DIFFERENTIATING THE HEALTH RISKS OF CATEGORIES OF TOBACCO PRODUCTS

EXECUTIVE SUMMARY

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This is a brief summary of the review by LSRO. It is not a complete document and should be considered within the context of the full report, which can be obtained at WWW.LSRO.ORG

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This report presents the findings, conclusions, and recommendations of the Life Sciences Research Office (LSRO) about whether sufficient scientific evidence exists to differentiate the health risks of categories of tobacco products. The report was developed under a contract between Philip Morris USA, Inc. and LSRO. An expert advisory panel, the Differentiating Tobacco Risks (DTR) Committee, guided the development of the report. From this point forward, LSRO, its staff, and the DTR Committee are collectively referred to as LSRO.

CIGARETTE HARM REDUCTION

Each year, more than 400,000 people in the US die prematurely because they smoke cigarettes. Cigarette smokers are advised to quit smoking, and never smokers, not to start smoking. Of the two-thirds of smokers who report that they want to quit smoking each year, more than one-third attempt to quit, but less than 3% of those who attempt to quit are successful. As a result, other approaches to reducing the harms from cigarette smoking have been explored.

Although no tobacco product is safe, accumulating data indicate that various types of tobacco products present different levels of risk to users and individuals in the product use environment. Consequently, it has been proposed that smokers who cannot or will not stop using tobacco can reduce their risk of cigarette smoking-related disease by replacing cigarettes with a tobacco product with a lower risk of adverse health effects. Smokeless tobacco (ST) is one class of potential reduced-risk product. ST is not combusted when used as intended, which eliminates exposure to mainstream smoke and environmental tobacco smoke. However, ST comprises a diverse group of products. Therefore, any risk reduction associated with one category of ST may not translate into risk reduction for other categories. This report focuses on comparing the risks of ST use with those of cigarette smoking and comparing the risks associated with using different types of STs.

DIFFERENTIATING TOBACCO RISKS OBJECTIVES AND APPROACH

The specific objectives of the DTR project were as follows:

1. Develop an independent consensus opinion as to whether ST products meet the criteria for reduced-risk (or reduced-harm) products compared with cigarettes;
2. Identify and characterize the critical characteristics of ST products that contribute to the evaluation of risk; and
3. Develop an independent consensus opinion as to whether sufficient evidence exists to stratify categories of ST products according to risk.

Although LSRO's review focused on evaluating whether ST reduces the risk of lung cancer (LC), chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD), diseases that account for approximately 350,000 of the 400,000 annual deaths from cigarette smoking-related diseases, LSRO also considered the relative risks of oral cancer, other cancers, and all-cause mortality. Comparative risk assessments of tobacco products were conducted by using the evaluative framework described in the LSRO report entitled *Scientific Methods to Evaluate Potential Reduced-Risk Tobacco Products*. LSRO comprehensively reviewed literature on preclinical studies related to ST and cigarettes (product characteristics, chemical composition, *in vitro* assays, and animal studies), clinical studies of biomarkers of exposure and biomarkers of effect, health outcome assessments (epidemiological and clinical studies), and behavioral studies. LSRO took a weight of evidence approach to evaluate the relative risks of cigarettes and STs and between different categories of ST products. The order in which the types of studies are mentioned above reflects increasing weight of evidence in the review. LSRO also considered written and oral comments on the topic from the public. LSRO's findings, conclusions, and recommendations were developed from the literature review, relevant oral and written public comments, and deliberations of the DTR Committee.

CONCLUSIONS AND RECOMMENDATIONS

Objective 1: Develop an independent consensus opinion as to whether ST products meet the criteria for reduced-risk (or reduced-harm) products compared with cigarettes

To conduct a comparative risk assessment of ST and cigarettes, LSRO considered the information summarized below.

Preclinical Studies

Product Characteristics

Cigarettes and ST tobacco differ in many ways. For example, moist snuff is made from dark tobacco, whereas cigarettes are made from various types of tobacco, such as flue-cured, Burley, Oriental, cut-roll stem, and reconstituted tobacco. Because cigarettes undergo combustion when used as intended and ST does not, smokers are exposed to combustion products and other substances in the cigarette that transfer directly into cigarette smoke. Cigarettes have diverse formulations and designs, including a wide variety of added ingredients, which may also influence smoke composition. ST products differ in many aspects of the manufacturing, production, and post-production processes. Although ST use eliminates exposure to cigarette smoke, the effects of various STs on individual and population risks of disease may differ.

Chemical Composition

Cigarette smoke contains carcinogens and other toxins. In contrast, because ST does not produce smoke when used as intended, the unburned tobacco leaf contains fewer carcinogens than cigarette smoke. However, ST contains other harmful substances that may contribute to increased risk of certain diseases for ST users compared with non-users of tobacco. Because the causal relationships between constituents of STs and of cigarette smoke and disease development have not been firmly established, it is not known how differences in specific constituents of ST extracts and cigarette smoke affect disease risk. Overall goals for risk reduction of STs should include eliminating or lowering levels of carcinogens and other tobacco product-related toxins as compared to smoking cigarettes' smoke and determining that ST is not a gateway to increased tobacco use.

In Vitro Assays

Many studies have shown that cigarette smoke is mutagenic. Some STs also exhibit mutagenicity. Because of varied dosing and methodology used in *in vitro* assays, LSRO found it difficult to draw conclusions from such studies about the risk of STs compared with cigarettes. LSRO recommends that investigators conducting future cigarette and ST studies use a recognized battery of tests for genotoxicity and cytotoxicity and consult the International Organization for Standardization (ISO) guidelines for extracting test substances for such studies. Future research should follow a standardized protocol, such as that proposed by ISO, and should include a range of doses of the test substance, positive controls, reference tobacco products, and products that represent those on the commercial market.

Animal Studies

Total particulate matter[1] from cigarette smoke promoted dermal tumor development in animal studies. In addition, inhalation of sidestream and mainstream smoke caused respiratory tract lesions in different rodent models. In contrast, animal studies provide limited evidence of carcinogenicity of ST products, particularly ST products from the US and Swedish. Oral cavity swabbing with ST extract (STE) did not increase tumor formation in rats, possibly because of inadequate STE dosing. Failure to produce tumors following oral swabbing with ST extract may also be due to total dose delivered and duration of exposure. Swabbing with tobacco-specific nitrosamines (TSNAs) increased tumor formation. Placement of moist snuff in a surgically created canal increased the incidence of tumor formation in oral and nasal cavities; however, this exposure method has been cricitized because cell proliferation and tumor formation have been associated with mechanical damage and persistent tissue

[1] Particles in smoke, larger than 1 μm in diameter, that are trapped as the smoke passes through a Cambridge filter; usually obtained from mainstream smoke.

injury. LSRO recommends that future long-term carcinogenicity studies provide a daily dose of the test substances to animals for at least 1 year and that studies adhere to guidelines for carcinogenicity studies. These approaches will result in standard exposures that will permit intra- and inter-study comparisons.

Although some animal studies have investigated the effect of ST on cancer risk, no studies have examined the relationship between ST and CVD and COPD. As is the case with cigarette smoke, STE has developmental effects. Research grade moist STE provided to pregnant mice reduced fetal weight in a dose-dependent manner.

Clinical Studies

Biomarkers of Exposure

A biomarker of exposure is a constituent or metabolite that is measured in a biological fluid or tissue or that is measured after it has interacted with critical subcellular, cellular or target tissues. Studies have investigated the effect of cigarette smoking and ST use on a limited number of biomarkers. Biomarker of exposure studies showed that compared with smokers, ST users have similar nicotine levels but higher plasma levels of the primary nicotine metabolite cotinine. ST users also have lower levels of serum thiocyanate, a biomarker of exposure for hydrogen cyanide, than cigarette smokers, and urine of ST users is less mutagenic than that of smokers. However, compared with smokers, ST users have higher median levels of the TSNA metabolite total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) *per* milliliter of urine and higher levels of the hemoglobin adduct of the TSNA 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB). The saliva of Swedish snuff users contain TSNAs, but questions remain about whether TSNAs are the substances responsible for oral lesions in ST users because the major conversion of TSNAs may occur in the gastrointestinal tract. Excretion of the minor tobacco alkaloids *N′*-Nitrosoanabasine, *N′*-Nitrosoanatabine, nornicotine, was higher for ST users than for smokers.

Biomarkers of Effect

Biomarkers of effect are measured effects including early subclinical biological effects: alterations in morphology, structure, or function or clinical symptoms consistent with the development of health impairment and disease. Biomarker of effect studies indicate that, like cigarette smoking, ST use alters electrical cardiac activity, hemodynamics, and endothelial function and causes cytological changes within the oral cavity. Biochemical risk factors for CVD such as plasma fibrinogen, C-reactive protein, and serum lipid and lipoprotein levels are changed toward an increased CVD risk for smokers but not for ST users.

Because biomarkers for inflammation and measures of atherosclerosis, which are more predictive of CVD than some other biomarkers, show more favorable levels for ST users than for smokers, ST may present a lower risk of CVD than cigarette smoking. ST also causes cytological changes in the oral cavity.

Health Outcomes Assessment (Epidemiological Studies and Clinical Trials)

Lung Cancer

Studies have consistently reported that cigarette smoking significantly increases the risk of LC. Most studies reported that ST users do not have an increased risk of LC compared with non-smokers. Studies with significant methodological issues such as confounding from misclassification of smokers as ST users and exposure of subjects to environmental tobacco smoke reported that ST users have an elevated risk of LC.

Chronic Obstructive Pulmonary Disease

Studies have consistently reported that cigarette smoking significantly increases risk of COPD. Few studies have examined the relationship between ST use and the risk of COPD. Some studies with significant confounding indicate an increased risk of COPD for ST users compared with non-tobacco users; however, one study indicated no increased risk of respiratory disease for ST users in the US. No biologically plausible relationship exists between ST and COPD, but this issue would benefit from additional research.

Cardiovascular Disease

Studies have consistently found a significantly increased risk of CVD for smokers compared with non-tobacco users. Two studies showed that Swedish ***snus*** users have slightly elevated CVD risk compared with non-users, but several studies reported that ***snus*** does not increase risk. One study determined that US snuff elevates CVD risk; however, another study did not find an increased risk of CVD. A study reported that chewing tobacco used in 52 countries increases CVD risk. In summary, epidemiological studies show that although ST use appears to increase CVD risk above the CVD risk for non-tobacco users, the risk is lower than that associated with cigarette smoking.

Oral Cavity Cancer

Many studies have shown that cigarette smoking increases oral cancer risk. Oral cancer risk appears to be different for various ST products. Available evidence suggests that Swedish ***snus*** either does not increase risk of oral cancer or increases it minimally. Some studies reported that US chewing tobacco and dry snuff increase oral cancer risk, but confounders such as alcohol consumption and smoking were not considered in the interpretation of data. Other studies of

US STs reported no increased risk of oral cancer. International STs (*i.e.*, tobacco products other than US STs and Swedish *snus*) may pose a significantly greater risk of oral cancer than do US and Swedish STs. LSRO has a moderate level of confidence that US STs and Swedish *snus* present a lower risk of oral cancer compared with cigarette smoking. LSRO also has a moderate level of confidence that some international ST products present a higher risk of oral cancer compared with cigarettes.

Other Cancers, All-cause Mortality, and Pregnancy Outcomes

Cigarette smoking increases the risk of laryngeal cancer, esophageal squamous cell carcinoma, gastric cancer, pancreatic cancer, and bladder cancer. Studies of the relationship between ST consumption and risk of laryngeal cancer have produced mixed results. Few studies have investigated the relationship between esophageal cancer and ST; however, some studies reported that ST does not increase the risk of esophageal cancer. Most studies did not demonstrate an increased risk of gastric cancer for ST users, but one study reported an increased risk of non-cardiac gastric cancer.

Epidemiological studies have indicated that risk of pancreatic cancers may be elevated for ST users compared with non-tobacco users but lower compared with cigarette smokers. The magnitude of increased risk of bladder cancer for ST users is lower than that for cigarette smokers. Whether cigarette smoking is associated with renal cell carcinoma is controversial. A weak association between renal cell carcinoma and ST use has been reported. The risk of all-cause mortality is significantly lower for ST users of Swedish *snus* and American STs than for cigarette smokers. LSRO's conclusion about the risk of other cancers and all-cause mortality is summarized below. Further research is needed to clarify the relationship between ST use and risk of cancers. Some evidence exists that snuff use is associated with lower birth weight infants, preterm delivery, and/or pre-eclampsia.

Behavioral Studies

Cigarette smokers and ST users have similar overall maximal nicotine levels but different nicotine pharmacokinetics. LSRO concluded that ST is not likely to reduce the risk of nicotine addiction compared with cigarettes. There are concerns that ST could be a gateway product for tobacco use in the US; however, some data from Sweden demonstrate its use as a cessation aid and do not support the gateway hypothesis. Few data are available to assess whether easier availability of some types of ST products leads to increased tobacco use.

Summary of LSRO's Confidence That Smokeless Tobacco Is a Reduced-Risk Product Compared with Cigarettes

LSRO used the descriptors low, moderate, and high to summarize its levels of confidence in the potential for risk reduction of ST compared with cigarettes. These definitions for levels of confidence in risk reduction were adapted from the Manual for American College of Cardiology and the American Heart Association Guideline Writing Committees.

Low confidence in risk reduction: Evidence is insufficient to assess risk reduction and/or there is general agreement of the DTR Committee that the weight of evidence indicates that ST does not reduce the risk of disease.

Moderate confidence in risk reduction: The weight of evidence supports risk reduction, but critical evidence is lacking and/or there is general agreement of the DTR Committee that available data are inconsistent about whether ST reduces the risk of disease compared with cigarettes.
High confidence in risk reduction: Available evidence is sufficient to assess risk reduction and there is general agreement of the DTR Committee that the weight of evidence indicates that ST reduces disease risk compared with cigarettes.

- LSRO's confidence is high that, compared with cigarettes, ST presents a lower risk of LC and COPD.
- LSRO's confidence is moderate that ST reduces the risk of CVD and pharyngeal, laryngeal, esophageal, and gastric cancer compared with cigarettes.
- LSRO's confidence is moderate that US and Swedish ST products present a lower risk of oral cancer than cigarettes.
- LSRO's confidence is moderate that some international STs present a higher risk of oral cancer than cigarettes.
- LSRO's confidence is low that, compared with cigarette smoking, ST use reduces the risk of pancreatic and bladder cancer.
- LSRO's confidence is high that, compared with cigarettes, ST presents a significantly lower risk of all-cause mortality.

Because LSRO has a high level of confidence that compared with smoking, ST reduces risk of LC and COPD (which together account for approximately 49% of smoking-attributable deaths), a moderate level of confidence that ST reduces risk of CVD (which accounts for approximately 32% of smoking-related deaths), and a high level of confidence that ST reduces risk of all-cause mortality, LSRO's overall confidence that ST is a reduced-risk product compared with cigarettes is high.

Objective 2: Identify and characterize the critical characteristics of ST products that contribute to the evaluation of risk

One component of LSRO's charge was to identify critical characteristics that contribute to a characterization of risk. In the scientific literature, distinctions have been made among STs on the basis of:

- Geographic origin of tobacco,
- Fermentation of tobacco,
- Heat treatment of tobacco,
- Chemical composition of the ST,
- Manufacturing conditions for the ST,
- Refrigeration of the ST after production,
- Genotoxicity and cytotoxicity assays,
- Animal toxicity studies,
- Biomarker of exposure and biological effect studies,
- Health effects assessment (epidemiological studies and clinical trials), and
- Behavior related to the use of STs.

LSRO concluded that existing information is insufficient to determine the critical factors that influence risk associated with ST products. Consequently, LSRO utilized information from preclinical, clinical, health outcomes assessment, and behavioral studies to compare risks of cigarettes and STs. LSRO placed the highest weight of evidence on health outcomes assessment studies and behavioral studies, intermediate weight of evidence on clinical studies, and lowest weight of evidence on preclinical studies. LSRO categorized ST products into Swedish *snus*, traditional US STs, newer STs, and international STs, because data in the scientific literature were generally organized in this way.

Objective 3: Develop an independent consensus opinion as to whether sufficient evidence exists to stratify categories of ST products according to risk

To determine whether data were adequate to allow stratification of ST products according to risk, LSRO focused on the types of STs that are primarily used in the US and Sweden: moist snuff, loose-leaf chewing tobacco, plug/twist chewing tobacco, dry snuff, and Swedish *snus*. LSRO emphasized these STs because of their importance (or potential importance) to the US market and because they are associated with the most data with which to evaluate evidence related to health risks.

Preclinical Studies

Product Characteristics

Differences among STs may include the species of tobacco incorporated in the product, aging of the tobacco, fertilization practices during tobacco growth, pesticide use and soil conditions, and climate during tobacco growth. The tobacco cutting size, moisture content, pH, added ingredients, convenience of use, and aspects of the manufacturing processes, such as whether tobacco is

fermented, are other ways in which STs may differ. For example, tobacco in Swedish *snus* is heat-treated, whereas tobacco in US moist snuff products is fermented in closed containers under controlled conditions for weeks, which permits survival of bacteria and other microorganisms. Comparing STs may be difficult because manufacturing of some international products is not standardized and is poorly characterized. Post-production handling of STs also differs. Swedish *snus* is refrigerated until used, whereas other STs are not typically refrigerated after production.

Chemical Composition

The composition of ST products is heterogeneous. As noted previously, some international ST products are manufactured non-commercially, *via* non-standardized processes, which is likely to increase the variability of their chemical composition.

Levels of some ST constituents (*e.g.*, TSNAs, nicotine, polycyclic aromatic hydrocarbons, heavy metals, and radionuclides) are routinely measured, and STs differ in levels of these substances. As an example, Swedish *snus* contains lower levels of TSNAs than does US moist snuff, and hard snuff products contain lower TSNA levels than does Swedish *snus*. However, TSNA levels in US moist snuff products have decreased. International STs generally have higher levels of TSNAs than do Swedish *snus* and US STs, with Sudanese *toombak* having up to 100 times the levels in US and Swedish STs. The biological significance of these differences in product constituent levels remains a question because the extent to which TSNAs and other ST constituents alter human health risk has not been determined.

One ST manufacturer, Swedish Match, has set a quality standard for its products called GothiaTek® that defines maximal permissible limits for "suspected harmful elements," and some other tobacco companies appear to be voluntarily conforming to that standard. In general, there is no rationale for inclusion or exclusion of ST analytes, nor is it known whether use of a product with reduced levels of one constituent would reduce risk compared with another product with or without lower levels of the constituent.

Certain newer ST products—*i.e.*, "hard snuff,", which is compressed, powdered, low-nitrosamine tobacco lozenges designed to dissolve in the mouth without expectoration—are more convenient to use than traditional ST products[2]. This increased convenience has the potential to increase frequency of tobacco consumption by allowing discreet ST use.

[2] Traditional ST products refers to US ST products other than hard snuff and US *snus* products that have recently been developed.

The pH of the various ST brands varies, resulting in differences in availability of nicotine for uptake by ST users. The pH of one Swedish *snus* product was higher than that of 5 traditional US moist snuff products, which indicated a higher proportion of unbound nicotine and suggested more efficient nicotine uptake than that for moist snuff products. Recently, US tobacco companies have developed what they have called *snus* products, but these products do not have all the attributes of Swedish *snus*. One recently marketed US *snus* product is controversial because it has a lower pH than Swedish *snus*, which reduces nicotine availability for uptake and potentially limits its ability to satisfy individuals consuming it, in particular, tobacco users who are attempting to switch from cigarettes to ST.

In Vitro Assays

Limited data suggest that Swedish *snus* and hard snuff products are not mutagenic in *Salmonella* mutagenicity assays. In contrast, traditional US chewing tobacco, moist snuff, and dry snuff, and many Indian and Saudi Arabian ST products (*e.g.*, betel quid with tobacco, *gutkha*, *shammah*, *zarda*, and *mishri*) increase the number of revertants in *Salmonella typhimurium*. Some international products also increase the frequency of chromosomal aberrations and number of micronucleated cells (*e.g.*, betel quid with tobacco and lime, *mishri*, and Indian dry snuff) as well as induce sister chromatid exchange. International products also decrease expression of the DNA repair enzyme methylguanine-DNA methyltransferase. There are currently no published *in vitro* studies on US *snus* products.

Animal Studies

Studies have shown some STs to be carcinogenic, but carcinogenicity studies are not available for all STs. Extracts of the Indian ST betel quid led to formation of murine lung tumors and increased squamous cell carcinoma of the cheek pouch of golden hamsters. At present, there are no published animal studies about US *snus* products.

Clinical Studies

Limited biomarker information is available comparing exposure from and biological effects of the use of different STs. Swedish *snus* users had higher nicotine levels than did users of some newer STs. US *snus* products delivered lower amounts of nicotine than cigarettes. Studies have reported differences in TSNA metabolite levels for ST users. Urine and saliva of *toombak* users had extremely high TSNA metabolite levels. At present, there is limited information about US *snus* products. No firm conclusions can be reached from biomarker studies about risk for users of different STs.

Health Outcomes Assessment (Epidemiological Studies and Clinical Trials)

More well-conducted studies exist for Swedish *snus* than for other STs. More data are also available for some international STs, such as betel quid with tobacco, than for others. Epidemiological data about hard snuff and non-Swedish *snus* products have not been published. The disparity of available data also adds to the complexity of a comparative risk assessment of STs. Because all ST products reduce the risk of LC and COPD compared to cigarettes, the effects of ST on risk of these diseases cannot be used to discriminate between the health risks of different products, and other health outcomes must be utilized for this purpose.

Although some evidence is available that ST users have increased CVD risk compared with non-users, these data do not allow for a distinction to be made among ST products with regard to their risks. Studies from India, Pakistan, and Sudan report a substantially increased risk of oral cancer for users of betel quid with tobacco, chewing tobacco, *toombak*, and *shammah* compared with non-tobacco users. Epidemiological studies indicate that Swedish *snus* has a substantially lower risk of oral cancer than do some international products and that US ST products may confer an intermediate level of risk. Available data do not allow a distinction to be made between STs with regard to risk of all-cause mortality.

LSRO's Stratification of Smokeless Tobacco Products According to Risk

The following reflects LSRO's stratification of ST products. Epidemiological studies, which are the most heavily weighted of the available studies, suggest that Swedish *snus* may be the least harmful of STs and convey the lowest disease risk of STs. Preclinical studies, such as genotoxicity and cytotoxicity assays and animal studies, which LSRO weighted less heavily than epidemiological studies, also support this idea. LSRO concluded that traditional US STs confer an intermediate risk to ST users. Some data indicate the potential for differences in risk among US STs; this area would benefit from additional research. Preclinical data suggest that some newer STs such as hard snuff products may be less toxic than some moist snuff products; however, no epidemiological studies of these and US *snus* products have been conducted to determine the risk of disease. Swedish *snus*, traditional US STs, and some international products are manufactured commercially and may have a less variable composition than the international STs that are manufactured under non-standardized and poorly-characterized conditions. Less information is available about international products than is available for Swedish *snus*. In general, LSRO considers international ST products to be the most harmful STs on the basis of epidemiological and other studies. LSRO's stratification of STs is based on limited available information and could change with additional studies.

Future Directions

During the course of the DTR project, LSRO identified several areas in which additional research, application of standardized methods, and use of established guidelines are warranted. LSRO identified the need for rigorous characterization of the chemical composition of ST products using standardized, state-of-the-art analytical methods. Use of available reference ST products and development of a reference ST for Swedish *snus*-like products are recommended. In addition, ISO guidelines for STE preparation and for genotoxicity and cytotoxicity testing according to International Conference on Harmonization and US Food and Drug Administration Guidelines should be applied. In animal studies, daily doses of the test substance should be given for a minimum of 1 year. Development of newer, less invasive, validated animal models of disease for ST studies is also recommended.

LSRO identified a need for additional studies to identify relevant biomarkers of nicotine exposure in ST users. Further investigation of the interaction between constituents of ST and saliva is also needed. Additional studies of the relationship between ST consumption and risk of CVD, oral cancer, and other diseases would allow better characterization of disease risk. Additional, well-designed epidemiological studies of ST products in use today and international products would also contribute to improved understanding of the relationship between ST use and disease. Additional research on health effects of dual use of STs and cigarettes in the US would provide insight into risk associated with ST use. ST is used as a smoking cessation aid, but randomized clinical trials evaluating its efficacy in this capacity are required. Also needed are information about whether ST product design and flavoring affect tobacco initiation rates in youth and studies of the effects of STs on smoking initiation. Population studies detailing patterns of ST use among various demographic groups are also recommended.