (OR=0.37; 95% CI=0.30, –0.45). However, even after 25 years, the decrease in risk did not reach the level of the never smokers (OR=0.20; 95% CI=0.17, –0.24). The proportion of bladder cancer cases attributable to ever smoking was 0.66 (95% CI=0.61, –0.70) for all men and 0.73 (95% CI=0.66, –0.79) for men younger than 60. These estimates are higher than previously calculated. Using a modeling approach to mortality data, the RR for 20 cigarettes per day for 20 years was 2.9 for men and women in England and Wales (Stevens and Moolgavkar, 1979). Another important bladder cancer risk factor is occupational exposure to aromatic amines (Ross et al., 1996). Several studies report an interactive effect for increasing risk in such workers who smoke (D'Avanzo et al., 1990; Vineis et al., 1984; Vineis and Martone, 1996). For bladder cancer, PREPs for individuals must be considered in the context of the workplace.

A recent study focused on the relationship of smoking and the progression of superficial cancers (Fleshner et al., 1999). Continued smokers experience worse disease-associated outcomes than patients who quit smoking. The authors recommended that smoking cessation be employed as a tertiary prevention strategy for patients with superficial cancers.

Cigarette type can influence bladder cancer risk. There is a higher risk with black tobacco than with blond tobacco (D'Avanzo et al., 1990; Vineis et al., 1984; Vineis and Martone, 1996). Filter-tip cigarettes pose a lower risk (Vineis et al., 1983, 1984), although this finding is not consistent (Burch et al., 1989). Importantly, only one study of which the committee is aware collected data for switching from nonfilter to filter cigarettes conflicts (Burch et al., 1989; Hartge et al., 1987). In this, there was a small benefit from switching, but this was more pronounced in persons who had switched more than 15 years prior to diagnosis, and there was no benefit

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when the data were examined for persons aged 21-64 years rather than 21-84 years (Anwar et al., 1993; Hartge et al., 1987). The data were adjusted for smoking duration and cigarettes per day, but compensation was not specifically queried. Moreover, although there was a decreased risk with filtered cigarettes, there was no difference between smokers who smoked only nonfiltered cigarettes and those who switched. Increasing depth of inhalation has been reported as a separate risk factor (Burch et al., 1989; Slattery et al., 1988).

Doll and Peto (1976) found that among male British physicians followed for 20 years since an initial survey of smoking habits, the annual age-adjusted rate of bladder cancer deaths was 11 per 100,000 among men who had quit smoking, compared to 9 among nonsmokers and 19 among men who smoked cigarettes exclusively. Benefits from giving up cigarette smoking were quantified in a large cohort study of Kaiser Permanente Medical Care Program members in the United States (Habel et al., 1998). Among current smokers, former smokers, and never smokers the standardized bladder cancer incidence ratios were 0.56, 0.68, and 1.04, respectively.

Chromosome 9 alterations and TP53 mutations are among the most frequent events in bladder cancer. Several studies have explored the relationships between epidemiological risk factors (especially smoking) and these genetic alterations. Elevated odds ratios were found for chromosome 9 alterations in smokers compared to nonsmokers (OR=4.2, 95% CI=1.02, –17.0) after controlling for age, sex, race, occupational history, and stage of disease. For chromosome 9 alterations, the OR was 3.6 for those smoking 20 cigarettes per day (Zhang et al., 1997). One study reported an association of smoking status and p53 mutations (Zhang et al., 1994), although others disagree (Spruck et al., 1993; Xu et al., 1997). For p53, a significant association between the number of cigarettes smoked per day and p53 protein nuclear overexpression was found (p=.02; Zhang et al., 1994). The odds ratios were 2.3 for those smoking one to two packs per day and 8.4 for those smoking more than two packs a day. In addition, a distinct mutational spectrum for the p53 tumor suppressor gene in bladder carcinomas was reported in patients with known exposures to cigarette smoke (Spruck et al., 1993; Xu et al., 1997).The P53 mutations in bladder cancers from workers with aromatic amine exposure have the same spectra (Djordjevic et al., 2000). These data support the hypothesis that certain carcinogens derived from cigarette smoking and occupation may induce p53 mutations, which in turn are involved in early steps of bladder carcinogenesis.

Aromatic amines are metabolically conjugated in the liver, excreted in the urine, and then metabolically activated in the bladder (Ross et al., 1996). DNA adducts have been described in the bladder epithelium of

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smokers and nonsmokers (Phillips and Hewer, 1993; Talaska et al., 1991). Although most of the DNA binding appears not to be smoking related, the levels of several specific adducts were found to be significantly elevated in DNA samples of current smokers, as opposed to never smokers or former smokers (five years' abstinence). Detection of DNA adducts in cells in voided urine may be a noninvasive method for following subjects at increased risk (Talaska et al., 1993).

Studies have shown that smoking-related bladder cancer risk and survival increases with genetic susceptibilities for carcinogen metabolism and detoxification, mostly for GSTM1 and NAT2 (Bell et al., 1992; Brockmoller et al., 1996, 1998; Katoh et al., 1995, 1998; Mommsen and Aagaard, 1986; Okkels et al., 1996, 1997; Rebbeck, 1997; Risch et al., 1995; Taylor et al., 1995). Persons with low activity of CYP3A were associated with higher p53 overexpression (Romkes et al., 1996). Only one study relates adduct levels to bladder cancer risk (Peluso et al., 1998), but because this was a case-control study, conclusions are limited. However, in a small group of patients *(N=45)*, adduct levels were not related to p53 mutations in tumors, but this was not a prospective study (Martone et al., 1998).

In summary, the bladder is a remote site from carcinogen entry into the body. Because urine is easily accessible, there are unique opportunities to study the effects of PREPs on bladder epithelial cells, especially in the context of genetic susceptibilities. However, although there are data showing that some cigarettes produce lesser risks if they are filtered, there also are data to indicate that changing to lower-tar cigarettes is not beneficial. If these data can be replicated, then it is suggested that the potential benefits of PREPs will be difficult to measure. In persons with occupational exposures that increase risk of bladder cancer, the potential benefit of a PREP may be minimized.

ENDOMETRIAL CANCER

Several studies have found that cigarette smoking reduces the risk of endometrial cancer. Although there are no prospective studies, case-control studies are fairly consistent. For example, in a study by Lesko and coworkers, 510 women with endometrial cancer were compared with 727 women with other types of cancers; the RR for current smokers was 0.7 (95% CI=0.5, 1.0), and a dose-response effect was noted (Lesko et al., 1985). The effect occurred predominantly in postmenopausal women. A study by Brinton and coworkers reported a RR of 0.6 (95% CI=0.4, –0.9) in postmenopausal women, where current smokers had the lowest risk and former smokers had an intermediate risk (Brinton et al., 1993). Other studies are in agreement (Austin et al., 1993; Levi et al., 1987; Parazzini et al.,

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1995). This reduced risk is thought to be related to an effect of smoking on circulating estrogens and androgens, which are also affected by other factors such as increased weight (Austin et al., 1993). In a study of postmenopausal women, smoking was associated with a decreased risk in women who did and did not use estrogens, although the effect was greater in the former (Franks et al., 1987). Smoking was found to modify the association of increased weight and endometrial cancer, where there was no increased risk in smokers (Lawrence et al., 1987; Parazzini et al., 1995). No studies have reported data for the effects by cigarette type.

ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke (ETS), also termed passive smoking or exposure to secondhand smoke, has been estimated to cause 2,600 to 7,400 lung cancer deaths per year among nonsmokers in the United States, according to a review of nine studies of lung cancer mortality (Repace and Lowrey, 1990). Animal models have established the carcinogenicity of ETS (Witschi, 1997a; Witschi et al., 1997b) Despite widespread workplace restrictions on smoking and public education about the dangers of secondhand smoke to adults and children, millions of people continue to be exposed to ETS. Data from NHANES III, a representative sample of the health of the U.S. population, show that 43% of children were living in a house with one or more smokers, and 37% of adult nonsmokers reported either having one or more smokers living in the same house or being exposed to tobacco smoke in the workplace (Pirkle et al., 1996). Also, 88% of nonsmokers tested positive for serum cotinine. Workplace bans on smoking have been highly effective in reducing ETS, but lesser workplace restrictions have been shown to be much less effective and many nonsmokers continue to be exposed to ETS on the job (Hammond, 1999). Any future strategies to reduce the harm from smoked tobacco products must therefore consider the potential effects on persons exposed to ETS.

Many studies have focused on indirect markers of ETS exposure, such as the presence in the home of a spouse who smokes or the number of years exposed to ETS. Direct measurements of ETS biomarkers (e.g., cotinine in urine, blood, or saliva) have also been widely implemented. Cotinine, the direct metabolic breakdown product of nicotine, with a biological half-life of 20 hours in urine, has been shown to meet all of the criteria for a highly sensitive and specific marker of ETS (Benowitz, 1999). Cotinine levels in children are highly correlated with adult cotinine levels (Crawford et al., 1994) and with the number of adult smokers in the household and the number of cigarettes smoked by the adults (Bono et al., 1996). ETS results in increased adduct levels and carcinogen metabolites in humans (Hecht et al., 1993; Maclure et al., 1989).

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The initial evidence linking ETS with increased risks of lung cancer came from studies in Japan and other countries in which smoking among women is rare. The conclusion that ETS is a cause of lung cancer has been opined by several reviewers and persons conducting meta-analysis (Brownson et al., 1997, 1998). In many studies, the risk of lung cancer among nonsmoking women was evaluated in relation to the presence or absence of a husband who smokes. For example, Fontham et. al. (1991) reported an OR of 1.5 for the association of lung cancer among lifetime nonsmoking women who lived with a spouse who smoked. In that study, there was no significant association with childhood ETS exposures. On the other hand, (Janerich et al., 1990) found no association with ETS exposure in adulthood, but an OR of 2.0 was found for high levels of household tobacco smoke in childhood. (Stockwell et al., 1992) compared 210 women with lung cancer who were lifetime nonsmokers with 301 controls assembled by random-digit dialing. The maximum effect detected was an OR of 2.4 (95% CI=1.1, –5.3) for more than 40 smoke-years of exposure (with p=0.004 for trend). Childhood ETS exposures yielded ORs and trends very similar to those associated with adult ETS exposures. Numerous other studies support the conclusion that ETS exposure increases lung cancer risk (Brownson et al., 1992a, 1998; Darby and Pike, 1988; Hirayama, 1981; Stockwell et al., 1992; Tweedie and Mengersen, 1992).

A recent review by Lee of 44 ETS studies revealed that the RR of lung cancer among nonsmokers is between 1.16 and 1.24 for women having a husband who smokes, relative to nonsmokers whose husbands are also nonsmokers (Lee et al., 1998). Furthermore, this report assessed the impact of a number of potential covariates on the magnitude of the ETS association. This is a critical question when the RR is weak (i.e., <1.5) because the impact of statistical confounding can obscure the true level of risk in such situations. Although Lee concluded that it was impossible to determine that ETS exposure is linked to increased lung cancer risk because of potential biases, his own estimates examining the available literature in many different ways still lead to the conclusion of an association. For example, providing a summary estimate where dose-response data are available, thereby reducing some biases, a risk estimate of 1.24 (95% CI=1.15, 1.35) was found. In that review, Lee reported evidence for confounding by a number of factors: (1) continent—with RRs in European studies exceeding those in Asia and the United States; (2) publication date—with earlier publications (1981-1989) tending to report higher risks than more recent publications; (3) histology—with RRs in studies that confirmed primary lung tumors tending to be greater than those using unconfirmed cases; (4) dose-response data—with studies providing such

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data more likely to detect significant effects of ETS than those that did not provide such data; (5) type of control—with RRs from studies using disease controls tending to be higher than studies using healthy controls; (6) assessment of confounders, which tends to reduce RRs compared to studies that did not adjust for confounders; and (7) age matching, which tends to produce lower risk estimates than unmatched studies. Additionally, Lee noted that many studies of ETS did not match on marital status, most only adjusted for one or two confounders (leaving a high potential for uncontrolled confounding), and most considered only a single source of ETS rather than taking multiple sources into account. Still another factor that should be mentioned is the method of interviewing proxies when a case is deceased, which tends to introduce information bias or at the least nondifferential errors.

Considering other sources of bias, one study examined recall bias and misclassification of smoking status by examining smoking histories reported by spouses and concluded that there was no recall bias (Nyberg et al., 1998). Examining studies that use cotinine to classify ETS exposures, Tweedie and Mengersen used a meta-analysis approach and concluded that ETS risk was 1.17 (95% CI=1.06, 1.28; Tweedie and Mengersen, 1992).

Epidemiological studies of ETS risks that incorporate cotinine measurements are able to validate the classification of subjects according to self-reported levels of ETS. For studies lacking this biomarker, a major issue in estimating the cancer risks associated with ETS is the potential misclassification of former smokers as nonsmokers, which would tend to inflate the true risk ratios. A study of two large cohorts in Sweden, one involving twins and the other of randomly surveyed adults in the population, estimated that about 5% of former smokers were misclassified as never smokers, with roughly equal proportions in men and women. The RR for lung cancer among misclassified men was 1.9 (95% CI=0.5, –9.1), indicating no statistical association, compared to 4.5 for correctly classified former smokers and 13.3 for current smokers (Nyberg et al., 1997). The authors of that study concluded that misclassification occurs mainly among very light smokers and long-term ex-smokers. Future studies of ETS should use cotinine measurements to estimate the impacts of such classification errors.

It was not easy to show that ETS affects biomarkers of cancer risk (Scherer et al., 1992). However, improved methodologies now show that ETS-exposed persons have elevated levels of TSNA metabolites in their urine (Hecht, 1999b). Other studies have reported an increase of aryl amine-related adducts (Maclure et al., 1989).

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CIGAR SMOKING

Cigar smoking has increased tremendously in the United States in recent years, with sales increasing as much as 50% between 1993 and 1998 according to a recent commentary by the Surgeon General (Satcher, 1999). In that report, Dr. David Satcher notes that the popularity of cigar smoking has been especially pronounced among well-educated people. During this same period, cigarette sales fell by 3%, and taxes on cigarettes, but not cigars, were increased nationwide. Regular cigar smoking, however, is not a safe substitute for cigarette smoking. Cigar smoking is associated with increased risks of oral, esophageal, laryngeal, and lung cancers and with coronary heart disease and chronic obstructive pulmonary disease. Accordingly, the Surgeon General warned that cigars should not be viewed by the public as a safe and lower-cost alternative to cigarette smoking and called for warning labels, increased public awareness, and youth education efforts about the risks of cigars.

One of the limitations in studying the effects of cigar smoking on lung cancer risk is the relative rarity of cigar smokers compared to cigarette smokers in the population, and the fact that some smokers tend to mix tobacco products presents further challenges to disentangling potential cigar-related effects from cigarette-related effects. Many case-control studies have not had sufficient numbers of cigar smokers to analyze the risks.

Boffeta et al. (1999) Pooled data from seven large case-control studies in Germany, Italy, and Sweden. All except one of the studies used population-based controls in comparison to lung cancer cases, and proxies provided interview data for deceased cases. In Europe, small cigars (cigarillos) are popular, and these were analyzed separately from large cigars. Relative to lifelong nonsmokers, age- and study-adjusted analyses revealed that the risk of lung cancer was elevated among people who smoked only large cigars (OR=5.6; 95% CI=2.9, 10.6), and among those who smoked only cigarillos (OR=12.7; 95% CI=6.9, –23.7). The OR was 14.9 (95% CI=12.3, –18.1) among exclusive cigarette smokers and 12.7 (95% CI=10.3, –15.6) among smokers of mixed tobacco products. The dose-response relationship between cigar and cigarillo use and lung cancer risk was strong, whether analyzed by years of use (P=.0003 for trend), grams of tobacco per day (P=.01), or age at smoking initiation (P=.002).

The above risk ratios have been described independently and consistently in several other European studies, among them the Seven Areas Study in which (Lubin et al., 1984b) reported an OR of 5.6 for large cigars and 11.6 for cigarettes. Boffeta et al. (1999) suggested that the lower OR for cigars compared to cigarettes is not due to lower carcinogenic potential, but rather to lower cumulative lifelong consumption and later age at smoking initiation of cigars.

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In comparison, a review of 14 American studies (Shanks and Burns, 1998) documented cigar-associated lung cancer risks as lower than those of cigarette users, but the risk estimates for cigars were only modestly elevated. Reasons for the risk-level discrepancies in European and American case-control studies of lung cancer and cigar smoking may include several factors: (1) Americans overall prefer large types of cigars, whereas Europeans favor cigarillos; (2) differences in the constituents of the products; (3) differences in inhalation and other behavioral parameters of smoking; (4) consistent misclassification of cigar smokers in American studies; (5) differences in the proportions of histological types of lung tumors; and (6) differences in age at taking up smoking. Clearly, more research is needed to resolve these issues.

Several large, prospective studies of cigar smokers have documented significantly increased risks of lung cancer during long periods of follow-up compared to nonusers of tobacco. For example, (Iribarren et al., 1999) followed a cohort of nearly 18,000 men enrolled in the Kaiser Permanente Health Plan, among whom 1,546 cigar smokers were studied for several decades. The RR for lung cancer, adjusted for age and other covariates, was 2.14 (95% CI=1.12, –4.11). Shapiro and coworkers (2000) studied the risk of lung cancer in cigar smokers who never used cigarettes. These individuals had an RR of 5.1 (95% CI=4.0, 6.6).

In addition to the increased risk of lung cancer among cigar smokers in the Kaiser Permanente study Iribarren et al. (1999), a synergistic effect of cigars and alcohol consumption was observed for oropharyngeal cancer, in which the RR for this cancer due to cigars and alcohol combined was much greater than for the independent effects of each substance alone.

Relatively few studies have examined the association of cigar smoking with bladder cancer. In their 20-year mortality follow-up study of 34,440 male British physicians who answered a questionnaire about smoking habits, Doll and Peto (1976) documented a significantly higher rate of bladder cancer deaths among men who smoked only pipes and cigars (14 per 100,000, age standardized) than among nonsmokers (9 per 100,000), compared to 19 per 100,000 among men who smoked only cigarettes. In the CPS-II cohort of male cigar smokers who never smoked cigarettes Shapiro also found an association between cigar smoking and bladder cancer (Shapiro et al., 2000).

SMOKELESS TOBACCO PRODUCTS

Smokeless tobacco is consumed in a variety of different ways in various cultures around the world. Examples of smokeless tobacco products include chewing tobacco, dry snuff (used in the nasal cavity), wet snuff (a moist wad of tobacco, usually placed between the lips and gums), and

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nass (a mixture of tobacco, lime, ash, and cotton oil), with many local variations in Asia, the Middle East, and Africa. Large geographical differences in the prevalence of smokeless tobacco consumption are evident, with particularly high consumption in Scandinavia (where a popular form of snuff is known as snus), India, Southeast Asia, Sudan, and parts of the United States. Smokeless tobacco products from these different regions are produced differently and have different levels of carcinogens (Gupta et al., 1996; Hoffmann and Djordjevic, 1997). The popularity of smokeless tobacco increased sharply in the 1980s among young men in the United States, particularly among athletes and high school or college students (Christen, 1980). Data from the 1986-1987 National Survey of Oral Health in U.S. School Children examined relationships between smokeless tobacco, alcohol, and the presence of oral soft-tissue lesions (Tomar et al., 1997). In the study sample of more than 17,000 children between the ages of 12 and 17, 1.5% had mouth lesions from smokeless tobacco. Factors associated with these lesions included male gender, white race, current snuff use, and current chewing tobacco use, with snuff having the highest OR (18.4). There was little evidence for risk modification by the use of alcohol.

Persistent use of snuff in the oral cavity causes a characteristic lesion, "snuff pouch keratosis," with a prevalence of 1.6 per 1,000 adults in a population-based study of 23,616 white American adults over age 35 (Bouquot, 1986). Almost 7% of the leukoplakias examined in that study were either carcinomas or severely dysplastic lesions. Early lesions can commonly be found in adolescent snuff users (Tomar et al., 1997). In India, chewing tobacco is associated with erythroplakia (Hashibe et al., 2000), and oral dysplasia (Kulasegaram et al., 1995). Stopping the use of smokeless tobacco results in the disappearance of oral leukoplakia (Martin et al., 1999).

Smokeless tobacco products are associated with cancers of the head and neck, depending on the type of tobacco used (Brinton et al., 1984; Jacob III et al., 1999; Rao et al., 1994; Winn et al., 1981; Winn, 1997; Wynder et al.,1957), although not all studies are supportive of this conclusion. A large number of studies in India, including cohort, case-control, and intervention studies, support the association between oral cancer and smokeless tobacco, and these studies are consistent, strong, coherent, and temporally plausible (Idris et al., 1998; Nandakumar et al., 1990; Sankaranarayanan et al., 1990; Wasnik et al.,1998). Idris et al., compared oral cancer risks in the Sudan, where there is an extremely high consumption of smokeless tobacco and found that users of toombak had an extremely high RR for such tumors (Idris et al., 1998). Research from other parts of the world is far less complete, so it is not known at this point whether ethnic or cultural differences in susceptibility explain any of the

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geographic variability. Studies conducted in the United States are more conflicting. In some of these studies it is difficult to separate the effects of chewing tobacco from alcohol drinking because of the few nondrinkers. In the United States, Winn and coworkers reported a 4.2-fold increased risk (95% CI=2.6, 6.7) in southern white women who exclusively use snuff (Winn et al., 1981). In contrast, an analysis of the relationship between smokeless tobacco and cancer of the oral cavity in the National Mortality Followback Study did not detect increased risk (Sterling et al., 1992). In spite of the conflicting U.S. data, it can be concluded that snuff use in the United States also increases the risk of oropharyngeal cancers.

In Sweden, there is a very high rate of Swedish snuff (snus) use. But, the use of snus in Sweden has generally not been associated with oral cavity cancer (Idris et al., 1998; Kresty et al., 1996; Lewin et al., 1998; Nilsson, 1998; Schildt et al., 1998). Snus is not fermented and so has a much lower level of *N*-nitrosamines (Nilsson, 1998) and has a lower genotoxic potential (Jansson et al., 1991), which might be related to the lack of increased risk.

The risks of other types of head and neck cancers from smokeless tobacco products have not been studied as extensively. Evidence for an elevated risk of nasal cancer in association with the use of snuff was reported in a case control study in North Carolina and Virginia (Brinton et al., 1984). Chewing tobacco was not associated with salivary gland cancer in a recent study of cases and controls in the United States (Muscat and Wynder, 1998).

Some authors have concluded that there is no association between smokeless tobacco and bladder cancer risk, but few studies have examined this association and the results are inconsistent (Burch et al., 1989). One of the few studies to report an increased risk of bladder cancer among snuff users was a very small study of 76 female cases and 254 controls, among whom 3 cases and 1 control reported snuff use (Kabat et al., 1986). In a larger case-control study of 332 white men with bladder cancer and 686 population-based controls, Slattery et al. (1988) reported an increased but statistically nonsignificant risk among nonsmokers who used snuff or chewing tobacco. In another population-based study, Burch et al. (1989) found no association of bladder cancer with chewing tobacco or snuff among men or women, but neither of these studies incorporated any exposure biomarkers and neither was specifically designed to test the hypothesis of smokeless tobacco risk.

The p53 gene is commonly mutated in cancers associated with smokeless tobacco products, and while some differences in the spectra have been reported for different regions of the world, no hotspots or patterns have been consistently shown compared to oral cavity cancers related to

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smoking (Ibrahim et al., 1999; Kannan, 1999; Lazarus et al., 1996 a, b; Saranath et al., 1999; Xu et al., 1998).

A major concern of health professionals is the presence of carcinogenic *N*-nitroso compounds in smokeless tobacco, which have been demonstrated to cause cancers of the mouth and lip, nasal cavity, esophagus, stomach, and lungs in laboratory animals. Hemoglobin adducts to these carcinogens are measurable in the blood of smokeless tobacco users (Carmella, et al., 1990) and, thus, may be useful biomarkers for measuring exposure levels among users. Urinary metabolites of TSNAs have been measured in persons using smokeless tobacco products, and higher levels were associated with oral leukoplakia, indicating greater use of the products (Kresty et al., 1996). Also, levels in snuff users were higher than those of chewing tobacco users. Hemoglobin adduct levels have been found to be higher in snuff users than in nonusers (Carmella et al., 1990). However, such markers have been used only rarely in epidemiological studies to date and have not been used frequently in studies of human cancer risk. Users of smokeless tobacco products have higher rates of endogenous nitrosation, as well (Nair et al., 1996). Other exposures that occur with the use of smokeless tobacco products include compounds that cause oxidative DNA damage (e.g., polyphenols), where the amount may be related to pH (Nair et al., 1996). Genetic susceptibilities, namely GSTM1 null, is associated with an increased risk of oral leukoplakia in India (Nair et al., 1999).

STUDIES OF NICOTINE MUTAGENICITY AND CARCINOGENICITY

Several studies have been conducted to determine if nicotine is genotoxic. Almost all studies that could be identified failed to find increased genotoxicity (Doolittle et al., 1991, 1995; Mizusaki et al., 1977; Trivedi et al., 1990, 1993; Yim and Hee, 1995), although there are conflicting data about the potential mutagenic activity of cotinine (Yim and Hee, 1995; Doolittle et al., 1995). Urine from rats exposed to nicotine was not mutagenic (Doolittle et al., 1991). The effects of coculture of nicotine and known genotoxic substances indicated an increased rate of mutations for some compounds and a decrease for others (Yim and Hee, 1995). Experimental animal studies using nicotine alone have not found that nicotine is carcinogenic to the exposed animal (Martin et al., 1979; Schuller et al., 1995) or to offspring of animals treated with nicotine (Martin et al., 1979). However, in experimental animals, nicotine can increase the frequency of tumors induced by other agents such as 7,12-dimethylbenz[*a*]anthracene (Chen and Squier, 1990), *N*-nitrosamines (Chen et al, 1994; Gurkalo and

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Volfson, 1982), hyperoxemia (Schuller et al., 1995), and *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (LaVoie et al., 1985), although there was no effect for other *N*-nitrosamines (Habs and Schmahl, 1984) and an antitumor effect in some cases (Zeller and Berger, 1989). Nicotine also is reported to reduce apoptosis in normal and transformed cells (Wright et al., 1993), but not in lung cancer cell lines (Maneckjee and Minna, 1994). Nicotine was shown not to induce growth of lung cancer cell lines (Pratesi et al., 1996). Long-term studies of persons treated with nicotine replacement therapy are not yet possible because of the short time during which such products have been available. Even though it is possible that nicotine might increase tumor occurrence due to other agents (e.g., have a promotional effect), the risk from co-treatment with nicotine replacement therapy in persons who continue to smoke is likely to be small compared to continued use of tobacco products at a higher rate. The amount of nicotine replaced is less than that available from cigarettes, and it does not have the spectrum of carcinogens present in tobacco products. Human studies have shown that the use of nicotine replacement products does not result in the formation of TSNAs such as NNK (Hecht et al., 1999), although no human liver microsomes in vitro increase the formation of NNK precursors (Hecht et al., 2000).

CONCLUSIONS

There are sufficient laboratory and human data to suggest that harm reduction might be an achievable goal for persons who cannot stop smoking, because there is evidence of decreasing risk for persons who quit smoking, and there are differences in risk for persons who use different tobacco products and differ in the way they use them. Clearly, quitting smoking is the most effective method of reducing cancer risk, and the cancer risk to former smokers is the lowest-level risk that might occur from the use of any PREP. Importantly, it must be recognized that the use of any PREP will likely increase the risk of cancer at some level as long as there is exposure to tobacco carcinogens, in contrast to quitting, which stops exposure to all tobacco constituents. Nonetheless, reduction of exposures to tobacco smoke and tobacco products to the lowest possible levels may provide some benefit to individual users and to the general population. However, data are insufficient to conclude how much reduction in exposure would yield a measurable benefit for whom. Currently, methods that would reduce exposure to tobacco constituents to the greatest extent would likely provide the greatest benefit, but this remains to be proven.

A thoughtful approach to the assessment of PREPs and cancer risk requires consideration of many factors obtained from laboratory and hu-

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man studies. Data are sufficient to conclude that a dose-response relationship exists for the use of tobacco products and cancer risk. In laboratory animals, the shape of the dose-response curves differs for different tobacco constituents, so that understanding the relationship to tobacco smoke as a complex mixture is difficult. In humans, there are sufficient data for different cancer types and tobacco products, although more data exist for tobacco smoking and lung cancer risk. These studies suggest a curvilinear response that increases most around 5 cigarettes per day and plateaus at 20 cigarettes per day. However, these studies do not consider actual smoking behavior and exposure, so the shape of this curve is not certain. There is some evidence to indicate that when internal exposure is considered through biomarkers, the shape of this curve follows a quadratic equation. Thus, data are insufficient to conclude a greater or lesser effect for a PREP at particular levels of smoking history. There are sufficient data to suggest that different populations have different dose-response relationships depending on gender, race, age, and ethnicity, although the actual risk levels have not been sufficiently defined to draw definitive conclusions about risks among groups. Based on these type of data and possible modifiers of cancer risk (e.g., genetic susceptibilities, diet, lifestyle, occupation), it should be considered that PREPs might benefit people differently or not at all.

There is no evidence of a threshold for tobacco smoking and cancer risk. This conclusion is consistent with the knowledge that there are many carcinogens in tobacco smoke, the aggregate would work to increase risk at any level. Modeling for low-dose exposures indicates an increased risk with less than one cigarette per day. Thus, persons who initiate smoking with PREPs that contain tobacco would increase their risk for cancer, and there is unlikely to be a "safe" cigarette. Former smokers who resume smoking with such products would increase their risk further.

It is possible to conceptually extrapolate the regression of risk using PREPs and assume that the use of such products would bring a smoker to a risk equal to some lower level of lifetime exposure. However, it must be acknowledged that there are insufficient data to validate this assumption or indicate that a decrease in risk would be measurable for all or some smokers. There are insufficient data to indicate what the shape of the curve for regression of risk would look like.

Data are sufficient to conclude, with some caveats, that filtered cigarettes pose a lower risk than nonfilter cigarettes for lung cancer and possibly other cancers. The caveats are that this only occurs in persons who do not substantially increase the number of cigarettes they smoke per day or otherwise compensate for their smoking behavior due to lower delivered levels of nicotine. Also, these studies may be confounded by diet, lifestyle, or other characteristics of people who choose filtered cigarettes.

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The available data are suggestive, but not sufficient, to conclude that smokers of so-called low-tar cigarettes have a lower cancer risk compared to those who smoke higher tar cigarettes, with the same caveats as for filter smoking studies. However, there are insufficient data to assess the differences in risk for "ultralow-", low- and high-tar cigarettes that are filtered. This is because these cigarettes became available at a later date, so there was not enough latency in the general population to assess them until recently. There are insufficient data to adequately consider how risk changes from switching types of cigarettes.

This chapter has not reviewed potential cancer risks due to fibers released from cigarette filters or tobacco additives, because it is thought that the risk from these exposures is substantially less than the risk from tobacco smoke constituents. However, there are no existing data to prove this assumption. Importantly, as PREPs are developed that substantially reduce exposure to tobacco constituents, the role of fibers and additives in carcinogenesis might become more important. Thus, fiber and additive exposure should be considered when assessing PREPs.

There are some experimental models (e.g., in vitro cell culture and laboratory animal) that are useful for the assessment of PREPs. Although there are many reasonable models for assessing individual tobacco smoke products, better models are needed to assess exposures to complex mixtures. Such studies are not sufficient alone to support claims of potential harm reduction, and no claim of potential harm reduction should be allowed without adequate human clinical and epidemiological studies. These studies, however, are very important for (1) determining those products that are not likely to result in measurable harm reduction (e.g., if a product results in exposures that increase genotoxicity, there would be less enthusiasm for it, while the converse indicates only that further testing should be considered in humans) and so should not be tested in a human clinical study in anticipation and should not be introduced into the marketplace; (2) identifying unforeseen reactions (e.g., if a product reduces exposure but does not decrease tumors then there might be some constituent or combination of constituents that are either new or more important than those targeted for reduction in the product); (3) providing supportive evidence for the use of a particular bioassay in humans (e.g., if the same biomarker predicts cancer risk in experimental animals) and; (4) assessing the dose-response and the shape of the regression of risk for the PREP, although the data should be considered qualitative or semi-quantitative and cannot be extrapolated directly to human smoking risk. Both in vitro cell culture and experimental animal studies should be used in assessing PREPs, where both can assess genotoxic and nongenotoxic end points, and chronic animal bioassays are needed to assess the end

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point of cancer risk. It is beyond the scope of this committee to recommend a specific panel of assays, but such a panel needs to be developed. Also, these studies should assess changes both for specific carcinogens and for complex mixtures in which the latter should be mandatory.

There is sufficient evidence to conclude that human experimental studies and short-term clinical studies can indicate the harmful effects of tobacco products. Thus, such studies can be used to assess harm reduction. Through the use of biomarkers and surrogate indicators of cancer risk these studies can evaluate the manipulation of carcinogens and nicotine to reduce exposures and how these changes might affect smoking behavior, metabolic activation, enzymatic induction, conjugation, excretion, biologically effective doses (or their validated surrogates), and biomarkers of potential harm. Separately, these studies can assess differences in risk and provide evidence for modifying effects by genetic susceptibility, diet, lifestyle, occupation, and so forth. However, at the current time, there is no single biomarker or panel of biomarkers that can be considered adequate indicators of cancer risk by themselves because most have not been sufficiently validated. New technologies are offering new opportunities for biomarkers. Thus, experts will be needed to devise a panel of biomarkers that reflect different exposures, biologically effective doses, and pathways for potential harm.

It is clearly possible to assess the effects of PREPs on cancer as the ultimate outcome, and only such studies can provide definitive evidence for the success of a product. However, the long latency for cancer renders these studies infeasible for making such claims today or in the near future. Preneoplastic lesions or the identification of harmful effects in single cells might be used as indicators of the carcinogenetic pathway, but the technology to identify these in the general population or in large epidemiological studies is not yet available. In these studies, the characterization of smoking history and behavior is well validated for recent exposures but problematic for assessing lifetime exposure. Also, self-reported smoking history is insufficient to adequately assess risk in the context of PREP assessments, so biomarkers also are needed to assess exposure, biologically effective dose, and potential harm.

Currently, the best means of assessing PREPs and cancer risk is to focus on lung cancer because this is the most common cancer and so will provide studies with the greatest statistical power. However, data are sufficient to conclude that a risk exists that the widespread use of PREPs will shift the burden of cancer in the population from one type of cancer to another or from cancer to a different disease. Thus, a particular cancer type cannot be the sole indicator for the success of a PREP, and other cancers, diseases, and overall mortality must be evaluated.

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There has been sufficient study of nicotine in the laboratory to conclude that it is unlikely to be a cancer-causing agent, although there are no studies of long-term human exposure. The consideration of nicotine as a carcinogenic agent is trivial compared to the risk from other tobacco constituents.

Smokeless tobacco products are associated with oral cavity cancers, and a dose-response relationship exists. However, the overall risk is lower than for cigarette smoking, and some products such as Swedish snus may have no increased risk. It may be considered that such products could be used as a PREP for persons addicted to nicotine, but these products must undergo testing as PREPs using the guidelines and research agenda contained herein.

Studying of the effects of PREPs on cancer risk from ETS is problematic because of the difficulties in measuring reductions in exposure. Also, while there is clearly an increased risk of lung cancer from ETS, the determination of changes in risk from the use of PREPs will require studies of large numbers of people, and smoking currently is prohibited in many places where ETS might have occurred.

RESEARCH AGENDA

Use of Laboratory Studies to Predict Effects of Potential Reduced-Exposure Products

Both in vitro cell culture and in vivo experimental animal studies are needed to identify the possible benefits of a PREP. It is beyond the scope of this report to recommend specific assays or animal models, but it is clear that no single model is sufficiently validated to be solely relied upon. Given that there is insufficient confidence in extrapolating results from laboratory studies to human risk, such studies should not be used alone to support a claim of possible or potential harm reduction. However, these studies are considered important because they can (1) reduce the enthusiasm for a product if there is an increased amount of harm compared to current marketed products; (2) can be used to identify mechanisms of carcinogenesis and how the PREP affects these mechanisms; and (3) identify unanticipated affects such as exposures to new or different carcinogens, different carcinogenic effects, or other unanticipated toxic effects.

The design of experimental studies that assess PREPs should be done in two ways. The first would focus on exposure to the components of the PREP as the sole exposure (i.e., tar fraction or a mixture of carcinogens that simulates yields from the product), preferably as a complex mixture. The main value of these studies would be not to identify the potential

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benefits of the product, but to assess its impact on persons who initiate smoking with this product and then stay with it. The second experimental design would be to use initial exposures that simulate those from reference cigarettes at different levels and times, and then change the exposure to simulate the PREP at different levels and times. This would better mimic the human scenario where persons who cannot quit will switch to such a product. These models would provide supportive evidence to identify the range of exposure situations that might provide the most benefits and whether some circumstances might result in absolutely no benefit.

There has been difficulty in developing animal models of tobacco-related cancers because animals breathe smoke differently than humans. Thus, additional efforts are needed in developing such models. Separately, genetically altered animals and cell lines can be used in the context of harm reduction in order to elucidate effects on different carcinogenic pathways.

It is important that laboratory experimental studies incorporate biomarkers along the range from exposure to potential harm and that molecular analysis of tumors be undertaken to provide data that would prioritize biomarker use in humans.

Development and Validation of Biomarkers for Cancer Risk Assessment

The following research agenda is intended to provide sufficient data to develop methods that can assess PREPs. It does not describe the methods for assessing a PREP.

Currently, the best biomarkers assess internal exposure, such as the use of exhaled carbon monoxide. There has been significant progress in developing biomarkers that measure the biologically effective dose, but these generally are not sufficiently sensitive or are too labor intensive to be used in large epidemiological studies. Thus, there are some biomarkers that can be used in smaller studies for assessing PREPs, such as the measurement of carcinogen-DNA adducts, where there are some data to support a relationship to cancer risk. There is less enthusiasm for markers where less specificity exists (i.e., chromosomal aberrations and sister chromatid exchanges).

Great emphasis is needed on developing more sensitive technologies for biomarkers of harm in normal-appearing tissues. For example, mutational load studies measuring p53 or K-ras mutations in normal tissues, LOH in sputum and urine cells, and so forth, have the potential to identify effects very early in the carcinogenic process. These biomarkers would have more importance than biomarkers that reflect mostly exposure.

It is clear that human studies and surrogate biomarkers will have the

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greatest applicability for assessing PREPs. However, although there are some data to show that the use of surrogate biomarkers can reflect the effects in a target organ, a need clearly exists for more studies of both existing and new biomarkers.

Biomarkers are needed that will assess the effects of specific carcinogens as well as complex mixtures. They also should consider exposures from particulate and gaseous phases, as well as oxidative damage.

Many new technologies are being used in studies of carcinogenesis and cancer diagnosis, such as proteomics and expression arrays. These technologies have the potential to provide important information about the use of a PREP and how the product would affect the carcinogenic process. Currently, the use of these technologies in cancer risk studies is embryonic, but such studies should begin for PREPs at the present time, notwithstanding the significant bioinformatic and data interpretation issues. If, for example, it is shown that enzyme induction in human lymphocytes is not substantially different between product types for key genetic pathways, then there would be less enthusiasm for the PREP.

Current and new biomarkers should be tested in different populations in order to understand the range of results and how they relate to different populations. It is important to understand the utility of biomarkers in relation to conventional tobacco products in order to evaluate difference among PREPs. For example, dose-response relationships can be established in ETS-exposed persons, former smokers, low- and high-level smokers, women and men, and different races and ethnic groups. Many biomarker studies classify persons only as current, former, and never smokers. However, this classification is inadequate to provide supporting evidence for use of these biomarkers in the assessment for PREPs. When a dose-response relationship does not exist, modifying factors have to be identified, and until then, the enthusiasm for a particular biomarker is lessened because its laboratory validity would be questioned.

Determine Whether There Are Susceptible Subpopulations That Might Benefit More or Less from a Potential Reduced-Exposure Product

Data are sufficient to conclude that certain subpopulations are susceptible to tobacco-related harm, although there are insufficient data to conclude that any specific group carries different risks based on genetic susceptibilities, race, gender, et cetera. Human studies must consider different subpopulations and assess whether some who would benefit differently from a product.

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Determine How Potential Reduced-Exposure Products Affect Human Exposure and Harm in Short-Term Human Clinical and Epidemiological Studies

Clinical trials should be used. These studies would focus on biomarkers of exposure, biologically effective dose, and potential harm. Studies should be designed for smokers willing to try PREPs continuously for a specified period (e.g., six months). Accurate assessment of smoking behavior, such as cigarettes per day and smoking topography, and effects on biomarkers should be determined. Baseline specimens should be collected (sputum, buccal swabs, blood, and urine and, for some studies, possibly bronchoalveolar lavage or biopsies of internal organs) and then are followed frequently throughout the study. The choice of the biomarkers would depend on the criteria described in this report. The study of smoking behavior alone is insufficient because persons who increase use of a PREP might still have reduced exposure and harm. Biomarkers of internal exposure, biologically effective dose, and harm should be used.

In the context of harm reduction, developing fluorescent bronchoscopic techniques, coupled with molecular analysis, has the potential to identify smokers who have already sustained molecular damage and, depending on the type of damage, to indicate who might benefit most from harm reduction strategies.

The design of studies should allow for sufficient time to acclimate the smoker to the new PREP.

Determine How Potential Reduced-Exposure Products Affect Human Exposure and Harm in Long-term Epidemiological Studies

These studies are the most problematic in early assessments of PREPs, because the latency period for cancers is too long to provide the needed results. Also, the technology for PREPs will likely change quickly, and an individual may use multiple types over a period of time. However, such studies should be started immediately in order to provide the definitive proof of success. Specifically, the emphasis in long-term epidemiological research should be on prospective cohort studies. Either existing cohorts should be modified, or new cohorts should be established. While it is recognized that such studies are expensive, additional costs will have to be added. These studies must follow subjects closely to document smoking behavior, use of all types of tobacco, modifying factors, and so forth. Smoking topography after switching brands should be assessed in at least a subset of individuals. Specimens should be collected at regular intervals, including buccal swabs, sputum, blood, and urine.

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Given the long time for such cohorts to mature, emphasis might also be placed on establishing a complementary cohort of former smokers, because these persons will have the highest risk of recurrence in shorter periods of time. Biomarkers used in the former-smoker cohort that are found to be predictive of risk could then be used sooner in short-term epidemiological studies of PREPs.

Another group of subjects that might provide useful information about PREPs would be persons with surgically resectable cancers who will remain at high risk for developing new primary tumors or experience recurrence. These products might reduce the risk of either, so cohorts should be established to study these persons. Such studies would also provide valuable data for the worthiness of biomarkers.

SPECIAL ISSUES IN STUDY DESIGNS

Harm Reduction Compared to What Exposures?

Depending on study design, different exposure comparisons can be made, some of which are more applicable than others. For the development of biomarkers that are tested first in the laboratory setting (in vitro and in vivo animal studies), authentically synthesized tobacco carcinogens, or components of a reference cigarette (i.e., the tar fraction or cigarette smoke condensate from a Kentucky reference cigarette), would be preferable. Levels of exposure should be quantitated accurately so that the results can be interpreted in relation to the range of human exposures.

Experimental human studies in which the product is initially tested would optimally be compared to both reference cigarettes and separately to the smokers' usual cigarettes, where a range of smokers and cigarette types are used (i.e., low- and high-tar contents, menthol). The decreasing use of nonfilter cigarettes would make comparison to nonfilter cigarettes a low-priority consideration.

The comparison group for short- and long-term epidemiological studies would have to be usual cigarettes, because it is not feasible to ask persons to smoke reference cigarettes, which are not designed for appeal. Thus, these studies must carefully characterize smoking behavior, and a range of cigarette types and smoking behaviors must be included.

Harm Reduction Compared to What Risks?

It is clear that any PREP will likely bring some risk of cancer to the user. Comparison groups could be either never smokers, former, smokers or continuous smokers. Preferably, a PREP should reduce risk for the

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individual compared to the risk for that individual from the usual smoking behavior before switching to the PREP.

Is There a Threshold for Cancer Risk and Does It Matter?

It is important to consider whether a threshold exists for risk of cancer from tobacco products. This is important for new smokers who might initiate smoking with a PREP. It is possible that the delivered exposures from a PREP would be below the threshold, or at least this should be the goal of such a product. It is recognized that ETS data would suggest that the threshold, if any, is very low.

Do All New Products Need to Be Tested or Only Some That Would Serve as Indicators for Similar Products?

It would be efficient to have data that are representative of a class or type of product, where some screening tests could be used to ensure that a potential product fits within that class or type. However, data are needed to validate the assumption that representative products actually are representative.

Which Carcinogens Should Be Prioritized for Study, Given the Large Number Delivered By Tobacco Products?

While there is a need to study both individual carcinogens and tobacco exposure as a complex mixture, it will not be possible to evaluate all possible carcinogens. Thus, additional studies are needed that can compare the harmful effects of tobacco constituents, and models should be developed to prioritize their study. Further data are needed to achieve confidence that only a few key, but high-priority, carcinogens are sufficient to evaluate a PREP.

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13

Cardiovascular Disease

The impact of cigarette smoking on the U.S. national burden of cardiovascular disease (CVD) has been well documented. Each year, about 150,000 cardiovascular deaths are attributable to cigarette smoking, and of these, about 30,000 are attributable to environmental cigarette smoke exposure among nonsmokers (McGinnis and Foege, 1999, Taylor et al., 1992). The cardiovascular burden of smoking is amplified substantially because smoking significantly increases the risk for many types of cardiovascular morbidity: myocardial infarction (MI), sudden cardiac death, stroke, peripheral vascular disease, and abdominal aortic aneurysms (Green et al., 1993). Importantly, the risk of cardiac ischemic events is substantially and relatively rapidly reversible on cessation of smoking (U.S. DHHS, 1983).

In 1990-1994, an average of 430,700 Americans died each year of smoking-related illness. The largest portion of these deaths were cardiovascular-related illnesses. Approximately one in five deaths from cardiovascular diseases is attributable to smoking. According to the World Health Organization (WHO), 1 year after quitting, the risk of coronary heart disease (CHD) decreases by 50%, and within 15 years, the relative risk of dying from CHD for an ex-smoker approaches that of a long-time nonsmoker.

Despite this well-recognized association between smoking, and CVD, and sudden cardiac death, and the increasing amount of pathogenic information available, more needs to be known about the mechanisms of smoking-induced CVD injury. This is of particular importance because

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one constituent of tobacco smoke—nicotine—is currently used as short-term therapy for smoking cessation, and as discussed elsewhere in this volume, nicotine is being considered for extended use as an aid to smoking reduction. This necessitates a detailed consideration of the cardiovascular pharmacology of nicotine. The results of the Lung Health Study (Anthonisen et al., 1994) is notable in the consideration of the cardiovascular effects of long-term nicotine replacement therapy (NRT) since it was found that long-term use of nicotine gum for the purpose of smoking cessation did not result in an increased incidence of cardiovascular complications. Furthermore, it is pertinent to strategies being deployed by tobacco product manufacturers to eliminate selectively discrete constituents of tobacco and cigarettes and then market them as "safer." This implies a knowledge of the relative contributions of a myriad of tobacco constituents to CVD, which simply does not exist. This chapter summarizes the current scientific basis of our understanding of smoking and CVD, suggests modern methodologies that might usefully be applied to enhance understanding in this area, and highlights areas for further research.

CORONARY HEART DISEASE

The incidence of coronary artery disease (CAD), including sudden cardiac death, is more than doubled in cigarette smokers as a group and is increased fourfold in heavy smokers. There is a dose-response relationship between cigarette smoking and CAD, such that the risk increases with the number of cigarettes smoked daily, the extent of inhalation, and the number of years of smoking. Cigarettes that nominally deliver less tar or nicotine have not been shown to confer any protection from ischemic heart disease.

The clearest understanding of smoking-induced ischemic heart disease emerges from integration of data from epidemiological and pathophysiologic investigations. In considering the participation of smoking in the etiology of CHD, it is useful to separate the effects of smoking on the development of atherosclerotic stenosis of the coronary arteries from its effects on the process that converts coronary atherosclerosis to acute coronary events.

Acute coronary events represent an abrupt transition from stable chronic CAD to one of the major consequences of ischemia: unstable angina, myocardial infarction, and sudden cardiac death. Abundant evidence supports the concept that the rupture of a lipid-rich atherosclerotic plaque with attendant thrombus formation is the initiating event in the development of the vast majority of these ischemic syndromes (Davies and Thomas, 1984; Oates, 1989).

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Coronary Atherosclerosis

Age is a powerful predictor of coronary atherosclerosis, and angiographic studies indicate that the relative risk for coronary stenosis associated with having previously smoked is greatest in the youngest age groups, suggesting an acceleration of the process by smoking. Some of the best evidence is provided by a prospective autopsy study performed in Hawaii (Reed et al., 1987) and from the study of autopsies on young men who died violently (PDAY Research Group, 1990). These studies indicate that there is a strong dose-related association of smoking with atherosclerosis of the abdominal aorta, as well as an association with atherosclerosis of the coronary arteries that is significant but less robust. From these two autopsy studies, as well as from an overview of all relevant studies, one gains the impression that the significant increase in fibrous atherosclerotic plaques and atheroma of the coronary arteries is not of sufficient magnitude to account fully for the greater increase in acute coronary events that are linked to cigarette smoking.

The finding that the increase in involvement of the coronary arteries with atherosclerosis is of small magnitude is in agreement with the prospective epidemiological evidence that stable angina pectoris is increased modestly, if at all, in cigarette smokers over age 40. In men less than 40 years of age, an increase in stable angina has been detected (twofold), but at 40 years and older the risk is increased only slightly, even after adjusting the incidence of stable angina for the loss of persons at risk owing to acute coronary events (Dawber, 1980). However, excess smoking-attributable mortality rates due to heart disease continue to increase with age and smoking duration, suggesting that smoking continues to be an important independent risk factor in the elderly (Burns, 2000).

Acute Coronary Events

Prospective epidemiological studies have consistently demonstrated a substantial increase in acute coronary ischemic events in individuals who smoke (U.S. DHHS, 1983). The pernicious effect of cigarette smoking on MI and sudden cardiac death is seen at least to age 70, but the increase in risk for a given individual appears to be greatest during middle age. The largest body of prospectively acquired North American data indicates that middle-aged men who smoke have a tenfold greater risk of sudden cardiac death and a 3.6-fold increased risk of MI (Kannel et al., 1984). The risk for sudden cardiac death is disproportionately greater than that for MI, a finding that is replicated to varying degrees in other studies. Of all the coronary risk factors, cigarette smoking is the strongest predictor of sudden cardiac death. The risk for both of these acute coro-

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nary events (MI and sudden death) clearly exceeds that for stable angina. Although the incidence of coronary deaths in women during middle age is lower than that in men, cigarette smoking accounts for about half of these deaths. Pipe and cigar smoking are also associated with increased rates of heart attack rates (Nyboe et al., 1991) and coronary mortality, as well as stroke occurrence.

In most studies that have explored the relationship of cigarette smoking rates to CVD outcomes, a dose-response has been observed. Cumulative exposures in epidemiological studies are not easy to determine because of interindividual short- and long-term variations in smoking patterns and choices of products. Also, individual inhalation depth and retention may vary in order to titrate the delivery of certain levels of nicotine (Hee et al., 1995). However, population studies employing even a relatively simple measure of exposure, such as cigarettes per day, usually reveal increasing adverse CVD outcomes with increasing numbers of cigarettes consumed. An example is the Cancer Prevention Study (CPS), shown in Table 13-1. Here, although some cells have small numbers of participants, there is a general trend of increased risk of CAD death with increasing baseline cigarette usage, most prominent up to 20 cigarettes per day.

Cessation of Smoking

Smoking cessation in individuals without known coronary heart disease makes an important contribution to reducing the risk of MI (Cook et al., 1986; Rosenberg et al., 1985, 1990; U.S. DHHS, 1983). The excess risk of MI falls by about 50% within the first two years after cessation of smoking, consistent with a substantial component of the risk of acute ischemic events being reversible. An example of the rate of decline in risk of fatal CAD, total CAD, and nonfatal MI is shown in Table 13-2 from the CPS (Stellman and Garfinkel, 1986). For those who have ceased smoking for 10-14 years, their general CVD risk declines to that of "never smokers." A similar or even more accelerated risk reduction can be seen for stroke in women, as shown in Figure 13-1 (Kawachi et al., 1993). Even among individuals over 60 years of age, a decrease in risk for ischemic heart disease postcessation has been found, though smaller than for younger individuals (Burns, 2000).

For smokers who already have CAD, cessation is also very effective in reducing the incidence of further acute coronary events. Survivors of MI have a greater risk of reinfarction, and survivors of sudden cardiac death have a greater risk of sudden death if they continue to smoke. For individuals who have angina pectoris or a positive exercise test or who have had coronary artery bypass graft surgery, continuing the smoking

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TABLE 13-1 Age-Specific and Age-Adjusted Death Rates From Coronary Heart Disease, by Number of Cigarettes Currently Smoked

			Cigarettes per Day											
	Never Smoked		1-9		10-19		20		21-39		40		41+	
Age	M	F	M	*F*	M	F	M	F	M	F	M	F	M	F
30-34	—	—	—	—	—	—	—	—	( )	—	( )	—	( )	—
35-39	(0.9)	( )	—	—	—	—	—	( )	—	( )	—	( )	—	—
40-44	[1.3]	0.6	( )	—	( )	—	(10.4)	(1.4)	[5.7]	( )	12.4	—	(13.1)	( )
45-49	2.7	0.4	17.7	[2.1]	14.1	3.3	14.1	2.8	9.9	2.1	19.5	4.6	18.1	—
50-54	5.6	0.8	14.7	3.4	25.1	4.2	21.4	4.0	21.1	6.8	21.9	4.6	20.9	(6.4)
55-59	11.9	2.4	28.0	2.4	31.0	5.7	35.9	9.7	28.4	8.1	31.2	11.3	41.3	14.6
60-64	22.9	6.2	49.4	11.1	57.0	13.5	64.0	19.0	46.1	19.8	59.0	17.3	28.9	( )
65-69	40.5	12.6	65.2	22.6	76.9	30.4	82.5	35.4	82.1	29.2	65.6	29.1	78.5	[32.9]
70-74	68.5	25.4	114.1	35.6	110.4	52.6	132.9	49.2	101.0	51.4	114.4	54.8	39.2	—
75-79	123.1	53.0	128.9	72.9	148.7	76.9	176.6	94.4	222.5	103.2	177.9	92.9	[110.0]	—
80-84	189.5	97.5	248.5	127.2	279.6	114.2	309.7	149.1	201.9	81.4	315.1	(103.7)	—	( )
85+	329.7	265.5	363.3	167.1	308.6	479.4	430.0	333.9	852.3	( )	( )	( )	—	—
Age adjusted[a]	24.1	11.5	37.0	13.1	38.2	20.3	44.7	20.2	46.9	16.2	37.6	15.9	30.0	13.3

NOTE: —=0 deaths; ( )=1 death; (rate)=2 deaths; [rate]=3 deaths.

[a]Age-adjusted death rates per 10,000 person-years standardized to 1980 U.S. population.

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TABLE 13-2 Time Since Quitting and Age-Adjusted and Multivariate RRs of Fatal Coronary Heart Disease and Nonfatal Myocardial Infarction, Compared with Current Smokers.[a]

Event	Never Smoker	Current Smoker	Years Since Quitting				
			<2	2-4	5-9	10-14	≥15
Fatal coronary heart disease							
cases	49	123	7	9	14	4	13
RR[b]	0.24 (0.18-0.33)	1.00	0.53 (0.25-1.12)	0.68 (0.35-1.34)	0.68 (0.39-1.19)	0.26 (0.10-0.65)	0.31 (0.18-0.53)
RR[c]	0.23 (0.17-0.33)	1.00	1.47 (0.42-5.20)	0.58 (0.23-1.44)	0.72 (0.36-1.42)	0.28 (0.09-0.87)	0.32 (0.16-0.66)
Nonfatal myocardial infarction							
cases	166	418	36	22	26	13	41
RR[b]	0.26 (0.22-0.30)	1.00	0.85 (0.60-1.19)	0.51 (0.34-0.78)	0.40 (0.27-0.59)	0.26 (0.15-0.43)	0.29 (0.21-0.39)
RR[c]	0.24 (0.20-0.28)	1.00	0.81 (0.51-1.29)	0.43 (0.25-0.74)	0.38 (0.23-0.62)	0.26 (0.13-0.49)	0.27 (0.18-0.41)
Total coronary heart disease							
cases	215	541	43	31	40	17	54
RR[b]	0.25 (0.22-0.30)	1.00	0.77 (0.57-1.05)	0.55 (0.39-0.79)	0.47 (0.34-0.64)	0.26 (0.17-0.40	0.29 (0.23-0.38)
RR[c]	0.24 (0.20-0.28)	1.00	0.75 (0.49-1.15)	0.46 (0.29-0.74)	0.44 (0.30-0.66)	0.26 (0.14-0.45)	0.28 (0.20-0.40)

NOTE: RR=relative risk.

[a]Missing for 29 cases, including 6 fatal coronary heart disease and 23 nonfatal myocardial infarction.
[b]Age-adjusted RR.
[c]Adjusted for age in 5-year intervals, during follow-up period (1976-1978, 1978-1980, 1980-1982, 1982-1984, 1984-1986, or 1986-1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, menopausal status, postmenopausal estrogen therapy, parental history of myocardial infarction before age 60, and daily number of cigarettes consumed.

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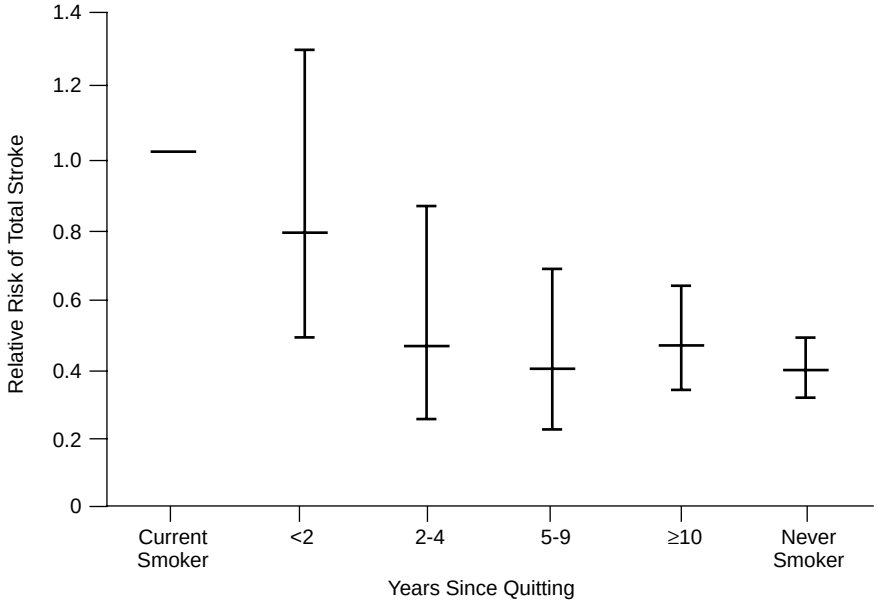


FIGURE 13-1 Risk of total stroke by time since quitting.

NOTE: Age-adjusted relative risk of total stroke in relation to time since stopping smoking. Current smoker was the reference category. Error bars represent 95% confident intervals.
SOURCE: Kawachi et al., 1993. Copyright (1993), American Medical Association.

habit confers a worse prognosis. Cessation of smoking after coronary angioplasty or vascular surgery reduces the rate of restenosis by one-third. Thus, there is a major incentive for smoking cessation in this group of patients. When efforts to cease smoking are effective, they probably confer a greater benefit than any pharmacological or surgical intervention aimed at coronary disease.

Overall, these observations are encouraging for the motivation to quit. The decline of risk upon smoking cessation can be variable in different risk groups and according to behaviors during cessation, potentially affording insight into interindividual differences in mechanisms relevant to healing smoking-induced cardiovascular injury. An initial interpretation of these data suggested that acute factors, such as hemostatic activation, dominated over more gradual processes, such as occlusive atherosclerotic

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disease contributed to the smoking-induced CVD burden. It is now appreciated that anatomic atherosclerosis may also restructure toward more normal vessels at rates comparable to the clinical and epidemiological findings, bringing vascular factors relevant to plaque stability into consideration. In summary, the kinetics of declining CVD risk after smoking cessation do not serve to discriminate easily between hemostatic and other vascular factors as mediators of smoking-induced disease.

However, the pattern of decline in CVD risk after quitting suggests that CVD may offer a particular advantage in assessing tobacco-related harm reduction over a reasonable time. That is, patterns of change in morbidity and mortality rates after changes from a conventional to a risk reduction tobacco product may help reveal whether lower toxic exposures are actually being achieved and whether they lead to altered CVD outcomes, without waiting the decades necessary to evaluate the outcomes of smoking these products beginning from initiation of the smoking habit. The issues of compensation, nicotine dose-response relationships, and aspects of nicotine-related cardiovascular risk are discussed in Chapter 9.

Smoking and Other Cardiac Risk Factors

Cigarette smoking, hypercholesterolemia, and hypertension have been the most extensively studied risk factors for CAD. The risk of CAD imposed by cigarette smoking is magnified by the presence of several other factors that cause coronary heart disease. Cigarette smoking alone imposes a risk for CHD that is independent of other risk factors. However, smoking in conjunction with another risk factor increases the actual rate of coronary heart disease events to a greater extent than smoking alone, and these risk factors may work additively or geometrically. In one large study (The Pooling Project Research Group, 1978), smoking increased the ten-year rate of a first CAD event (MI or sudden cardiac death) by 31 per 1,000 persons when neither hypercholesterolemia nor hypertension was present. In conjunction with either hypercholesterolemia or hypertension, cigarette smoking increased the rate by 49 per 1,000 persons, and when both hypercholesterolemia and hypertension were present, the superimposition of smoking increased the rate by 97 per 1,000 persons. In women, there is a tenfold increase in the risk of MI among oral contraceptive users who smoke. Therefore, hypercholesterolemia, hypertension, and oral contraceptive use provide an incentive to not smoke or to cease smoking that exceeds the abundant benefit of avoiding this addiction in the rest of the population. Further, control of elevated cholesterol and high blood pressure reduces the risk of CAD (Brown, 2000; Mormando, 2000; The sixth report, 1997), as does smoking cessation.

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The pathophysiological impact of various environmental exposures and risk factor states may be modified by host genetic factors. For example, a certain polymorphism in coagulation Factor V (Q506) confers resistance to interaction with the endogenous antithrombotic protein activated protein C. Following presentation with an acute coronary syndrome, smokers with this polymorphism have an increased risk of MI and death compared to smokers with a normal genotype, extending to at least two years after the initial event (Holm et al., 1999). Another example is the interaction between smoking and the guanosine-adenosine at the G455A polymorphism in the b-fibrinogen gene. This polymorphism is associated with higher levels of circulating fibrinogen, which in turn have been associated with increased risk of CAD (Humphries et al., 1999). This association is more pronounced in smokers (Green et al., 1993; Humphries et al., 1999). Similarly, polymorphisms in the coagulation factor VII gene have been associated with reductions in risk of CAD (Donati et al., 2000). Cigarette smoking interacts to a variable degree with genes related to other aspects of cardiovascular risk, including antioxidant enzymes such as paraoxonase (Sen-Banerjee et al., 2000), apoliprotein B (Glisic et al., 1995), DNA repair genes (Abdel-Rahman and El-Zein, 2000), and proteins that regulate the availability of cardiotoxic autacoids such as the serotonin transporter (Arinami et al., 1999). Finally, the cardiovascular hazards of tobacco may be modulated by the presence of functionally important polymorphisms in enzymes that detoxify harmful constituents of tobacco smoke (Li et al., 2000). Clearly, emerging information about genetic polymorphisms that are of functional significance and relevance to the cardiovascular system will afford an increasing opportunity to understand and predict the effect of smoking on CVD risk at the individual level.

Environmental Tobacco Smoke

There is considerable evidence that exposure to environmental tobacco smoke (ETS; passive smoking) has an adverse effect on cardiovascular health (Kawachi et al., 1997a). Pooled results of epidemiological studies indicates a 20% excess coronary heart disease death rate among nonsmoking spouses of smokers (Steenland et al., 1996). As many as 40,000 deaths from MI each year may be the result of passive smoking. The mechanisms linking ETS exposure and cardiovascular disease are probably similar to those for active smoking.

Pathophysiology

A review of the mechanisms linking cigarette smoking and coronary heart disease must consider the fact that whereas smoking accelerates

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coronary atherosclerosis, it has an even greater effect on the process that abruptly converts atherosclerosis to the acute ischemic events of MI, unstable angina, and sudden cardiac death. The effect of chronic smoking on the initiation of acute ischemic events appears to be largely reversible, given the substantial and rapid reduction in the incidence of acute ischemic events after smoking cessation. Although there is likely overlap between the mechanisms by which smoking accelerates atherosclerosis and promotes acute ischemic events, it is useful to consider these adverse effects of smoking separately.

Acceleration of Atherosclerosis

As for other risk factors, vascular endothelial dysfunction likely plays a central role in the promotion of atherosclerosis in chronic smokers (FitzGerald et al., 1988; Heitzer et al., 1996a). Extensive endothelial abnormalities are present in the umbilical arteries of infants born to smoking mothers, and lesions of endothelial cells, subendothelial damage, and platelet adhesion have been described in vessels of experimental animals exposed to cigarette smoke. Increased in vivo prostacyclin biosynthesis and functional abnormalities of vascular endothelium also result from cigarette smoking. Impaired endothelium-dependent vasodilatation in both forearm and coronary vascular beds has been demonstrated even in young smokers (Campisi et al., 1998; Heitzer et al., 1996b; Zeiher et al., 1991). These functional abnormalities may be due to smoking-induced inhibition of nitric oxide (NO) release (Campisi et al., 1999; Kugiyama et al., 1996) or to acceleration of NO breakdown. Structural endothelial damage may result either from a direct toxic effect of nicotine or other components of cigarette smoke on endothelial cells or from smoking-induced oxidative stress (Heitzer et al., 1996a, b). Smokers have reduced levels of antioxidant vitamins and increased levels of oxidized low-density lipoprotein (LDL), a potent inhibitor of endothelial function (Heitzer et al., 1996b; Morrow et al., 1995). Smoking-induced acute and chronic systemic hemodynamic changes may also contribute to vascular endothelial dysfunction. For example, some but not all studies suggest that smoking a single cigarette causes an acute rise in systemic blood pressure and heart rate, and chronic smoking results in a persistent elevation in daytime blood pressure. The effect of chronic smoking on blood pressure is more complex as outlined later.

Smoking is associated with lipid abnormalities that may contribute to the development of atherosclerosis (Duthie et al., 1993; Craig et al., 1989). In addition to increased levels of oxidized low-density lipoprotein, smoking produces an increase in very low density lipoprotein (VLDL) and triglycerides and a reduction in high-density lipoprotein (HDL) levels.

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Smoking has been shown to increase monocyte adhesion to endothelial cells, an important early event in atherosclerosis (Adams et al., 1997; Weber et al., 1996). Additional factors that may contribute to the development of coronary and other atherosclerotic events in smokers include smoking-induced platelet activation, increased fibrinogen levels, and increased blood viscosity.

Promotion of Acute Coronary Events

In addition to the effect of smoking on the development of atherosclerosis, there is a dramatically increased risk of acute ischemic events, including MI and sudden death. Acute systemic and coronary hemodynamic effects of smoking are likely to play an important role in the development of these ischemic events. After smoking a single cigarette, systemic arterial pressure, heart rate, and myocardial contractility increase, resulting in a rise in myocardial oxygen demand (Cryer et al., 1976; Nicod et al., 1984). Simultaneously, in patients with atherosclerosis, smoking causes acute vasoconstriction of both conduit and resistance coronary vessels, with a decrease in coronary blood flow (Czernin et al., 1995; Nicod et al., 1984; Quillen et al., 1993). Even in the absence of a hemodynamically significant stenosis, coronary flow may fall by more than 20% despite a significant increase in myocardial oxygen demand. In some individuals, smoking causes intense focal vasoconstriction or spasm that can lead to myocardial ischemia (Moauad et al., 1986). These acute hemodynamic effects of smoking in the coronary bed are most likely adrenergically mediated, since they can be prevented by α-adrenergic blockade (Winniford et al., 1986). Adrenergic stimulation has been shown to cause exaggerated coronary vasoconstriction in the setting of endothelial dysfunction (Vita et al., 1992; Zeiher et al., 1989). Plasma norepinephrine and epinephrine levels rise acutely after smoking (Cryer et al., 1976); this catecholamine release may lower arrhythmia threshold and increase the risk of sudden death.

In addition to lowering anginal threshold, repeated episodes of coronary vasoconstriction and elevations of systemic arterial pressure may increase hemodynamic stresses at the site of an atherosclerotic plaque. An increase in shear stress at the site of a vulnerable plaque is considered a potentially important cause of plaque rupture.

Smoking has also been shown to exacerbate the cardiovascular effects of cocaine (Moliterno et al., 1994). Both the epicardial coronary constriction and the increase in myocardial oxygen demand caused by cocaine are potentiated by concomitant smoking, perhaps increasing the risk of MI and sudden death attributed to cocaine use.

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Inhaled carbon monoxide (CO) in cigarette smoke binds to hemoglobin, reducing oxygen delivery to myocardial cells. The carbon monoxide levels found in smokers have been shown to lower anginal threshold (Allred et al., 1989; Aronow, 1981) and increase ventricular fibrillation threshold (Aronow et al., 1979). Carbon monoxide may also have a deleterious effect on vascular endothelial cells (Thom et al., 1997).

Coronary thrombosis plays a major role in acute coronary events, and smoking is associated with several changes in the hemostatic system that lead to a hypercoagulable state. These hemostatic changes include an increase in fibrinogen (De Maat et al., 1996), red cell mass, and blood viscosity; platelet activation with thromboxane A_2 release (Benowitz et al., 1993); and impaired release of tissue plasminogen activator from endothelial cells (Newby et al., 1999).

Most research on the effects of smoking on the cardiovascular system has focused specifically on nicotine and carbon monoxide, but there are more than 4,000 other components in cigarette smoke, some of which may also contribute to smoking-induced vascular disease (Penn and Snyder 1996).

Coronary Vasospasm

A much less common cause of ischemia than plaque rupture, primary coronary vasospasm usually manifests as variant angina but may also cause MI and sudden cardiac death. Coronary vasospasm is strongly associated with cigarette smoking (Okasha et al., 2000).

EXTRACARDIAC VASCULAR DISEASE

Smoking markedly accelerates atherosclerosis in the abdominal aorta, and occlusive disease of its branches is increased as well (Reed et al., 1987; PDAY, 1990). Aortic aneurysm, peripheral vascular disease, and renal artery stenosis are increased in smokers. Renovascular hypertension should be strongly suspected in cigarette smokers who have severe hypertension. Cigarette smoking is an independent risk factor in the development of atherosclerosis in the internal pudendal and penile arteries of young men with impotence.

Two types of stroke are increased in cigarette smokers (U.S. DHHS, 1989). Smoking is a risk factor for cerebral infarction, and the magnitude of risk increases with greater smoking exposure. This occurs in conjunction with an increase in atherosclerosis of the carotid arteries in smokers. Subarachnoid hemorrhage is markedly increased in cigarette smokers, and in women who take oral contraceptives, this risk if further enhanced.

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OTHER VARIABLES INFLUENCED BY SMOKING

Blood Pressure

The effect of cigarette smoking on chronic blood pressure levels in uncertain, in part because of concomitant effects of lower body mass index (BMI) and more frequent alcohol consumption among smokers. Some studies have reported lower ambulatory blood pressure levels (Mikkelsen, et al., 1997; Okasha et al., 2000), while others have reported increases (Minami et al., 1999; Mundal et al., 1997). Findings may depend in part on when in the day pressure recordings are made and whether smoking is assessed by self-report or by biochemical verification (Istvan et al., 1999). Smoking in healthy volunteers has been reported to alter the change in blood pressure response to changes in body position (Nardo et al., 1999) and to cause abnormal baroreceptor function (Gerhardt et al., 1999). Of note, maternal smoking has been associated with increased blood pressure levels in the children of these pregnancies (Blake et al., 2000).

Insulin Resistance

The insulin resistance syndrome, as well as insulin resistance per se, has been associated with increased risk of atherosclerotic vascular disease, independent of most other major risk factors and is a risk factor for non-insulin-dependent diabetes mellitus (NIDDM) (Mikhailidis et al., 1998). Increased insulin resistance has been associated with increased intimal-medial thickening in the presence of vasospastic angina (Shinozaki et al., 1997). The syndrome occurs in healthy young men and is sixfold more common in cigarette smokers (Tahtinen et al., 1998). Insulin resistance is also increased among smokers with existing NIDDM (Targher et al., 1997). Smoking cessation improves insulin sensitivity among healthy middle-aged men (Eliasson et al., 1997).

Other Lipid or Lipoprotein Measures

Lipoprotein (a) (Lp(a)) cholesterol levels are positively and independently correlated with the risk of coronary events in some but not all prospective studies (Seman et al., 1999). Cigarette smoking does not appear to alter blood Lp(a) levels (Chien et al., 1999; Kamboh et al., 2000). However, smoking appears to alter the ratio of LDL subfractions in the direction associated with increased CVD risk (Griffin et al., 1994).

Inflammation

There is substantial evidence that inflammation plays a role in the pathogenesis of atherosclerotic lesions in many parts of the arterial tree

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and that elevated blood levels of cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP) are associated with increased risk of coronary events (Ridker et al., 2000; Koenig et al., 1999). Smoking is associated with increased levels of CRP, suggesting that inflammation is one mechanism by which smoking promotes the pathogenesis of these lesions. Smoking has also been shown to increase local tissue levels of some cytokines in organs other than the vascular tree, such as tumor necrosis factor-alpha (TNF-α) in gingival cervicular fluid, but not IL-6 (Bostrom et al., 1999) or IL-8 and ICAM-1 in small respiratory airways (Takizawa et al., 2000).

Homocysteine

Blood homocysteine levels have been related to an increased risk of coronary heart disease and other atherosclerotic diseases in several studies (Saw, 1999). Cigarette smoking has been shown to be associated with higher blood homocysteine levels, both in the basal state and after a methionine load (Reis et al., 2000; Nygard et al., 1998). In a study in which the dose-response was explored, there was a clear positive correlation between the number of cigarettes smoked and blood homocysteine levels. This raises the possibility that smoking cessation may have its effects in part through this mechanism and that homocysteine level might be developed as a biomarker of smoking exposure.

SURROGATE MARKERS

The identification and validation of quantitative indices that reflect biochemical mechanisms of cardiovascular injury caused by cigarette smoking would be useful. Such surrogate indices might permit the study of both progression and regression of smoking-related cardiovascular disease and clarify the factors that contribute to interindividual differences in susceptibility to such complications. They might also be useful correlates of the relative bioavailability of individual constituents of cigarette smoke and aid in the evaluation of harm reduction strategies, including potentially "safer" smoking devices and nicotine replacement therapies. They might also prove of value in assessment of the cardiovascular risk of secondhand smoke. Presently, little information is available relating to the mechanisms of cigarette-induced cardiovascular damage, but the emergence of promising technologies relating to potentially important mechanisms, including platelet activation and oxidative stress, illustrates the potential of the approach.

Cigarette smoking causes platelet activation in vivo, as reflected by an accelerated platelet turnover time (Fuster et al., 1981). However, the development of noninvasive approaches to assessment of platelet activa-

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tion facilitates repeated investigation of the effects of smoking on platelet function. Platelets are extremely susceptible to platelet activation ex vivo during blood sampling, and this has constrained the usefulness of circulating biomarkers of platelet activation, such as circulating platelet aggregates and β-thromboglobulin or, indeed, of more contemporary approaches such as P selectin expression on platelets ex vivo. Studies of the platelet aggregation response ex vivo have also proven uninformative. Platelets activated by cigarette smoke in vivo might be less available for harvesting for such ex vivo studies. Indeed, platelet responses to adenosine 5´-diphosphate (ADP) were reportedly diminished ex vivo in smokers in one large-scale epidemiological study (Meade et al., 1985). By contrast, urinary excretion of the 2,3-dinor and 11-hydro metabolites of thromboxane have proven to be noninvasive indices of platelet activation in vivo (FitzGerald et al., 1983). Thus, phasic increases in excretion of these metabolites occur during the ischemic episodes of unstable angina and in patients undergoing therapeutic thrombolysis (Fitzgerald et al., 1988; Lewis et al., 1983), two situations in which the functional importance of thromboxane dependent platelet activation is implied by the therapeutic efficacy of aspirin (Intravenous streptokinase, 1987; Lewis et al., 1983).

Excretion of thromboxane metabolites is increased in apparently healthy individuals who smoke and decreases on short-term cessation (Nowak et al., 1987). This observation has been confirmed, both in a large population study and in a case-control study of monozygotic twins discordant for the smoking habit (Lassila et al., 1988; Wennmalm et al., 1991). Interestingly, excretion of the major metabolite of prostacyclin, 2,3-dinor-6-keto-$PGF_{1\alpha}$ (prostaglandin $F_{1\alpha}$) (Brash et al., 1983), is also elevated in chronic cigarette smokers. Prostacyclin, like thromboxane, is a product of cyclooxygenase (COX) catalyzed metabolism of arachidonic acid. While prostacyclin is the major product of COX in endothelial cells, thromboxane is the principal product of the same enzyme in platelets. Platelets express exclusively COX-1, and the suppression of thromboxane biosynthesis by low-dose aspirin (Nowak et al., 1987) implies that this is the major source of its formation in smokers (Lassila et al., 1988). However, COX-2 in the vessel wall or in infiltrating cells, such as monocyte or macrophages, represents a second theoretical source of thromboxane formation. Indeed, COX-2 seems the likely source of prostacyclin formation (Wennmalm et al., 1991; Brash et al., 1983; McAdam et al., 1999), although the effects of selective inhibitors of COX-2 on the formation of either eicosanoid in cigarette smokers remains to be reported. Although cigarette smoke reduces the capacity of endothelial cells to form prostacyclin in vitro (Reinders et al., 1986), the capacity of cells to form this and other eicosanoids greatly exceeds actual biosynthetic rates in vivo (FitzGerald et al., 1983). The increment in prostacyclin biosynthesis coincident with

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that of thromboxane is consistent with the capacity of thromboxane analogues to evoke its formation by endothelial cells in vitro (Nicholson et al., 1984) and its role as a homeostatic response to accelerated platelet vessel wall interactions in vivo (FitzGerald et al., 1984). Deletion of the prostacyclin receptor increases the response to thrombotic stimuli (Murata et al., 1997). While an abundant literature supports the use of these indices of platelet-vascular interactions, they could be usefully related to other, more functional surrogates of the cardiovascular response to smoking, such as impaired endothelial function (Raitakari et al., 2000) and noninvasive assessment of atherosclerosis progression, using ultrasonography or electron beam computerized tomography (EBCT) (O'Malley et al., 2000; Raggi et al., 2000). Such surrogates could represent an intermediate link between the noninvasively acquired biochemical indices and true functional outcomes of smoking, such as myocardial infarction and sudden death.

Another mechanism that has been widely implicated in cigarette-induced tissue injury is oxidative stress. Free-radical-catalyzed damage has been suggested to be of relevance to both atherogenesis and tumor progression and, as such, may well be relevant to the harm caused by cigarette smoking. Indeed, cigarette smoke contains abundant radicals, and smoking is known to cause activation of platelets and neutrophils, which may in turn increase radical generation (Pryor, 1997; Shinagawa et al., 1998; Yamaguchi et al., 2000). Until recently, the study of oxidative damage in vivo has been constrained by the specificity of available biomarkers. However, the discovery of isoprostanes (iPs), free-radical-catalyzed products of arachidonic acid (Lawson et al., 1999; Roberts and Morrow, 2000), has transformed this situation. These products are formed initially in situ in the phospholipid domain of cell membranes, where they may be immunolocalized or quantitated directly (Roberts and Morrow, 2000). Following phospholipase-dependent cleavage, iPs circulate and are excreted in urine. Urinary iPs reflect the oxidant stress attendant on inflammation (McAdam et al., 2000) and are increased in a dose-dependent manner in cigarette smokers (Reilly et al., 1996). Some evidence exists suggesting their elevation by secondhand smoke and in the children of smokers (Sinzinger et al., 2000). Elevated urinary iPs in smokers appear to fall rapidly on quitting (McAdam et al., 2000; Morrow et al., 1995; Reilly et al., 1996; Sinzinger et al., 2000). It is possible that iPs may be of functional relevance to smoking-induced cardiovascular injury besides serving as a marker of the process. Thus, individual iPs may act as incidental ligands both at membrane receptors for prostanoids (Kunapuli et al., 1998; Morrow et al., 1995) and at peroxisomal proliferator activated receptors (PPARs) (Audoly et al., 2000). Thus, certain iPs activate platelets via thromboxane receptors in smokers (McNamara et al., 1999) and may,

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in turn, lead to generation of thromboxane itself, creating a vicious cycle (Davi et al., 1999). In this setting, effective antioxidants might suppress both iP generation and thromboxane biosynthesis. Cigarette smokers are susceptible to depletion of endogenous vitamin C, and supplementation of smokers with vitamin C depresses elevated iPs (Valkonen and Kuusi, 2000). By contrast, their endogenous levels of vitamin E are replete, and exogenous vitamin E does not suppress elevated iPs in smokers (Reilly et al., 1996). Other noninvasive indices of lipid peroxidation, such as 4-hydroxynonenal (Benedetti et al., 1980), and of radical-induced protein (Pennathur et al., 1999) and DNA (Marnett, 2000) damage have begun to emerge in clinical investigation. No information is available on relative effects of these distinct targets for radical-induced damage or their relevance to smoking-induced cardiovascular injury.

In summary, the examples of urinary thromboxane, prostacyclin, and isoprostanes illustrate the potential value of developing and validating quantitative, noninvasive biochemical indices of the mechanisms of smoking-induced cardiovascular damage and tissue injury in general. Initially, the methodology involved (e.g., mass spectrometry) is often expensive and labor intensive. However, once the proof of principle for such approaches has been established, effort can be rationally devoted to the development of simpler, more widely applicable, but validated methodologies, such as enzyme immunoassays. The power of this approach, which can also be applied to animal models (Pratico et al., 1998; Heinecke, 1999), will be greatly enhanced by its integration with surrogate markers of functional impairment and, ultimately, with actual clinical events in the assessment of the cardiovascular risks of smoking.

Potential surrogate markers to be used in animal models developed to detect potentially adverse effects of smoking and of the use of potential reduced-exposure products (PREPs) on arteries throughout the body and in the lungs and heart include measurements of platelet activation, blood pressure and heart rate, and oxidative stress. Other surrogate markers that may be utilized in clinical studies include measurements of oxidative stress, measurements of platelet activation, elements of the coagulation system, lipids and lipoproteins, pulmonary function studies, studies of endothelial function, myocardial stress perfusion studies, and periodic evaluation by ultrasound of the carotid, abdominal aortic, and lower-extremity arteries.

CONCLUSIONS

Dose-Response Relationship

Highly informative information on the existence of a dose-response relationship between cigarette exposure and cardiovascular risk comes

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from many studies such as the CPS-2 (Thun et al., 1997) and Harvard Nurses' Health Studies (Kawachi et al., 1997b). In both instances, there is a relationship between the number of cigarettes smoked and the incidence of cardiovascular events. This is illustrated for the incidence of myocardial infarction (Table 13-3) and stroke (Table 13-4). In both cases, the most striking difference is between nonsmokers and individuals who smoke the least number of cigarettes recorded. The relationship becomes somewhat less pronounced as the number of cigarettes smoked per day increases. Interestingly, ex-smokers tend to occupy a space intermediate between nonsmokers and those with the lowest daily smoking frequency.

This dose-response curve prompts several considerations. First, there is no persuasive evidence of a threshold below which a cardiovascular risk does not exist. This observation affirms the primary objective of encouraging smokers to quit completely. Second, the shallow dose-response relationship, with the impression of a plateau, accords with similar observations relating the number of cigarettes smoked and measurements of systemic bioavailability, such as nicotine and cotinine. The same is true of the relationship with CO (Gori and Lynch, 1985). Although this may represent saturation kinetics of nicotine or CO, the most likely explanation is compensation for lower numbers of cigarettes smoked. Thus, the smoker titrates nicotine delivery toward a range of convergence that is reflected by the measurement of nicotine delivery, which in turn, may reflect dose-dependent convergence of the delivery of additional toxic, but unmeasured, constituents of cigarette smoke. The relative contribution of distinct constituents of cigarette smoke to smoking-related cardiovascular morbidity and mortality is unknown. In this regard, the available information is incomplete regarding any differences between the dose-response relationship of filter or low-tar versus high-tar or unfiltered cigarettes.

Feasibility of Harm Reduction in Therapy

There are no data that are directly informative on the issue of harm reduction. Thus, although a dose-response relationship exists for cardiovascular and cerebrovascular events, we do not know if reducing the number of cigarettes smoked results in a quantitative reduction in the risk of these events. However, the intuitively appealing prospect that this is indeed the case is supported by evidence from individuals who quit smoking. Thus, quitting results in a time-dependent reduction in the incidence of myocardial infarction (Table 13-2) and stroke. The latter is most nicely illustrated by data relating to subarachnoid hemorrhage, which was significantly elevated in women smokers in the Nurses' Health Study (Figure 13-1). In addition to evidence from such unequivocal clinical events,

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TABLE 13-3 Number of Cigarettes Smoked Daily and Age-Adjusted and Multivariate RRs of Fatal Coronary Heart Disease and Nonfatal Myocardial Infarction, Compared with Never Smokers[a]

Event	Never Smoker	Former Smoker	Cigarettes Smoked per Day Among Current Smokers					
			1-4	8-14	15-24	25-34	35-44	≥45
Fatal coronary heart disease cases	49	53	4	18	53	28	14	4
RR[b]	1.00	1.63 (1.11-2.40)	1.87 (0.69-5.09)	2.78 (1.66-4.67)	4.29 (3.00-6.15)	5.36 (3.53-8.14)	5.56 (3.26-9.50)	10.00 (4.35-22.97)
RR[c]	1.00	1.62 (1.09-2.40)	<————2.85————> (1.53-5,32)		4.85 (3.01-7.81) 3.90-12.43	6.96 (3.71-16.57)	<————7.84————>	
Nonfatal myocardial infarction cases	166	161	15	56	189	95	54	7
RR[b]	1.00	1.47 (1.19-1.83)	1.97 (1.17-3.30)	2.46 (1.83-3.29)	4.21 (3.48-5.11)	4.87 (3.87-6.13)	5.58 (4.24-7.35)	4.64 (2.34-9.21)
RR[c]	1.00	1.44 (1.16-1.79)	<————2.45————> (1.69-3.56)		4.77 (3.64—6.26) (3.73-7.28)	5.21 (3.61-7.86)	<————5.32————>	
Total coronary heart disease cases	215	214	19	74	242	123	68	11
RR[b]	1.00	5.51 (1.25-1.82)	1.94 (1.23-3.08)	2.53 (1.96-3.26)	4.22 (3.56-5.00)	4.97 (4.06-6.08)	5.57 (4.36-7.11)	5.74 (3.36-9.81)
RR[c]	1.00	1.48 (1.22-1.79)	<————2.53————> (1.84-3.50)		4.79 (3.78-6.08) (4.10-7.35)	5.49 (3.87-7.77)	<————5.49————>	

NOTE: RR=relative risk.

[a]Daily number smoked was missing for four cases, including two cases of fatal coronary heart disease and two cases of nonfatal myocardial infarction.

[b]Age-adjusted RR.

[c]Adjusted for age in five-year intervals, during follow-up period (1976-1978, 1978-1980, 1980-1982, 1982-1984, 1984-1986, or 1986-1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, menopausal status, postmenopausal estrogen therapy, and age at starting smoking.

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TABLE 13-4 Age-Adjusted RRs of Stroke (Fatal and Nonfatal Combined), by Daily Number of Cigarettes Consumed Among Current Smokers[a]

Event	Never Smoker	Former Smoker	Current Smoker	Cigarettes Smoked per Day Among Current Smokers			
				1-14	15-24	25-34	≥35
Total stroke cases	126	114	208	40	92	38	34
RR[b]	1.00	1.34 (1.04-1.73)	2,58 (2.08-3.19)	1.79 (1.26-2.54)	2.84 (2.19-3.67)	2.70 (1.91-3.84)	4.23 (2.99-6.00)
RR[c]	1.00	1.35 (0.98-1.85)	2.73 (2.18-3.41)	2.02 (1.29-3.14)	3.34 (2.38-4.70)	3.08 (1.94-4.87)	4.48 (2.78-7.23)
Subarachnoid hemorrhage cases	19	25	64	13	21	17	11
RR[b]	1.00	2.01 (1.12-3.61)	4.96 (3.13-7.87)	3.68 (1.91-7.11)	4.05 (2.30-7.14)	7.31 (4.15-12.85)	8.28 (4.45-15.42)
RR[c]	1.00	2.26 (1.16-4.42)	4.85 (2.90-8.11)	4.28 (1.88-9.77)	4.02 (1.90-8.54)	7.95 (3.50-18.07)	10.22 (4.03-25.94)
Ischemic stroke cases	85	70	120	23	58	19	18
RR[b]	1.00	1.20 (0.88-1.65)	2.25 (1.72-2.95)	1.54 (0.98-2.44)	2.69 (1.95-3.72)	2.06 (1.27-3.36)	3.43 (2.13-5.51)
RR[c]	1.00	1.27 (0.85-1.89	2.53 (1.91-3.35)	1.83 (1.04-3.23)	3.57 (2.36-5.42)	2.73 (1.49-5.03)	3.97 (2.09-7.53)
Cerebral hemorrhage cases	19	16	18	4	10	<————4[d]————>	
RR[b]	1.00	1.27 (0.66-2.44)	1.46 (0.77-2.78)	1.18 (0.40-3.46)	2.01 (0.94-4.28)	1.18 (0.41-3.46)	
RR[c]	1.00	1.24 (0.64-2.42)	1.24 (0.64-2.42)	1.68 (0.34-5.28)	2.53 (0.71-6.05)	1.41 (0.39-5.05)	

NOTE: RR=relative risk.

[a]Number unknown for four cases, including two subarachnoid hemorrhage and two ischemic stroke.

[b]Age-adjusted RR.

[c]Adjusted for age in five-year intervals, during follow-up period (1976-1978, 1978-1980, 1980-1982, 1982-1984, 1984-1986, or 1986-1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, and age at starting smoking.

[d]These two categories were combined due to small numbers.

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there is evidence that the increase in biomarkers of oxidant stress, platelet activation, and inflammation (Benowitz et al., 1993), all of potential mechanistic relevance to tobacco-related cardiovascular injury, rapidly falls toward the normal range on quitting cigarettes. The offset kinetics of more functional surrogates, such as endothelial dysfunction, remain to be determined in smokers. In summary, the data from quitters encourage the prospect that a graded reduction in cardiovascular risk and in biomarkers of this risk may accompany a reduction in the number of cigarettes smoked in pursuit of a harm reduction strategy. It is possible, indeed likely, that individuals and perhaps populations, differ in their susceptibility to tobacco-induced cardiovascular risk and, indeed, in their potential benefit from a harm reduction strategy. Data from quitting studies indicate a considerable variance in the rate of offset of risk, which declines with time. No data are available to address such issues across ethnic groups or gender. Acquisition of such information and research on the environmental and genetic factors that condition interindividual variability in exposure-risk relationships are necessary.

Utility in a Preclinical Setting

Studies in cell culture and model systems can afford much needed information on tobacco-related cardiovascular risk. These might include a profiling of gene expression and translation in cardiovascular tissues in response to cigarette smoke, constituents of smoke, and potential risk reduction substituents. These might identify proteins of potential functional relevance to the transduction of cardiovascular risk. Such studies might be coupled with gene inactivation and overexpression studies to address the role of these proteins in vivo. Similarly, studies of exposure to cigarette smoke or to discrete constituents of smoke might be deployed to investigate effects on atherosclerosis progression, susceptibility to vascular injury, thrombotic stimuli, graft rejection, cardiovascular development, or endothelial dysfunction in model systems such as mice. Studies of cardiovascular genomics and ultimately proteomics can also be extended to model systems to investigate gene expression and translation in response to exposure to tobacco-related products in vivo. These observations may, in turn, be related to the pattern of gene expression and translation in cardiovascular tissues obtained from cigarette smokers.

Biomarkers of Tobacco-Related Disease

The predominant mechanisms by which cigarette smoking induces cardiovascular injury is unknown. However, small studies in smokers of potentially relevant biomarkers of platelet and vascular activation, lipid

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peroxidation, and inflammation afford evidence of a dose-response relationship and a decline on quitting. There is even evidence of a signal in individuals exposed to ETS in the case of some of these markers. More mechanism-based clinical studies are required to confirm and expand these findings. Where possible, these should be related to surrogate measurements of cardiovascular function, such as hemodynamics, flow-mediated endothelial function and estimates of plaque progression by ultrasound or EBCT. Furthermore, biomarker studies can usefully be integrated into many studies in model systems (see above) as well as studies of clinical outcome (discussed below) to afford their ultimate validation.

Clinical Assessment of Tobacco-Related Disease

The time course of offset of myocardial infarction and stroke in people who stop smoking suggests that cardiovascular disease represents a tractable scenario in which one might evaluate harm reduction strategies. Clearly, assessment of the impact of such events can occur in a fairly reasonable time compared to that which is possible for cancer or lung disease.

RESEARCH AGENDA

1. Determine whether physiological and biochemical measures that are altered by tobacco products may be used as indicators of disease risk and as a means to distinguish various forms of tobacco use in a broad range of exposures (doses), including:
   - activation of platelet function;
   - endothelial function;
   - endothelial thickening and plaque formation;
   - blood pressure and heart rate alterations;
   - vascular aneurysm formation;
   - vascular thrombosis (arterial and venous);
   - cardiac electrophysiology, including ventricular and atrial ectopy, heart rate variability, and variations in conduction times, especially QT intervals; and
   - other risk factors for cardiovascular disease including lipid and carbohydrate abnormalities, homocysteine, folic acid and antioxidant vitamins, markers of inflammation, and immune function.

Based on current evidence, oxidative stress seems likely to play an important role in mediating the cardiovascular effects of smoking. Determining reliable biomarkers of oxidative stress and the interaction of un-

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stable oxygen intermediates with lipids, proteins, and DNA should receive high priority. Since inflammation is a proximate cause of oxidative stress, further work on biomarkers of inflammation such as C-reactive protein, cytokines, and acute-phase proteins and the effects of tobacco exposure appears to be an important research direction. Similarly, further assessment of the effects of various tobacco products on biomarkers of hemostatic activation and platelet function should be fruitful in understanding and predicting atherogenesis.

2. Develop studies to determine whether new biomarkers, such as products of lipid peroxidation and corresponding adducts to DNA, and products of arachidonic acid metabolism can serve as intermediate indicators (risk factors) of cardiovascular disease risk related to different tobacco products, and tobacco-related PREPs in particular. Through well-designed clinical trials, determine the ability of antioxidant or related therapies to counter the tobacco-related perturbations due to oxidative stress that are likely to be caused by both conventional and new tobacco products.
3. Develop long-term observational studies in individuals exposed to conventional and modified tobacco products primarily *and* secondarily (i.e., passive smoking), better to identify actual risks for cardiovascular disease, including dose-response characteristics. Included should be evaluations of the variables described in items 1 and 2, subsequent cardiovascular disease development, and potential differences in different tobacco or smoking products.
4. Further apply modern in vitro and other model systems, and ex vivo in humans, to assist in elucidating the comparative toxicology or adverse effects of cigarette smoke and PREPs. Such studies might include the use of gene array and proteomic technologies to study differential gene expression and translation; the use of chronic exposures to investigate effects on atherosclerosis progression, response to thrombotic and arrhythmogenic stimuli, and cardiovascular disease development; and studies of the effects of cigarette smoke and its constituents on the function and integrity of cardiovascular cells in vitro, including platelets, leukocytes, endothelial cells, vascular smooth muscle cells, and myocytes.
5. Apply modern genomic and proteomic analyses to elucidate the array of genes of potential relevance to cardiovascular hazards differentially induced by exposure to conventional tobacco products and PREPs. Utilize such techniques as transgenic and knockout model systems to elucidate the relevance of single genes to vascular injury induced by cigarette smoke and its discrete constituents, including nicotine. Assess the possibility of allelic varia-

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tion in such genes and its relevance to smoking-induced cardiovascular disease risk.

6. Continue to elucidate further aspects of the vascular biology of nicotine in view of its effects on flow-mediated vasodilation and the particular susceptibility of young smokers to prolonged exposure to nicotine products. Further careful evaluation of the dose-related effects of nicotine on platelet, leukocyte, hemostatic, and endothelial function and subsequent vascular injury, thrombogenesis, and atherogenesis is indicated.

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14

Nonneoplastic Respiratory Diseases

In persons who smoke, the cells that line the bronchi and alveoli come into direct contact with high concentrations of tobacco toxicants. Not surprisingly, respiratory diseases such as chronic obstructive pulmonary disease (COPD) are major health problems in smokers (Murin and Silvestri, 2000). Tobacco-related respiratory diseases predominately affect male smokers, but the prevalence of COPD in women is rising rapidly and it appears to follow the prevalence of smoking by 20-30 years (Tanoue, 2000). Children exposed to environmental tobacco smoke (ETS) are also affected (Joad, 2000). Because low levels of tobacco toxicants from ETS come in direct contact with the lung, it is necessary to consider the health effects of both mainstream and secondary smoke.

In evaluating harm reduction strategies for tobacco-related lung diseases, three major nonneoplastic respiratory diseases linked to cigarette smoking must be considered: COPD, asthma, and respiratory infections. Numerous other respiratory diseases are strongly related to cigarette smoking as shown in Table 14-1 (Murin et al., 2000). The relative risks of mortality due to smoking-related nonneoplastic respiratory diseases are considerable, and approximately 91,000 Americans died annually of respiratory diseases attributed to smoking during 1990-1994 (Table 14-1 and 14-2) (Novotny and Giovino, 1998). Cigarette smoking is estimated to contribute to 80-90% of cases of COPD, and the amount and duration of cigarette smoking directly influence the progression of COPD. Asthma and respiratory infections, on the other hand, are not caused by tobacco smoke but are worsened by exposure to cigarette smoke. Of special im-

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TABLE 14-1 Smoking-Affected Pulmonary Diseases

Disease Incidence or Severity Definitely Increased by Smoking
Common cold
Influenza
Bacterial pneumonia
Tuberculosis infection
Invasive pneumococcal infection
Pulmonary hemmorrhage
Pulmonary metastatic disease
Spontaneous pneumothorax
Eosinophillic granuloma
Respiratory bronchiolitis-associated interstitial lung disease
Idiopathic pulmonary fibrosis
Asbestosis
Rheumatoid arthritis-associated interstitial lung disease
Disease Incidence or Severity Possibly Decreased by Smoking
Sarcoidosis
Hypersensitivity pneumonitis

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portance in considering harm reduction strategies is the contribution of ETS to asthma and respiratory infections in children. Abatement strategies for susceptible children exposed to environmental tobacco smoke may differ from those used to reduce harm in tobacco smokers.

An extensive knowledge base exists describing the contribution of tobacco smoke exposure to nonneoplastic respiratory disease, and key points are described briefly here. The major goal of this chapter is to summarize studies designed to test whether reducing exposure to tobacco toxicants improves health outcomes for respiratory diseases. As will be described below, there are considerable gaps in information about reducing harm and uncertainties about the quality of the existing knowledge base in this regard. Consequently, a research agenda is proposed to guide future studies aimed at reducing the harm from smoking in COPD.

BIOMARKERS OF RESPIRATORY DISEASES

There are currently no specific biomarkers of respiratory disease due to smoking tobacco products (see Chapter 11). The rare genetic deficiency of α_1-antitrypsin is a risk factor for disease, not a biomarker (see below). No unique molecular or genetic defect specific for tobacco-related respi-

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TABLE 14-2 Relative Risk (RR) for Smoking-Attributable Mortality and Average Annual Smoking-Attributable Respiratory Disease Mortality (SAM) Among Current and Former Smokers, by Sex and Disease, United States, 1990-1994

	Men			Women			
Respiratory Disease	Current Smokers RR	Former Smokers RR	SAM	Current Smokers RR	Former Smokers RR	SAM	Total SAM
Pneumonia, influenza	2.0	1.6	11,267	2.2	1.4	8,060	19,327
Bronchitis, Emphysema	9.7	8.8	9,642	10.5	7.0	6,475	16,117
Chronic airway obstruction	9.7	8.8	32,132	10.5	7.0	21,893	54,025
Other respiratory diseases	2.0	1.6	776	2.2	1.4	721	1,497
Total			53,817			37,149	90,966

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ratory disease has been identified. The processes involved, such as inflammation and increased levels of oxidants, are not unique to tobacco-related respiratory diseases. Identifying unique biomarkers is further confounded by the heterogeneous nature of these diseases, the complex mixture that makes up tobacco smoke, and the range of individual susceptibilities to the harmful effects of tobacco smoke among users (see Chapter 11). In COPD, for example, the majority of smokers develop abnormal lung function (Camilli et al., 1987), but only 15-20% will develop symptomatic COPD (Fletcher and Peto, 1977). There appears to be no specific clinical or physiological feature to predict which smokers exhibit a rapid decline in lung function (Habib et al., 1987). The most widely used markers of tobacco-related respiratory diseases in population studies are symptom questionnaires and pulmonary function testing. These have well-known limitations of specificity and sensitivity, particularly for detecting the early effects of tobacco smoke on lungs (U.S. DHHS, 1989). Subtle effects of tobacco smoke exposure on the lung can be detected by sampling fluid in

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the lower respiratory tract via a bronchoscope inserted into the airways, but the significance of these changes to clinically important pulmonary disease has not been established. Newer approaches such as sampling the subjects' urine (Pratico et al., 1998) or exhaled gas (Ichinose et al., 2000; Paolo et al., 2000) for metabolic products due to tissue injury have the advantage of noninvasive sampling but must be validated. Clearly, the greatest obstacle for developing a specific biomarker is the lack of fundamental information on mechanisms by which exposure to tobacco smoke causes specific respiratory diseases. Insight into understanding the molecular basis of diseases may come from unraveling the complex interactions between genetic makeup and the environment that could evolve from the Human Genome Project or similar molecular studies.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and Epidemiology

Chronic obstructive pulmonary disease is an all-inclusive term that encompasses chronic bronchitis (the presence of chronic productive cough) and emphysema (permanent enlargement of the distal airspaces) (Aubry et al., 2000). Usually, chronic bronchitis and emphysema occur in combination. The major clinical features of COPD are chronic cough, expectoration of sputum, breathlessness during exertion, and airflow obstruction on forced expiration that tends to worsen over time (Barnes, 2000; Piquette et al., 2000).

The natural history of COPD and its health care implications have been extensively reviewed (Hensley and Saunders, 1989). The course of COPD is characterized by loss of ventilatory function from the peak attained in early adulthood (Figure 14-1). Clinical symptoms of COPD develop after substantial loss of ventilatory function, typically in the fourth and fifth decades of life. In longitudinal studies, the average loss of function in nonsmokers begins at about age 30 as assessed by the relationship of change in forced expiratory volume at 1 second (FEV_1) with age. In nonsmokers, this amounts to about 20 ml per year. The rate of decline in FEV_1 is somewhat greater (40 ml per year) in smokers of 30 cigarettes per day compared to nonsmokers (Camilli et al., 1987; Fletcher and Peto, 1977). A subset of smokers, who will develop COPD, lose function more rapidly (60 ml per year; Habib et al., 1987). However, there is variation in these rates and the rate of decline increases with age (Camilli et al., 1987; Fletcher and Peto, 1977). Smokers who cease smoking do not regain lost function, but the rate of decline of FEV_1 slows to that of nonsmokers (Burrows, 1990). Loss of lung function appears to be a risk factor for mortality even among "never smokers" (Ashley et al., 1975; Beaty et al.,

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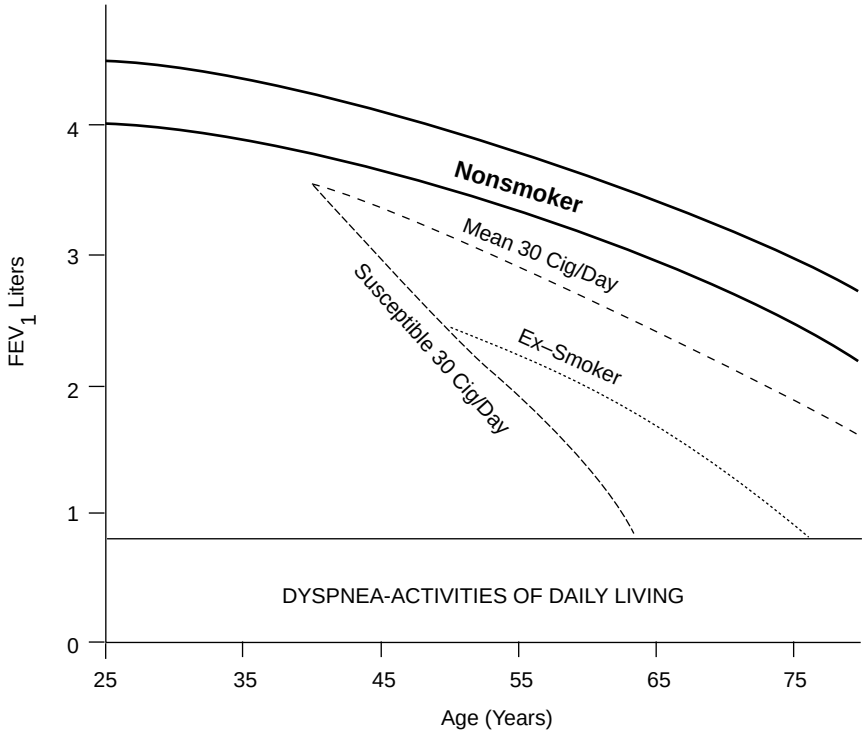


FIGURE 14-1 FEV_1

NOTE: Scheme showing loss of forced expiratory volume at 1 second (FEV_1) with age. Nonsmokers lose lung function with age, about 30 ml per year. Smokers of 30 cigarettes/day have a greater rate of loss (dashed line). A small proportion of smokers (10-15%) have a steeper rate of decline, about 60 ml per year (dot and dashed line). This susceptible group of smokers reaches an FEV_1 of 0.8 liter (the level at which shortness of breath occurs on activities of daily living) at approximately 60-70 years of age. If a susceptible smoker stops smoking at age 50, the rate of decline follows that of the nonsmoker (dotted line), showing that smoking cessation may prolong onset of symptoms.
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1985). A loss of lung function may reflect other diseases such as heart disease that decrease life expectancy (Beaty et al., 1985). The annual number of deaths attributable to chronic airway obstruction, bronchitis, and emphysema in the United States during 1990-1994 was 70,000 (Table 14-2). The relative risk of death from COPD in smokers who have symptoms is reduced by cessation, but remains almost as high as that of current smokers. Many of those who eventually die of COPD suffer from prolonged disability due to dyspnea, cough, and sputum production.

Pathogenesis

The role of inflammation and exposure to toxins in cigarette smoke is central to the pathogenesis of COPD (Aubry et al., 2000). There is considerable evidence to support the theory that pulmonary emphysema is caused by excessive exposure to elastolytic enzymes in relation to inhibitors of these enzymes, the "protease-antiprotease" theory (Barnes, 2000; Piquette et al., 2000). Cigarette smoke promotes injury to the lungs by increasing the proteolytic burden and compromising the antiproteolytic defenses leading to a breakdown in lung structure. The major antiproteolytic protein in the lower respiratory tract is α_1-antitrypsin (α_1-AT), although other proteinase inhibitors play a lesser role (Senior and Shapiro, 1998). In chronic bronchitis, an inflammatory airway response caused by chronic exposure to airborne toxins (cigarette smoke, dust, air pollutants) is the central pathogenic mechanism (Barnes, 2000; Piquette et al., 2000). Inflammation leads to edema, cellular infiltration, fibrosis, smooth-muscle hypertrophy, and secretions that narrow the bronchioles.

Animal models of emphysema and chronic bronchitis have been used to study the pathophysiology of COPD (Drazen et al., 1999; Shapiro, 2000), including the contribution of tobacco smoke (Witschi et al., 1997) (see Chapter 10).

Several etiologic factors in COPD have been investigated with regard to cigarette smoking (Sethi and Rochester, 2000). One factor is airway hyperreactivity, measured by the provocation of airway constriction following inhalation of a bronchoconstricting drug or physical condition. Several longitudinal studies have shown that airway hyperreactivity is related to accelerated decline in lung function in cigarette smokers (Frew et al., 1992; O'Conner et al., 1995; Postma et al., 1986; Rijcken et al., 1995; Tashkin et al., 1996; Tracey et al., 1995). Hyperresponsiveness in the presence of blood eosinophilia increases the risk of developing respiratory symptoms (Jansen et al., 1999). If airway hyperreactivity plays a role in the progression of COPD, it is possible that regular use of bronchodilators may slow the rate of decline. However, this conclusion was not supported by the Lung Health Study (Anthonisen et al., 1994; see below).

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Special tests of "small-airway" function were developed in the late 1960s and early 1970s to detect early changes in small airways (less than 2-mm diameter) that were are not detected on standard tests of pulmonary function (U.S. DHHS, 1984). When applied to prospective studies of populations, tests of small-airway function were not predictive for susceptible subjects who would progress to clinically significant airflow obstruction (U.S. DHHS, 1984). In subjects who exhibit accelerated deterioration of lung function (greater than 60 ml per year), this type of physiological testing was not predictive of the rate of development of clinically significant airway obstruction, probably because of the heterogeneous nature of COPD (Habib et al., 1987).

Mucous hypersecretion and infections have been postulated to play roles in the accelerated decline of pulmonary function in COPD. In adults, prospective studies have failed to show an association between acute chest infections and the rate of decline of FEV_1 (Bates, 1973). Chronic mucous hypersecretion in earlier studies (Fletcher and Peto, 1977; Higgins et al., 1982; Kauffmann et al., 1989; Peto et al., 1983) was not shown to be related to a decline in FEV_1 in COPD. More recent studies in larger samples of the general population have shown associations between chronic mucous hypersecretion and a decline in FEV_1 (Lange at al., 1990; Sherman et al., 1992; Vestbo et al., 1996). In children, however, population studies suggest that childhood respiratory infection is a risk factor for the development of COPD in adults (Gold et al., 1989; Samet et al., 1983). The role of infections is unclear, but it is believed that bacterial colonization/infection stimulates inflammatory responses that cause local damage and progression of disease. In addition, infections impair host defenses and tissue repair, leading to further infection and perpetuating tissue injury (Murphy and Sethi, 1992).

Considerable evidence from human and laboratory studies suggest that oxidant-antioxidant imbalance in favor of oxidants occurs in COPD (Figure 14-2). The evidence is based on a large number of studies showing an increased oxidant burden and markers of oxidative stress in the airspaces, breath, blood, and urine of smokers and patients with COPD (Koyama and Geddes, 1998; Macnee and Rahman, 1999). Oxidants in patients with COPD are derived from oxygen free radicals in both the gas and tar phases of cigarette smoke (Pryor and Stone, 1993; Zang et al., 1995). Inflammation itself induces oxidant stress in the lungs of smokers as suggested by studies showing greater production of oxygen free radicals by leukocytes in smokers compared to nonsmokers (Morrison et al., 1999) and increased iron content, which promotes formation of free radicals in alveolar macrophages of smokers (Mateos et al., 1998). Pathological examination of the alveolar regions of smokers' lungs has shown increases in the number and percentage of leukocytes compared to non-

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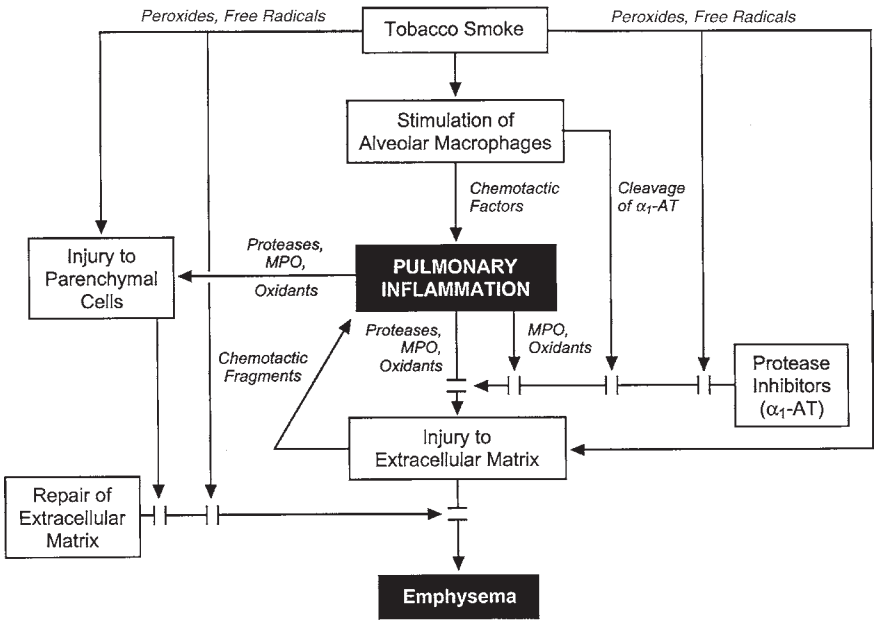


FIGURE 14-2 Pathogenesis of emphysema.

NOTE: Scheme of smoking-induced pulmonary emphysema. Smoking recruits inflammatory cells to the lower respiratory system via stimulation of alveolar macrophages. Inflammatory cells release enzymes (peroxidase, myeloperoxidase) and oxygen free radicals that degrade the extracellular matrix of the respiratory tissues and interfere with normal repair mechanisms. Tobacco smoke also contains oxygen free radicals that, together with products released from inflammatory cells, inactivate protease inhibitors such as α_1-AT.
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smokers (Hunninghake and Crystal, 1983). Recent studies have utilized analysis of exhaled gas in patients with COPD for gaseous products (i.e., reactive nitrogen species, ethane)(Ichinose et al., 2000; Paolo et al., 2000) and urinary products (isoprostane F_2-α-III) (Pratico et al., 1998) formed from oxidative stress. It is possible that measurement of products of oxidative stress in exhaled gas may be used as surrogate markers of inflammation in COPD. A possible mechanism whereby oxidants damage the lung is by inactivating the antielastase α_1-AT, thereby decreasing the ca-

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pacity of α_1-antitrypsin to inhibit proteases (Carp et al., 1982; Johnson and Travis, 1979). This mechanism has been expanded to include proteinases other than neutrophil elastase and antiproteinases other than α_1-AT (Senior and Shapiro, 1998). Dietary deficiency of antioxidants has been proposed as a factor accounting for airflow limitation in elderly people (Dow et al., 1996), but dietary supplements of antioxidants have not been shown to modify clinical symptoms of COPD (Macnee and Rahman, 1999; Rautalahti et al., 1997; Traber et al., 2000).

Mainstream Smoke Exposure

The predominant risk factor for COPD is cigarette smoking, and it is estimated to account for 80-90% of the risk of developing COPD (U.S. DHHS, 1984). Cigarette smoking is associated with a lower FEV_1 in cross-sectional studies (Burrows et al., 1977a; Dockery et al., 1988; Knudson et al., 1976) and with an accelerated decline in FEV_1 in longitudinal studies (reviewed in Sherman, 1991). The lower FEV_1 in cross-sectional studies and accelerated rate of decline in FEV_1 exhibit a dose-response relationship. Both the duration of smoking and the amount smoked are significant predictors of lung function impairment (U.S. DHHS, 1989).

Individuals who smoke have age-adjusted death rates for COPD that are tenfold higher than those of never smokers (U.S. DHHS, 1989). Mortality and morbidity rates for COPD are higher in pipe and cigar smokers than nonsmokers, although the rates are lower than in cigarette smokers. Factors predictive of COPD mortality include age at starting, current smoking status, and total pack-years. For reasons that are not known, only about 15% of smokers develop clinically significant COPD (Fletcher and Peto, 1977).

Data suggest that 10-15% of COPD cases are attributable to causes other than smoking, including occupational exposures to coal dust (Marine et al., 1988), grain dust (Zejda et al., 1993), air pollution (Bates, 1973; Buist and Vollmer, 1994; Rokaw et al., 1980), childhood respiratory infections (Burrows et al., 1977b; Shaheen et al., 1995), and airway hyperresponsiveness (Buist and Vollmer, 1994). Genetic factors that are independent of personal smoking history or environmental exposures also contribute to COPD (Khoury et al., 1985). These include a_1-antitrypsin deficiency, which accounts for less than 1% of cases of COPD (Snider, 1989). Additional genetic factors other than α_1-AT deficiency that appear to play a role in susceptibility to COPD have not been identified (Khoury et al., 1985).

Prospective population studies have shown an additive effect of air pollution on the decline in lung function in smokers (Tashkin et al., 1994;

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van der Lende et al., 1981). In a cohort study examining the additive effects of smoking and pollution on lung function decline, the mean adjusted decrement in FEV_1 attributable to smoking more than 24 cigarettes a day was 17.4 ml per year. An adjusted mean annual decrease of 8.9 ml per year was attributed to living in a moderately polluted environment compared to living in a clean environment (van der Lende et al., 1981). The conclusion of this study was that the decline in lung function attributable to smoking was twice as great when living in a polluted environment. In a prospective study of persons living in three communities with air pollution, a significant interaction between smoking more than 12 cigarettes a day and area of residence was found for mean decline of adjusted FEV_1 in males (Tashkin et al., 1994). These findings suggest an independent adverse effect of air pollution on decline of lung function in smokers.

Environmental Tobacco Smoke Exposure

Adults

Coultas (1998) has reviewed published reports of an association between ETS exposure and COPD. He classified three types of studies: two categories based on "indirect" measures of COPD (self-reports of symptoms of COPD; effects on lung function measurements) and a third category that used "direct" measures of COPD (mortality and hospitalizations). The studies focused on environmental tobacco smoke as a risk factor for developing COPD, not as factor that contributed to worsening of symptoms or lung function. In regard to self-reported outcomes, Coultas (1998) summarized the results of three studies (Dayal et al., 1994; Leuenberger et al., 1994; Robbins et al., 1993) published since the Environmental Protection Agency (EPA) report (EPA, 1993) that concluded environmental tobacco smoke "may increase the frequency of respiratory symptoms in adults." Results of one population-based survey of self-reported COPD suggest that 3-5% of nonsmokers may be affected (Whittemore et al., 1995). The three published reports combined asthma and COPD. These studies all report similar findings that passive smoking is associated with chronic respiratory symptoms found in adults with COPD.

The second type of study examined declines in lung function and passive smoking in the development of COPD. Epidemiological studies have investigated the association between environmental tobacco smoke, respiratory diseases, and reduction in pulmonary function tests (Sherman, 1991; Tredaniel et al., 1994). It is controversial whether ETS exposure is

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associated with COPD. Some studies have reported greater reduction in pulmonary function in nonsmokers married to smokers and exposed to environmental tobacco smoke in the workplace (Berglund et al., 1999; Hole et al., 1989; Leuenberger et al., 1994; Svendsen et al., 1987; White and Froeb, 1980). However, most of the studies used sensitive indicators of lung function, and the physiological significance of small changes in lung function to COPD is not established. In addition, the effect of bias and confounding factors were not taken into account. No relation between passive smoking and reduced lung function in adults was found in two large cross-sectional studies (Comstock et al., 1981; Schottenfeld, 1984) and one longitudinal study (Jones et al., 1983). Thus, whether environmental tobacco smoke causes COPD in adults remains uncertain.

Current evidence suggests that the development of COPD in adults results from impaired lung development and growth in childhood, premature onset of declines in lung function, and/or accelerated decline in lung function (Fletcher et al., 1976; Kerstjens et al., 1997; Samet and Lange, 1996). Although passive smoking is a biologically plausible risk factor, the impact of passive smoking during adulthood on the development of COPD remains controversial. In a review of this topic, Tredaniel and associates (1994) summarized the results of 18 relevant publications. Eight reports found no effect of ETS exposure on lung function, and ten demonstrated small decrements. The authors pointed out the methodological limitations of these studies and raised questions about the relevance of small declines in lung function to the development of COPD. Coultas (1998) reviewed the results of three additional studies published since the Tredaniel et al. (1994) review and concluded that the results were inconsistent (two showing no effect and one showing an effect). In the study showing an effect, a large sample of never-smoking adults in Switzerland (Leuenberger et al., 1994), the association between increased symptoms of chronic bronchitis and environmental tobacco smoke was dose-related. The adjusted odds ratio of chronic bronchitis symptoms increased by years of exposure to environmental tobacco smoke, number of smokers to whom the subject was exposed, and workplace exposures (Leuenberger et al., 1994). An additional report published after Coultas' review concluded that environmental tobacco smoke in adults is associated with small defects in lung function (Carey et al., 1999).

Children

Exposure to passive smoking in childhood has been associated with reduced rate of growth of the lung as determined by change of ventilatory function with age in children exposed to environmental smoke compared to unexposed children (Berkey et al., 1986; Tager et al., 1979, 1983, 1987)

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(see Chapter 15). However, one cohort study failed to find any effect of maternal smoking on lung growth (Lebowitz and Holberg, 1988), possibly due to differences in the amount of maternal smoking or differences in indoor environments (i.e., greater air mixing or exchange may decrease the concentration of environmental tobacco smoke). A recent study concluded that in utero exposure to maternal smoking is independently associated with decreased lung function in children of school age, especially for small-airway flows (Gilliland et al., 2000). Studies in neonates that excluded the effect of environmental tobacco smoke by measuring lung function after birth concluded that in utero exposure has an independent effect on reduced lung mechanics (Hanrahan et al., 1992; Stick et al., 1996). In a cross-sectional study by Milner et al. (1999), smoking was associated with a significant reduction in birthweight, but lung volume was not reduced when related to weight. Smoking was associated with a highly significant reduction in static compliance in boys and a small but significant reduction in respiratory conductance in girls. These authors concluded that smoking in pregnancy reduces static compliance in boys and conductance in girls although there was no evidence that maternal smoking adversely affected fetal development. Fetal lung hypoplasia has been produced in rats in a model of maternal cigarette smoke exposure (Collins et al., 1985). The weight of the evidence suggests that passive smoking contributes to COPD by causing a slight decrease in airway diameter that increases airway resistance.

Latency

There are limited data on the latency (Robbins et al., 1993) and dose-response (Dayal et al., 1994) between exposure to environmental tobacco smoke and the development of respiratory symptoms. Additional studies are needed, particularly of latency and dose-response relationships, to establish a causal relationship between passive smoking and COPD.

Review of Harm Reduction Strategies Applied to COPD

Impact of Smoking Reduction

It is plausible that reducing the number of cigarettes smoked per day would reduce disease risk. The presumption is that smoking causes morbidity and mortality in a dose-related manner. However, this presumption has never been formally tested (Hughes, 2000). One impediment to determining whether reducing smoking reduces risk is that a study would require a large number of subjects over a long time. Hughes (2000) estimated that 8,000 subjects would have to be followed for eight years. A

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large study would be required since there are no adequate surrogate markers of disease. Since a large study of this type would delay implementation of harm reduction measures, one school of thought is that the benefits from smoking reduction can be assumed and we need not wait eight years for the study to be completed (Hughes, 2000). Another school of thought argues that the decline in disease from smoking reduction may not be as great as presumed. This view is based on the following: (1) post hoc corrections for variables associated with smoking reduction may inflate mortality and morbidity among smokers, and (2) the expected reductions from "low-tar" cigarettes were not as great as expected (Hughes, 2000). It has been suggested that reducing smoking may undermine attempts at quitting, but based on limited evidence from three trials, Hughes (2000) concluded that there is no evidence to support this concern. It should be noted, however, that these results apply only to people who were self-motivated to reduce smoking, and the effects on quitting may not apply to the general population (Hughes, 2000).

There are data from retrospective cross-sectional, multicenter epidemiological studies suggesting that reducing smoking reduces the risk of COPD (Higgins et al., 1984). The risk for cigarette smokers of developing COPD was assessed in 958 men and 1,159 women ages 25 to 64 years over a 10-year period (1967-1969 and retested in 1978-1979). At entry, patients were excluded who already had borderline or definite COPD. Data for the change in daily cigarette consumption were available from only one center. The odds ratio (OR) for developing COPD within ten years predicted from the change in the number of cigarettes per day (number at follow-up minus number at entry into the study) was 1.7 for men and 2.4 for women. These results were interpreted as showing a benefit from stopping or reducing cigarette smoking. The limitations of this study are that it was not designed to show a change in mortality and morbidity for people who reduced smoking, that estimates are based only on survivors, and that it is a cross-sectional population study. Nevertheless, it does provide some evidence that reducing smoking might modify the risk of COPD.

The potential benefit to improving survival from COPD by reducing smoking can be analyzed from dose-response relationships between mortality and number of cigarettes smoked in a population. Such data are available from two large-scale prospective surveys of smoking and mortality among men and women in the United States sponsored by the American Cancer Society. The first survey of approximately one million people covered the period 1959 to 1972 and is referred to as Cancer Prevention Study I (Burns et al., 1997; CPS-I). The second survey was conducted from 1982 through 1986 on approximately 1.2 million people and is referred to as Cancer Prevention Study II (CPS-II; Thun et al., 1997).

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Methodological issues pertaining to calculations of risk-attributable mortality in these studies are discussed in the 1989 Surgeon General's report on reducing the health consequences of smoking (U.S. DHHS, 1989). Data are available from CPS-I that illustrate the relationship between cigarettes smoked per day and mortality rates from COPD among white male and female current smokers. Figure 14-3 shows data for two 15-year age groups (65-79 and 50-64 years). For both men and women age 65-79, the results show a monotonic increase in mortality rate from COPD as a function of number of cigarettes smoked per day, with higher rates in men than women. For men and women age 50-64, there is an apparent increase in mortality rate from COPD with number of cigarettes smoked per day, although the slopes are less steep than for the older group. These

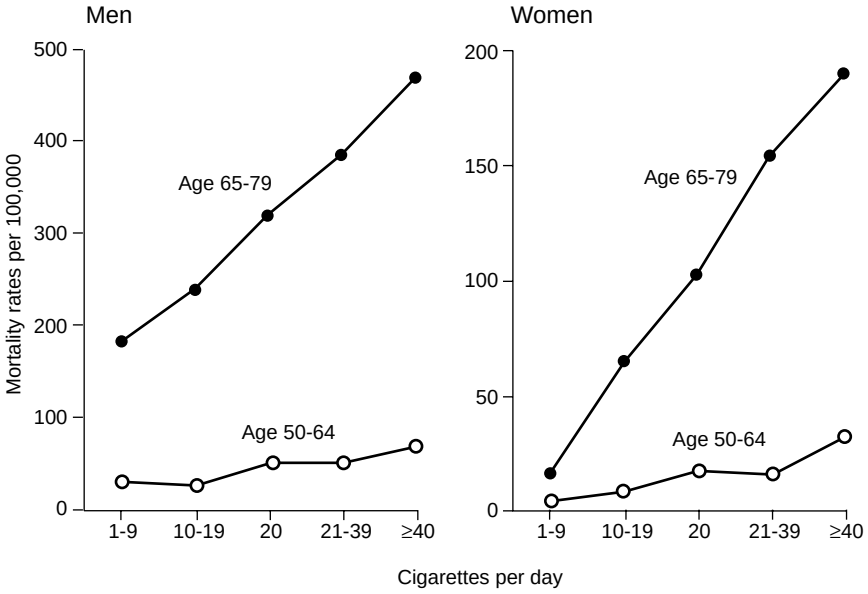


FIGURE 14-3 Mortality rates.

NOTE: Graphs showing relationships between mortality rates from COPD among current white smokers by level of cigarette consumption. Plotted are standardized mortality rates per 100,000 adjusted within 15-year age-specific rates to 1980 U.S. standard population for men and women.
SOURCE: Data for figure gathered from Burns et al., 1997.

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findings strongly suggest that increased cigarette smoking causes greater mortality due to COPD in current smokers.

One cannot infer from these results that reducing smoking will decrease mortality from COPD. However, the apparent by linear dose-response relationships suggest that decreasing the amount of cigarettes smoked may lead to fewer deaths from COPD. This may be particularly important to heavy smokers (more than 40 cigarettes per day). Caution is needed, however, in interpreting these results too simply. For example, it is unlikely that someone who smoked 40-plus cigarettes per day during adulthood will experience a substantial reduction in the risk of dying from COPD (e.g., comparable to that of a lifelong 20-cigarette per day smoker) if he or she were able to cut down on cigarette consumption. Only prospective studies of mortality in smokers who reduce their exposure to cigarettes will provide definitive answers to the question of how much mortality rates are decreased by reducing smoking.

Interventional Studies

A landmark study in smoking cessation in people at risk for developing symptomatic COPD is the Lung Health Study (Anthonisen et al., 1994). The study population consisted of 5,887 subjects from North America, 35 to 60 years old, who had presymptomatic COPD (no symptoms but abnormal lung function tests) and included a substantial fraction (37%) of women. Participants were moderate to heavy smokers (mean consumption, 31 cigarettes per day) who were motivated to quit smoking. They were randomized into three groups: (1) smoking intervention, (2) smoking intervention plus a brononchodilator, and (3) usual care. Smoking intervention was intensive and involved 12 group meetings in ten weeks. Behavior modification was stressed, and nicotine replacement therapy (NRT) with nicotine gum was used aggressively. Those who ceased smoking entered a maintenance program. Relapses were treated individually. The main outcome was the rate of change in FEV_1 measured annually over five years. The cessation rate was among the highest reported in any trial. In the intervention group, 35% were abstinent one year and 22% were abstinent for five years (compared to 5% in the non-intervention group). The most important finding of this intent-to-treat analysis was that smoking cessation reduced the rate of decline of FEV_1. In a separate analysis of the study population, symptoms of cough and sputum production, and dyspnea improved after smoking cessation (Kanner et al., 1999). The administration of a bronchodilator (ipratropium bromide) resulted in a small improvement in FEV_1 at the onset of use. However, this effect reversed when the drug was discontinued at the end

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of the study. The major conclusion of the Lung Health Study was that an aggressive intervention program of smoking cessation reduces the age-related rate of decline in FEV_1 in middle-aged smokers with mild airway obstruction in the first year. After that time, however, the rate of lung function decline was not different in the two groups. These results provide a measure of the impact of aggressive smoking cessation compared with the usual care in reducing the harm of cigarette smoking.

A particularly important audience at which to target harm reduction is young smokers who want to quit. To determine how rapidly lung function returns to normal after smoking is stopped in this group of subjects, Ingram and O'Cain (1971) used sensitive tests of lung function (frequency dependence of compliance) in six asymptomatic young smokers. Within eight weeks of smoking cessation, lung function had returned to normal in all subjects, suggesting that structural changes in the peripheral airways are reversible in these subjects after cessation of smoking.

There is a dearth of information on whether reducing cigarette smoking results in improvement in lung function. Two prospective studies in the 1970s and one in 1989 (Buist et al., 1976; Lange et al., 1989; McCarthy et al., 1976) examined the effect of reduced smoking over a one year period using volunteers with small-airway disease and either normal or mild reductions in FEV_1. Subjects who were able to reduce smoking consumption by 25% or more were considered to have reduced smoking. Tests of small-airway disease improved after smoking reduction, and in one study, FEV_1 showed slight improvement at one year (McCarthy et al., 1976). An observational study by Lange and colleagues in (1989) examined the effect of smoking habits on change in FEV_1 over a five-year period in more than 7,000 Danish men and women. Among these were a sample of 189 subjects who were grouped as reducing smoking from more than 15 cigarettes per day to less than 15 cigarettes per day between intake and final examination. Regression analysis of change in age-adjusted FEV_1 over five years showed that smoking reduction resulted in a beneficial effect in younger subjects (less than 55 years old) but not in older subjects (more than 55 years old). In the younger group, the annual decline in FEV_1 unadjusted for age in women who were able to reduce smoking was 14 ml per year versus 30 ml per year in women who continued to smoke more than 15 cigarettes a day. For younger men who were able to cut back on smoking, the reduction was 17 ml per year compared to 42 ml per year in those who continued to smoke more than 15 cigarettes a day. Limitations of this study were that it was an observational study, smoking habits were based on self-reported data, and there were wide interindividual differences in the rate of decline of FEV_1. Further limitations of these studies are that they were not designed primarily to test

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whether reducing smoking results in benefit as measured by less decline in lung function, but rather were designed to study the effect of cessation. Although they suggest that reducing smoking (at least in younger subjects) may slow the rate of decline in function, more rigorously designed prospective studies are needed to determine whether reducing smoking results in less harm to the lungs.

Decreasing Smoking Slows Decline in Lung Function

Numerous cross-sectional studies show that the level of smoking is a strong determinate of decline in lung function (U.S. DHHS, 1984, 1989). Multiple regression and analysis has been applied to these cross-sectional studies to determine the quantitative relationships between the rate of decline in FEV_1 and pack-years of cigarettes smoked (Burrows et al., 1977a; Dockery et al., 1988). In one study of over 8,000 men and women from U.S. cities (Dockery et al., 1988), it was estimated that the average male smoker lost 7.4 ml of FEV_1 for every pack-year of cigarettes smoked and that women lost 4.4 ml of FEV_1. FEV_1 values in the population were skewed toward lower values for the smokers compared to the nonsmokers. This suggests that the loss in FEV_1 was relatively larger in smokers than nonsmokers. It is uncertain whether these data could be used to predict a slower rate of decline in lung function if a smoker reduced the number of cigarettes smoked over a prolonged period of time. There are several uncertainties about using studies of longitudinal change in lung function to predict slowing of lung function after reducing smoking. For example, the observations were made over a limited span of the natural history of COPD and it is unclear whether the measured changes in reduced FEV_1 correlated with progression of disease. Function of pack-years smoked remains constant throughout the natural history of the disease. It is possible, for instance, that a more rapid decline in lung function takes place after an event such as an infection or that the rate of decline accelerates with age. Individual factors that contribute to the rate of decline of lung function are poorly understood and also influence progression of disease. Because of uncertainties about the natural history of COPD, it is not possible to use longitudinal studies of decline in lung function as a function of pack-years smoked to estimate the reduction in harm in terms of decline in lung function from reducing cigarette smoking.

Effect of Short-Term Smoking Reduction on Lung Inflammation

The beneficial effect of short-term smoking reduction has been studied in current smokers using a technique that enables inflammation in the lower respiratory tract to be examined directly (ECLIPSE, 2000; Rennard,

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2000; Rennard et al., 1990). In current cigarette smokers, three approaches to reduce smoking consumption were used: administration of nicotine medication, switching to a low-tar and nicotine cigarette, and using Eclipse™ (R.J. Reynolds Tobacco Company), a product that results in less combustion of tobacco and potentially generates relatively less tar than nicotine. All studies used a similar approach. Heavy smokers (at least two packs per day) who had no clinical or physiological evidence of COPD were enrolled. During the reduced smoking period, cigarette smoke exposure was monitored by exhaled carbon monoxide (CO) concentration, serum cotinine level, and self-monitoring the number of cigarettes smoked. Lung inflammation was assessed before and two to three months after reduced smoking using bronchoalveolar lavage. Inflammatory cells and protective antiproteinase molecules were measured in the fluid sample, and results were compared to those from nonsmokers. The degree of inflammation of the airways was scored by directly visualizing the degree of erythema and edema though the bronchoscope.

Reduced smoking by approximately 50% (measured by self-reporting and exhaled CO) was achieved by the use of nicotine medication (Rennard et al., 1990). The amount of visible inflammation decreased but remained greater than that of nonsmokers. In lavage fluid, the number of inflammatory cells (particularly the pigment-laden macrophages and neutrophils) and the amount of elastase complexed to its a_1-antiproteinase inhibitor decreased after smoking reduction. These results show that reducing smoking from two packs to one pack per day produces a significant decrease in lung inflammation within two to three months. Whether the reduced inflammation results in less risk of developing COPD remains to be determined.

A second study examined the effect of switching to low-tar and nicotine cigarettes (ECLIPSE, 2000; Rennard, 2000). This study differed from the nicotine replacement study in several ways: the subjects had moderate to heavy cigarette smoking (approximately 30 cigarettes per day) at enrollment, subjects chewed either nicotine gum (2 or 4 mg) or a placebo gum, and the duration of the study was six months. The groups that used NRT reduced their cigarette consumption (measured by self-reporting and exhaled CO). However, the group that used the low-tar and nicotine cigarettes did not reduce smoking because they changed their smoking strategy to compensate. The results showed no reduction in the inflammation score in the group that used low-tar and nicotine cigarettes, which was attributed to altered smoking strategy.

The study using heated tobacco (Eclipse™) was similar in design to the reports cited above and involved 12 smokers studied after a three-month intervention. Exhaled CO was used to monitor cigarette use. Although one-third of the study group smoked conventional cigarettes, the

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number of conventional cigarettes used was small (97% of all products consumed were Eclipse™). In Eclipse™ users, inflammation scores and number of recovered alveolar macrophages decreased after intervention as did the density of goblet cells (an index of the mucous secreting cells) on bronchial biopsies. (Results of neutrophil counts were confounded by outliers in the control group.) After three months of Eclipse™, inflammation scores and goblet cells density remained above levels found in nonsmoking controls. The small number of patients and control subjects limits interpretation of this study.

In summary, asymptomatic smokers clearly have inflammation in their lower respiratory tract, and this inflammation is likely to be involved in the pathogenesis of COPD. The major conclusion of Rennard's (Rennard, 2000; ECLIPSE, 2000) studies is that smoking reduction has measurable effects on inflammation. It is plausible that reducing inflammation by reduced exposure to cigarettes will mitigate the development of COPD. However, the hypothesis that reduced smoking will lead to less severe COPD needs considerably more study using prospective intervention trials in persons susceptible to developing COPD.

ASTHMA

Definition and Epidemiology

Asthma is defined as a "chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing airways hyperreactivity to a variety of stimuli" (NIH, 1997). There is no standardized method for measuring asthma, and the lack of standardization has hampered the investigation of asthma by making it difficult to compare results of different studies (Woolcock, 1994).

Asthma is an extremely common disorder in the United States, with approximately 10-15% of boys (Sly, 2000), 7-10% of girls (Sly, 2000), and 5% of adults having signs and symptoms consistent with asthma (Drazen, 2000). Asthma has its origins primarily in childhood, with 50% of all asthma diagnosed by three years of age and 80% by six years of age (Yunginger et al., 1992), although asthma may develop at any time

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throughout life. The worldwide incidence of asthma has increased more than 30% since the 1970s (Weiss et al., 1993). A disproportional fraction of these cases have occurred among socioeconomically disadvantaged urban dwellers. The reason for the increased incidence of asthma is not known. In the United States, the overall age-adjusted prevalence of asthma increased 54% from 1980 to 1993-1994 (from 31 to 54 per 1,000 population) (NCHS, 1999).

Pathogenesis

The factors that influence the pathogenesis of asthma include atopy (production of abnormal amounts of immunoglobulin E [IgE]), early respiratory illness (before age two), and parental history of atopy (Woolcock, 1994). Allergens act as triggers of asthma attacks and provoke inflammation of the airways. Other triggers include exercise and air pollutants such as ozone and sulfur dioxide (Woolcock, 1994). Inflammation of the airways with lymphocytes, mast cells, and eosinophils and production of certain interleukins by these cells creates an environment that promotes the production of IgE. The links between infiltration of cells and the pathobiologic processes that account for episodic airway narrowing have not been clearly delineated. The constriction of airway smooth-muscle cells due to the local release of bioactive mediators or neurotransmitters is a widely accepted explanation for acute constriction of the airways, but thickening of airway epithelium and the presence of liquid in the lumen may also contribute. The consequences of airway obstruction are decreased flow rates throughout expiration. As the asthma attack resolves, airway narrowing reverses and flow rates return toward normal. These physiological and pathological changes account for intermittent symptoms of shortness of breath, coughing, and wheezing (Drazen, 2000).

Mainstream Smoke Exposure

Asthmatics have extreme sensitivity of the airways to chemical, physical, and pharmacological stimuli, which can cause pronounced airflow limitation (Drazen, 2000). Cigarette smoke is a complex mixture of irritant compounds. Smoking can potentially lead to amplification of the airway inflammation already present in asthmatics by a number of mechanisms including recruitment of inflammatory cells, enhancement of some cellular function, and release of proinflammatory mediators (Floreani and Rennard, 1999). For example, cigarette smoking stimulates production of cysteinyl leukotrienes (Fauler and Frolich, 1997), a class of mediators that is increased in asthmatics, causes rapid proliferation of cells in small air-

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ways (Sekhon et al., 1994). In addition to inflammation, cigarette smoking is associated with increased airway wall remodeling (U.S. DHHS, 1990), a change asociated with chronic asthma. Physiological studies have shown that direct cigarette smoking causes acute bronchoconstriction in subjects with asthma (Nadel and Comroe, 1961). Many patients with asthma report worsening respiratory symptoms upon active cigarette exposure. In a cross-sectional study of 225 adult asthmatics, current smokers had a higher asthma symptom scores than nonsmokers when adjusted for age, gender, and physician visits (Althuis et al., 1999). However, there are methodological issues that might obscure the associations between active smoking and asthma in cross-sectional studies. One form of selection bias, referred to as the healthy smoker effect (Weiss et al., 1999), refers to self-selection of subjects with less mild asthma as active smokers compared to those who remain smokers. The probability of an asthmatic becoming an active smoker may be less in individuals who have a greater airway hyperreactivity or who become more symptomatic when they smoke. Similarily, adults who had childhood asthma may be more likely to remain nonsmokers than those who did not have asthma in childhood. Thus, cross-sectional studies of smoking and asthma have limitations of interpretation. Nevertheless, observational studies show that asthmatics who are unable to cease smoking have more serious problems with control of asthma and have more frequent hospital admissions than nonsmoking asthmatics (Abramson et al., 1995; Floreani and Rennard, 1999).

Since the 1960s, it has been suggested that airways hyperresponsiveness and atopy are risk factors for the development of COPD, the so-called Dutch hypothesis (Orie et al., 1961). Data from several longitudinal studies now clearly show that airways hyperreactivity is a susceptibility factor for accelerated decline of lung function in active cigarette smokers compared to smokers without airways hyperreactivity (Frew et al., 1992; O'Connor et al., 1995; Rijcken et al., 1995; Tashkin et al., 1996; Tracey et al., 1995). Data from the Lung Health Study, a five-year prospective study of subjects with mild COPD, showed that responsiveness to methocholine at the initiation of the study was a strong predictor of change in FEV_1 in continuing smokers even after controlling for baseline lung function, number of cigarettes smoked, and demographic variables (Tashkin et al., 1996). Moreover, airway reactivity appeared to be a more important determinant of subsequent lung function decline then baseline lung function. In addition, the magnitude of the decline in FEV_1 increased with greater levels of airways hyperreactivity. The design of the study did not permit the distinction of whether the risk factor for progression of COPD was airway hyperreactivity itself or an underlying mechanism of reactivity such as inflammation. The finding that the effect of reactivity on lung function decline was greatest in continuing smokers compared to subjects

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who quit smoking suggests that the effect is at least partially due to progressive airway damage induced by smoking. Since subjects who reduced smoking were not analyzed, there is insufficient information to determine whether decreasing the number of cigarettes smoked leads to less airways hyperreactivity.

Environmental Tobacco Smoke Exposure

Adults

The three major reviews of the health effects of passive smoking published between 1986 and 1992 cited no literature directly examining the association between passive smoking and asthma in adults (NRC, 1986; U.S. DHHS, 1986). Coultas (1998) reviewed studies on this topic from 1992 to 1998 and classified them as etiological studies (the association between passive smoking and the diagnosis of asthma) and morbidity studies (the role of passive smoking in causing symptoms or worsening lung function in patients with asthma). Among the papers reviewed was that of Hu and coworkers (1997) who observed in young adults that physician-diagnosed asthma was associated with parental smoking. The odds ratio was 1.6 (95% confidence interval [CI]=1.1, 2.3) for maternal smoking and 1.3 (95% CI=0.9, 1.8) for paternal smoking. Their investigators also found a dose-response relationship with the amount smoked and the number of parents smoking. Greer and associates (1993) studied a large, nonsmoking population over a ten-year period to examine the association between workplace exposure to environmental tobacco smoke and the development of asthma. After controlling for confounding factors, workplace ETS exposure was a significant risk for asthma (relative risk [RR]=1.5, 95% CI=1.2, 1.8). In another study of more than 4000 never-smoking adults, Leuenberger and associates (1994) found exposure to environmental tobacco smoke at home or work was associated with physician-diagnosed asthma (OR=1.4; 95% CI=1.0, 1.9).

Several studies have examined the role of environmental tobacco smoke as a factor for asthma in adults. There are limitations of present epidemiological studies including potential biases in both subject selection and misclassification of exposure and differing designs. The effects of environmental tobacco smoke on pulmonary function in otherwise healthy adults are likely to be small and unlikely to result in clinically significant chronic respiratory disease (Zeise et al., 1997). Although the results tend to indicate potential effects of environmental tobacco smoke as a cause of asthma in adults, the present epidemiological data are limited and have to be interpreted cautiously.

The results of published reports on the effects of ETS exposure on

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respiratory symptoms and lung function in adults have been summarized by Tredaniel and associates (1994) and Coultas (1998). Six observational studies in patients and six experimental studies of patients with asthma are reviewed. In general, these studies report that environmental tobacco smoke worsens respiratory symptoms and lung function among adult asthmatics. There are no published intervention trials in adults examining whether decreasing exposure reduces asthma symptoms or impairment of lung function.

A recent review evaluated the quality of the studies of the relation of environmental tobacco smoke as an exacerbating factor for asthma in adults (Weiss et al., 1999). Although exposure of adult asthmatics to environmental tobacco smoke was associated with increased symptoms of asthma, these studies are subject to recall and information bias, and no firm conclusions can be made. On the other hand, a number of controlled exposure studies have examined the effect of exposure to environmental smoke in healthy adult volunteers and subjects with asthma (Weiss et al., 1999). In general, the experimental studies show that brief exposure to ETS produces symptoms such as eye and nasopharyngeal irritation with less consistent responses in terms of lung function. Airway hyperreactivity after environmental smoke exposure was assessed by bronchoprovocation tests using methacholine. The majority of these studies failed to document an effect on ventilatory function or measures of airway responsiveness. In general, studies evaluating acute exposure of adult asthmatics to environmental tobacco smoke have generated conflicting data, yet there is evidence that some asthmatics and groups of asthmatics do respond to ETS levels that do not elicit responses in healthy volunteers. However, because of the limited number of studies and potential problems in their design, definitive conclusions cannot be drawn at this time.

Children

The relationship between environmental tobacco smoke and asthma, lung function, and respiratory symptoms in childhood has been reviewed (Cook et al., 1998; Cook and Strachan, 1997; NRC, 1986; Strachan and Cook, 1998; U.S. DHHS, 1986). Most of the studies support the notion that small but significant differences can be detected in respiratory symptom prevalence and pulmonary function studies comparing children exposed to environmental tobacco smoke and children who are unexposed. The incidence of wheezing illnesses in children whose parents smoke is greatest in early life, whereas the incidence of asthma during school years in less strongly affected by parental smoking. This may be due to a stronger influence of viral-associated wheezing in early childhood or less exposure to maternal smoke among older children.

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The results of effects on spirometric indices of passive smoking have been reviewed (Cook et al., 1998; Cook and Strachan, 1999). These analyses concluded that passive smoking is associated with a small but significant reduction in FEV_1 and other spirometric indices in school-age children without asthma. For example, the large Six Cities Study showed a very small but significant effect of maternal smoking on lung growth (minus 3.8 ml per year for FEV_1) (Tager et al., 1983). Such subtle reductions are unlikely to impact the rates of development of chronic obstruction in airflow unless data emerge demonstrating that children exposed in early life have more rapid decline of lung function. Unfortunately, none of the longitudinal studies have looked at changes in lung function in relation to change in maternal smoking behavior. Therefore, it is unknown whether their effects are reversible. Similarly, a study in infants demonstrated that a family history of parental smoking contributes to airway hyperresponsiveness at an early age (Young et al., 1991). Whether these normal, healthy infants with airway hyperresponsiveness develop asthma as adults is not known.

An important issue in evaluating potential strategies for reducing harm from environmental cigarette smoke among asthmatic children in smoking households is to assess the relationship between biomarkers of cigarette smoke exposure and severity of asthma. If a dose-effect relationship exits, these data might indicate the approximate extent of reduction in exposure that may be expected to reduce the severity of asthma in children residing with smokers. Several studies have examined the dose-response relationship in asthmatic children using cross-sectional or case-control designs (Table 14-3). Asthma was assessed by self-reporting, physical examination, or lung function studies, and cotinine was measured in urine or saliva. Two general types of analyses were done: (1) associations of mean levels of cotinine in asthmatic or control groups (Group A) and (2) relationships between cotinine levels and asthma severity (Group B). Two studies (Ehrlich et al., 1992; Willers et al., 1991) found higher levels of cotinine in urine of asthmatics than controls, and one study found that cotinine levels in saliva were no different in asthmatics and control subjects (Chang et al., 2000). Four studies showed a relationship between urinary cotinine levels and the severity of asthma (Chilmonczyk et al., 1993; Ehrlich et al., 1996; Oddoze et al., 1999; Rylander et al., 1995) (see Table 14-3).

There are methodological problems with these studies, however, since most have not controlled for confounding factors such as respiratory illnesses or exposure to house mite antigen. It is possible that children of parents who smoke are more likely to become allergic or to have respiratory infections. Moreover, the effects are applicable only to some age groups or some symptoms of asthma, leading to inconsistencies in the

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TABLE 14-3 Relationships Between Cotinine Levels in Asthmatic Children Exposed to Environmental Tobacco Smoke

Author and Year	Study Type and Sample Size	Asthma Population	Cotinine	Asthma	Finding
Group A–Association of high cotinine levels with asthma					
Willers et al., 1991	Case-control 49/77	3-15 yr. old, clinic	Urinary	Self-reporting symptoms	Cotinine levels greater in cases than controls ($p<0.005$)
Ehrlich et al., 1992	Case-control 72/121	3-14 yr. old, ER and clinic	Urinary, grouped <30 ng/ml or >30 ng/ml	Clinical exam	Cases had higher cotinine levels than control (OR=1.9, 95% CI 1.0-3.3)
Chang et al., 2000	Case-control 165/106	2 mo.-16 yr. old, ER	Salivary	Clinical exam	No difference in cotinine levels between case and control groups
Group B–Dose-effect relationship between cotinine and asthma severity					
Chilmonczyk et al., 1993	Case-control 199/199	8 mo.-13 yr. old, clinic	Urinary, grouped, <10, 10-39, >39 ng/ml	Asthma exacerbations; lung function	Monotonic relationship for ↑ exacerbations and ↓ function
Rylander et al., 1995	Case-control 199/351	4 mo.-4 yr. old, hospital	Urinary	Clinical exam	Risk of wheezing increased with cotinine concentration
Ehrlich et al., 1996	Case-control 368/294	7-9 yr. old; heavy household smokers	Urinary	Self-reported symptoms	Positive exposure-response relationship for asthma and cotinine by quartile ($p=0.02$)
Oddoze et al., 1991	Cross sectional 90	4-14 yr. old, clinic	Urinary	Bronchial responsiveness	Bronchial responsiveness correlated with cotinine level ($p<0.03$)

NOTE: ER=emergency room; OR=odds ratio; CI=confidence interval

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reported results. Finally, the clinical significance of the small differences in lung function or symptoms is unknown. Therefore, there is uncertainty about whether a dose-response relationship exists between cigarette smoke exposure as measured by cotinine levels and severity of asthma, and this subject requires more study before harm reduction studies can be planned.

Review of Harm Reduction Strategies Applied to Asthma

Several studies have examined the effect of reducing tobacco smoke exposure on wheezing symptoms. In one study (O'Connell and Logan, 1974), parents of a subpopulation of children in whom ETS exposure was considered a "significant factor" were given antismoking advice and followed for 6-24 months. Symptoms improved in 90% of children whose parents stopped smoking and in 27% of children who remained exposed to passive smoking. These results are difficult to interpret because this is an uncontrolled trial. In a second study (Murray and Morrison, 1989), severity of asthma was scored in a group of children with the diagnosis of asthma whose mothers smoked. When the group was scored three years later, there was a highly significant decline in lung function in children of mothers who continued to smoke but an improvement in lung function of children whose mothers no longer smoked. This reduction was attributed to an alteration of maternal smoking habits, but this explanation is based on anecdotal evidence. A randomized, controlled trial to investigate whether brief intervention by advising parents about the impact of passive smoking would reduce salivary cotinine levels in asthmatic children was found to be ineffective (Irvine et al., 1999). A study of the relationship between modifications of parental smoking behavior and nicotine exposure found that smoking outside the home was associated with lower urinary cotinine levels only when the parent was the only smoker in the house (Winkelstein et al., 1997). These intervention studies lack assessment of confounders and require a more rigorous design. Intervention studies, utilizing dose-response relationships between asthma severity and levels of environmental tobacco smoke, represent a future strategy for evaluating harm reduction from ETS in asthmatic children.

RESPIRATORY INFECTIONS

Definition and Epidemiology

Viral rhinitis, tracheobronchitis, and bacterial bronchitis are acute infections of the epithelium of the upper respiratory tract. According to the 1997 National Center for Health Statistics survey (NCHS, 1999), upper

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respiratory infections are the most common medical reason for school or work absenteeism in the United States. These infections can occur in healthy people during epidemics. Immunocompromised patients are at special risk of developing pneumonia and tuberculosis. More serious infections of the lower respiratory tract such as pneumonia are less common in normal hosts. In elderly hospitalized individuals, nosocomial pneumonia is a major health problem and risk to life. Tuberculosis is a disease of the lower respiratory tract present predominately in socially and economically disadvantaged populations and in immunosuppressed patients in the United States, but it is a major health problem worldwide.

Respiratory tract infections and pneumonia are particularly important causes of death in the United States. In 1997, the combined cause-of-death category "pneumonia and influenza" ranked sixth among the leading causes of death (CDC, 1999). The age-adjusted mortality rate for pneumonia and influenza was 12.9 deaths per 100,000 population. During the interval from 1977 to 1997, the death rate from pneumonia and influenza increased 15.2% (CDC, 1999). The number of deaths in the United States in 1990-1994 due to respiratory infections that were attributed to cigarette smoking was estimated to be 8,000 per year (Table 14-2). Pneumonia and influenza are particularly important in the elderly, and the death rate reaches 20% in community-acquired pneumonia (Feldman, 1999; Fine et al., 1996). During 1997, in children aged 1-4 years, the combined category pneumonia-influenza was the sixth leading cause of death, and it was the seventh leading cause of death in children 5-14 years of age (NCHS, 1999).

Pathogenesis

The respiratory tract in the normal host is effective in containing microbes present in the environment. The airways below the level of the major bronchi are mostly sterile, and special situations predispose to respiratory tract infections. These include the introduction of a new species into the environment, such as an antigenic shift in influenza virus. A second situation involves an overwhelming inoculum of organisms, such as exposure to contaminated ventilatory equipment. A third situation results from impairment of part of the host respiratory defense apparatus or systemic immune response. The major components of the respiratory host defenses are the mechanical barriers of the upper respiratory tract, locally secreted immunoglobulins, lymphoid structures of the bronchi, phagocytic macrophages, and a number of immune and nonimmune substances that line the alveolar surfaces (Reynolds, 1997). Components of the host defense system are specially designed to deal with large particulates (3-10 μm) in the upper respiratory tract and small particles (0.5-<3

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mm) that may reach alveoli. If inflammation occurs in the alveoli, various systemic immune components can enter the airspaces by leakage through the alveolar surface. If local host defenses are insufficient, the host can recruit additional phagocytic cells such as polymorphonuclear leukocytes (PMNs) and create a local inflammatory response. The creation of an inflammatory response considerably increases the repertoire of systemic immune responses that can be recruited to contain the spread of microbes (Delves and Roitt, 2000). If the infection is successfully contained, inflammation is terminated and lung tissue is restored to its normal state. If it is not contained, inflammation can spread locally, leading to pneumonia. If severe, the local responses may produce permanent damage such as scarring to lung structure.

The effects of exposure to cigarette smoke on immune and inflammatory responses have been studied extensively in humans (Holt, 1987; Johnson et al., 1990). Alteration of immune and inflammatory processes by cigarette smoke are also relevant to asthma and COPD. Both acute exposure and chronic exposure to cigarette smoke alter the responsiveness of the immune system. The magnitude and direction of the alteration depend on the quantity and duration of exposure and the particular immune functions being studied. In general, low concentrations and short exposures enhance immune response, whereas high concentrations and long-term exposures suppress the responsiveness of the immune system. Many of the effects appear reversible within several weeks or months following cessation of exposure even after long periods (years) of exposure. The pulmonary tissues directly in contact with the smoke and the associated regional lymphatics are more affected than the peripheral immune system. Smokers have serum immunoglobulin levels that are 10-20% lower than those of nonsmokers (Holt, 1987; Mili et al., 1991). In addition to impairment of the peripheral immune system, smoking impairs mucociliary clearance, enhances bacterial adherence to respiratory epithelium, and disrupts respiratory epithelium (Dye and Adler, 1994; Fainstein and Musher, 1979; Green and Carolin, 1967; Raman et al., 1983). These altered functions may explain the higher rates of nasopharyngeal colonization with meningococcus among active and passive smokers compared to nonsmokers (Stuart et al., 1989).

Mainstream Smoke Exposure

Cigarette smoking is associated with increased susceptibility to certain types of respiratory infections (Aronson et al., 1982; Finklea et al., 1969; Fischer et al., 1997; Haynes et al., 1966; Imrey et al., 1996; Kark et al., 1982; Nuorti et al., 2000; Parnell et al., 1966; Peters and Ferris, 1967; Stanwell-Smith et al., 1994; Straus et al., 1996). The dose-response rela-

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tionship between smoking and mortality from influenza and pneumonia has been studied in several cohort studies. In the American Cancer Society CPS-I, the standardized mortality ratio for deaths due to influenza and pneumonia for ever smokers compared to never smokers was 1.9-1.7 for males and 1.3 for females (Hammond, 1965). In the British Physician Study (Doll and Peto, 1976), there was a slight increase in risk for current smokers, and a dose-response relationship was noted by the amount smoked. Similar results were found in the U.S. Veterans Study (Rogot and Murray, 1980) and in a study of Swedish men (Carstensen et al., 1987).

Cigarette smoking is an independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults (Nuorti et al., 2000). A dose-response relation was found for invasive pneumococcal disease and number of cigarettes smoked daily, pack-years of smoking, and time since quitting. Thus, cigarette smoking increases the risk of certain respiratory diseases and predisposes to increased invasiveness of pneumococcal disease.

Smoking has been studied as a possible risk factor for tuberculosis. Although research has been sparse, it has been postulated that smokers are at increased risk of developing active pulmonary tuberculosis. A case-control study by Alcaide and associates (1996) found smoking to be linked to the development of pulmonary tuberculosis in infected subjects who were in close contact with a case of active pulmonary tuberculosis. The risk of active tuberculosis was increased by exposure to environmental tobacco smoke. The significance of the association remained after controlling for social and economic status, age, and gender, but it became not significant in those exposed only to passive smoking. A dose-response effect was also described in this study, although findings have been inconsistent in other studies. Children exposed to passive smoking were found to have increased risk of developing active pulmonary tuberculosis after having been infected (Altet et al., 1996). This association persisted after controlling for age and social and economic status. Although there are few studies, smoking has been linked to positive skin test conversions (Anderson et al., 1997). The mechanism postulated is that smoking decreases immune defenses and increases susceptibility to pulmonary tuberculosis (Plit et al., 1998).

Secondary Smoke Exposure

Compelling evidence exists for a causal relationship between parental smoking and lower respiratory infections (bronchiolitis, pneumonia) during childhood. Strachan and Cook (1998) have reviewed 40 published series on this topic, which included papers in previous reviews (DiFranza and Lew, 1996; EPA, 1993; U.S. DHHS, 1986). The studies sought to ascer-

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tain the relationship between lower respiratory illnesses and parental smoking in children less than three years old.

In one group, the occurrence of lower respiratory infections was based on data from a community or ambulatory care setting and included longitudinal studies, controlled trials, case-control studies, and retrospective prevalence surveys. The illnesses included unspecified lower respiratory illness, bronchitis, bronchiolitis, and pneumonia.

The most widely derived measures of effect related to either parent smoking (compared with neither parent) and the effect of maternal smoking (compared with father only or neither parent). Information was sought to determine whether there was a dose-response relationship by relating illness to the amount smoked by either parent. A second series of studies analyzed the association between hospital admissions for lower respiratory tract infections and parental smoking. Diagnoses included undifferentiated chest illness, bronchitis and/or pneumonia, wheezing illness, and bronchiolitis with or without confirmation of respiratory syncytial virus.

All 14 studies in this group found an increased risk associated with parental smoking. The results of the community and hospital studies were broadly consistent, with only one study reporting a reduced risk among children of smokers. The pooled odds ratios were 1.6 (95% CI=1.4, 1.9) for smoking by either parent and 1.7 (95% CI=1.6, 1.9) for maternal smoking. The associations for parental smoking were robust to adjustments for confounding factors. In general, the evidence was more convincing for an association with smoking by the mother only than by the father only, probably related to a greater degree of exposure to the mother. Twelve cohort studies presented evidence for dose-response within smoking families, either to the number of smokers or to the amount smoked in the household. A statistically significant dose-response relationship was found in 10 of the 13 cohort studies (Cook and Strachan, 1997; Cook et al., 1998). In two case-control studies (Reese et al., 1992; Rylander et al., 1995), urinary cotinine levels were measured, but in neither study was it possible to determine if the cotinine levels were related to the risk of respiratory illnesses. The effect of paternal smoking on respiratory illnesses was most marked in the first year of life (Colley et al., 1974; Fergusson et al., 1981; Fergusson and Horwood, 1985), but the effects of maternal smoking on hospital admissions for respiratory infections were similar at all ages up to five years (Taylor and Wadsworth, 1987). There appears to be no increased risk of respiratory infections in susceptible subgroups (i.e., history of parental allergy, prematurity, low birthweight) (Burr et al., 1989; Chen, 1994; Ehrlich et al., 1996; Lucas et al., 1990).

Although the studies are generally consistent with an association between parental smoking and lower respiratory tract infections in chil-

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dren, the summary odds ratios derived from the pooled studies should be interpreted with caution. Difficulties with the pooled analysis include the process by which the variables were selected, the different types of data collection and analytical approaches applied to each study, and the inconsistent methods used to account for confounding effects. In addition, the precise nature of the specific diagnosis of lower respiratory tract infections and overlap with childhood asthma are important barriers to the analysis. The quality and sizes of the populations in these studies varied considerably, possibly introducing certain biases. Despite these limitations, it is reasonable to conclude that there is a causal relationship between parental smoking and acute lower respiratory illnesses at least during the first two years of life.

Latency

The effect of active smoking and smoking cessation on age-adjusted mortality from infectious diseases was examined in the American Cancer Society CPS-II study. Male former smoker of less than 15 cigarettes per day have mortality ratios after ten years approaching unity, whereas former smokers of more than 21 cigarettes per day have mortality ratios near unity at 15 years. Female former smokers of any amount have mortality ratios from influenza and pneumonia approaching unity within 3-5 years. These results suggest that impaired host defenses are reversible after smoking cessation.

Review of Harm Reduction Strategies Applied to Respiratory Infections

One controlled intervention study has examined the effect of acute lower respiratory tract infection after an intervention designed to modify postnatal exposure to tobacco smoke (Greenberg et al., 1994). There was a reduced prevalence of lower respiratory symptoms among the intervention group of infants of smoking mothers whose education level was high school or less versus the control group (Greenberg et al., 1994). However, there was uncertainty about the effectiveness of the intervention since the mean cotinine levels did not differ between study groups despite a reduction in smoking levels in the intervention group.

SUMMARY AND CONCLUSIONS

In evaluating the use of potential reduced-exposure products (PREPs) in tobacco-related lung disease, three major nonneoplastic respiratory diseases linked to cigarette smoking should be considered: COPD, asthma,

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and respiratory infections. Respiratory diseases are major tobacco-related illnesses, and there is a clear need to mitigate the harmful effects of exposure to both mainstream and secondary tobacco smoke. It is plausible that decreasing smoking will reduce the severity of chronic lung diseases and the incidence of respiratory infections, but there is no adequate scientific evidence to support this conclusion because the effects of reduced smoking on harm reduction have not been extensively studied.

Important considerations are determining dose-effect relationships and use of respiratory disease biomarkers. Rational design of studies of harm reduction would rely on dose-effect data, but such data for respiratory diseases are limited and of uncertain quality. High-quality dose-effect data are required for adequate study design, and such data should be generated. Rational study design would also incorporate biomarkers of disease, and the testing of current and new biomarkers might be done concurrently in the populations studied for dose-effects. The Cancer Prevention Studies I and II, large-scale prospective studies, however, do suggest a linear dose-effect relationship between number of cigarettes smoked per day and mortality rates from COPD, indicating that decreasing the amount of cigarettes smoked may lead to fewer deaths from COPD.

There are currently no specific biomarkers of respiratory disease due to smoking tobacco products. No unique molecular or genetic defect specific for tobacco-related respiratory disease has been identified. The processes involved, such as inflammation and increased levels of oxidants, are not unique to tobacco-related respiratory diseases. Identifying unique biomarkers is further confounded by the heterogeneous nature of these diseases, the complex mixture of tobacco smoke, and the range of individual susceptibilities to the harmful effects of tobacco smoke among users. The most widely used markers of tobacco-related respiratory diseases in population studies are symptom questionnaires and pulmonary function testing. These have well-known limitations of specificity and sensitivity, particularly for detecting the early effects of tobacco smoke on the lungs (U.S. DHHS, 1989). Subtle effects of tobacco smoke exposure on the lung can be detected by sampling fluid in the lower respiratory tract via a bronchoscope inserted into the airways, but the significance of these changes to clinically important pulmonary disease has not been established. Newer approaches such as sampling the subjects' urine (Pratico et al., 1998) or exhaled gas (Ichinose et al., 2000; Paolo et al., 2000) for metabolic products due to tissue injury have the advantage of noninvasive sampling but must be validated. Clearly, the greatest obstacle for developing a specific biomarker is the lack of fundamental information on mechanisms by which exposure to tobacco smoke causes specific respiratory diseases.

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The availability of dose-effect data and validated biomarkers may improve the quality of, and provide greater confidence in, the results of contemplated intervention studies. However, the time frame for generating dose-effect data and testing biomarkers is uncertain, and it is unclear whether inclusion of dose-effect considerations and biomarkers will improve the quality of clinical trials of harm reduction in respiratory diseases.

An alternative is to proceed with interventional trials based on current knowledge if there are uncertainties about the added value of dose-effect data or untested biomarkers to study design. As an example, an intervention study of the effect of smoking reduction on COPD could be considered that is similar in design to the Lung Health Study, a large prospective trial of the effects of smoking cessation on rate of decline of FEV_1 in middle-aged smokers with mild COPD (Anthonisen et al., 1994). Another approach is to conduct a trial using a low-tar/moderate-nicotine product from a noncommercial source to avoid product endorsement issues. (A more detailed research agenda can be found in the next section.)

Design of population studies for harm reduction of major respiratory diseases is challenging because of uncertainties about effectiveness and long-term compliance with harm reduction interventions. Reducing the burden of tobacco-related respiratory diseases through harm reduction strategies should be a major priority of the nation's public health.

RESEARCH AGENDA

This section outlines a suggested research agenda for studying harm reduction due to cigarette smoking in respiratory diseases (i.e., COPD, asthma, respiratory infections).

Several specific suggestions for research design arise from this review. An interventional study of the effect of smoking reduction on COPD could be considered that is similar in design to the Lung Health Study, a large prospective trial of the effects of smoking cessation on rate of decline of FEV_1 in middle-aged smokers with mild COPD (Anthonisen et al., 1994). In a proposed smoking reduction trial, it might be possible to include an intervention group of smokers who are able to reduce their smoking spontaneously and maintain significant reductions for a long period using behavior intervention and/or nicotine replacement products. The goal would be to decrease the number of cigarettes per day to eight to ten, a point below which it is very difficult to reduce the number of cigarettes smoked (Hughes, 2000). The primary end point could be the change in FEV_1 over five years, and secondary end points could be exhaled carbon monoxide concentration, serum cotinine level, survival, and comorbid smoking-related disorders. If successful, this study should be

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able to determine whether reduced smoking as measured by change in FEV_1 mitigates harm to the lungs. Potential weaknesses are the self-selection of subjects, the large number of subjects required, ethical issues regarding the nonintervention group, and a probable large dropout rate in the intervention group.

Another approach is to conduct a trial using a low-tar/moderate-nicotine product from a noncommercial source to avoid product endorsement issues. This study might be conducted in two phases. Phase I would be a controlled-exposure study in human smokers to compare the effects of the low-tar/moderate-nicotine product versus a reference cigarette on inflammatory changes in the lower respiratory tract, similar to the observations of Rennard et al. (Rennard, 2000). The objective of Phase I would be to determine if inflammation is reduced by exposure to the low-tar/moderate-nicotine product. If so, a Phase II intervention trial would compare the low-tar/moderate nicotine product to reference cigarettes in cohorts of current smokers. The objectives and design of the Phase II trial would be similar to that described above for intervention using behavioral modification or NRT. Potential advantages of this trial are that the low-tar/moderate-nicotine product, if it reduces harm, could be used as a reference product for future regulation of marketed products. Uncertainties related to such a study include inference from results of short-term controlled exposures to longer-term studies, controlling use of the intervention product, and the large effort that would be needed to complete the study.

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