



SCIENTIFIC METHODS TO EVALUATE POTENTIAL REDUCED-RISK 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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EXECUTIVE SUMMARY

This report provides Life Sciences Research Office (LSRO)¹ findings and recommendations on scientific methods to evaluate tobacco products that may pose lower health risks to individuals who use them instead of conventional cigarettes. The term “Potential Reduced-Risk Tobacco Product” (PRRTP) is used in this report to refer to these products. This report was developed under a contract between Philip Morris USA, Inc., (Philip Morris) and LSRO. The findings, conclusions, and recommendations contained herein were developed independently of Philip Morris and are not intended to represent the views of Philip Morris or any of its employees.

BACKGROUND

According to estimates by the Centers for Disease Control and Prevention (CDC), more than 400,000 people die each year in the US as a result of past or current cigarette smoking; adult smokers lose an average of 13–15 years of life because they smoke (Centers for Disease Control and Prevention, 2002); and smoking adversely impacts the health of non-smokers who are exposed to environmental tobacco smoke (ETS), with an estimated 38,000 “passive smokers” dying each year of diseases caused by ETS (U.S. Department of Health and Human Services, 2006).

Despite widespread knowledge of the risks posed by cigarette smoking, approximately one in five US adults (approximately 44.5 million people) smokes (Centers for Disease Control and Prevention, 2002). The number of smokers increases to 59.9 million if adolescents are included (Substance Abuse and Mental Health Services Administration, 2004).

The most effective means to eliminate or decrease risk of dying due to smoking is to stop using cigarettes. According to a CDC report, although 70% of smokers want to stop smoking each year and 34% of all smokers attempt to quit, only 2.5% of all smokers are successful (Centers for Disease Control and Prevention, 2004). Unfortunately, because it is very difficult to remain tobacco-free, approximately one-third of those who quit for one year resume smoking within the following 12 months (Henningfield *et al.*, 1998).

The addictive nature of nicotine contributes significantly to the difficulty of cessation (Benowitz, 1996). Nicotine replacement therapies (NRT), such

¹ For the remainder of this report, LSRO, its staff, and the expert advisory “Core Committee (CC),” are referred to collectively as “LSRO”.

as the nicotine patch, assist in cessation, as do behavioral support programs (Giovino *et al.*, 1995); however, the statistics on cessation clearly demonstrate that the difficulties associated with quitting remain.

The low success rate for smoking cessation makes tobacco harm reduction (THR), intended to reduce adverse health effects to smokers who will not or can not abstain, a potentially valuable component of a comprehensive tobacco control program² (Boyle *et al.*, 2004; Institute of Medicine, 2001; Warner, 2002).

In 1999, the US Food and Drug Administration commissioned a study by the Institute of Medicine (IOM), *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction* (Institute of Medicine, 2001). The purpose of this study was to “formulate scientific methods and standards by which ‘potential reduced-exposure products (PREPs)’ [tobacco-based and other products such as NRT] could be assessed.”

The IOM report endorsed the concept of THR including PREPs as a part of a comprehensive tobacco control program. It also stressed the importance of adequate scientific evaluations of the effects of PREPs on exposure and risk and comprehensive regulation of tobacco products (Institute of Medicine, 2001).

LSRO STUDY OBJECTIVES AND APPROACH

LSRO reviewed scientific methods and approaches for evaluation of the effects of using PRRTTP on exposure and risk compared to smoking conventional cigarettes. Specific Reduced Risk Review Project (RRRP) objectives were to:

- Identify the types of scientific information needed to assess risk reduction;
- Establish criteria to evaluate the scientific information, including identification of comparison products [controls]; and
- Define a review process for the scientific information.

Because the RRRP focused on scientific methods to evaluate PRRTTPs, LSRO makes no recommendations concerning public policy, such as regulatory approaches; however, LSRO recognizes that public policy will affect the acceptance and use of scientific information in decision making.

² All forms of tobacco use are associated with serious health consequences; however, the most popular and most deadly form is the cigarette (Doll, 2004). As a result, THR efforts focus largely on cigarette smoking.

LSRO addressed two types of assessments that are related to PRRTPs:

- **Individual Risk Assessment.** The primary focus of the RRRP was the identification and critical assessment of scientific information that could be used prior to product marketing to determine whether a PRRTP is likely to reduce risk for individual smokers who use it instead of conventional cigarettes.
- **Population Risk Assessment.** LSRO also reviewed scientific methods to assess the health effects of a PRRTP on the population as a whole. The goals of a population risk assessment are to determine whether anticipated improvements in the health status of smokers who use a PRRTP are realized, whether prevalence of tobacco use (and associated health risks) among individuals who would otherwise be tobacco free is increased by PRRTP use, and whether net effects on public health are positive.

MAJOR CONCLUSIONS AND RECOMMENDATIONS

Individual Risk Assessment

Objective 1: Identify the types of scientific studies needed to assess risk reduction.

LSRO concluded that reliable testing and assessment methods for individual risk reduction are currently available for premarket evaluation of PRRTPs.

Prior to marketing, evidence that risk is likely to be reduced in smokers who switch to a PRRTP is, of necessity, indirect: diseases associated with cigarette smoking that are most responsible for premature death are chronic, requiring years, and in some cases, decades, to develop. A weight of evidence approach that includes preclinical and clinical studies of sufficient quantity, quality, and relevance to the population of smokers likely to use a PRRTP can provide reliable conclusions on the potential for risk reduction.

LSRO concluded that PRRTP assessments should focus on the risks posed by the three most deadly diseases caused by cigarette smoking: lung cancer (LC), chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD).

The rationale for this conclusion is two-fold: (1) scientific assessment of all diseases and conditions identified by the Surgeon General as caused by cigarette smoking is not feasible; and (2) approximately 90% of the estimated 400,000 annual smoking-related deaths of current or former smokers in the

US are due to LC, COPD, and CVD (Centers for Disease Control and Prevention, 2005c).

LSRO concluded that the data needed to evaluate risk reduction of PRRTTP use in individual smokers must be derived from comprehensive preclinical and clinical testing.

Preclinical studies that are required to fully evaluate a PRRTTP include product characterizations, smoke chemistry studies, cytotoxicity and genotoxicity assays, and animal studies. Clinical studies that are required include studies of biomarkers of exposure for critical emission constituents and whole smoke and studies of biomarkers of effects associated with the risk of developing LC, COPD, and/or CVD.

Objective 2: Establish criteria to evaluate the scientific information, including identification of comparison products.

LSRO relied on evaluation criteria that are widely used to assess preclinical and clinical study results for such purposes as evaluating the safety of consumer products and establishing regulatory limits for occupational and environmental exposures to toxic chemicals.

LSRO's data evaluation criteria included the following considerations: study type conducted; number and quality of studies; degree of consistency of findings across similar studies; and relevance of the study results to humans.

LSRO identified two broad categories of product controls for PRRTTPs: reference cigarettes and commercially available, conventional cigarettes.

Objective 3: Define a process to review the scientific information.

LSRO used a risk assessment approach to evaluate PRRTTPs.

PRRTTP risk assessments compare exposures to toxic constituents present in PRRTTP emissions with those associated with smoking conventional cigarettes and biological effects associated with disease risk in PRRTTP users with those in users of conventional cigarettes. The overall evaluation approach developed by LSRO to assess individual risk reduction is summarized in Figure 1. LSRO identified critical questions to be answered in the decision making ("risk management") for PRRTTPs (third column in Figure 1) and then developed testing and comparative risk assessment approaches to provide the necessary information to decision makers.

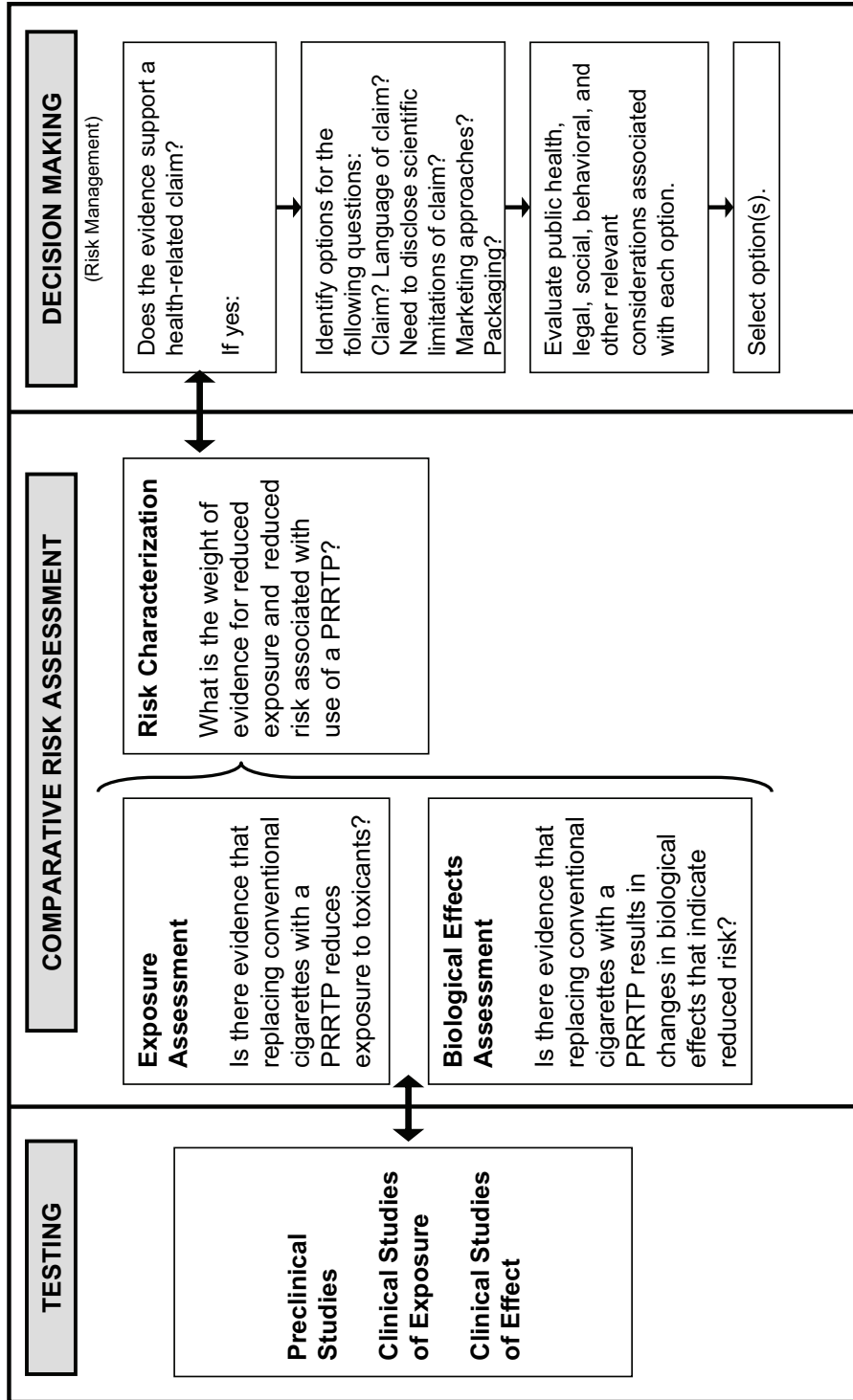


Figure 1. LSRO framework for the premarketing evaluation of a potential reduced-risk tobacco product (PRRTP).

Population Risk Assessment

LSRO concluded that a combination of clinical, behavioral, and epidemiologic methods are needed to determine the effects of a PRRTTP on population risk.

The effect of introducing a PRRTTP on the population as a whole is determined by the degree to which it reduces overall morbidity and mortality. A PRRTTP that decreases risk for individuals who use the PRRTTP instead of smoking conventional cigarettes could also increase risk for individuals who use the PRRTTP instead of remaining tobacco-free. Both decreases and increases in risk must be examined to determine the net effect on population risk.

Appropriately controlled clinical studies of exposure and effect in intended users (smokers who can not or will not quit) and behavioral assessments and surveys of tobacco use and attitudes in unintended users (individuals who would otherwise be tobacco free) can provide early indicators of population effects of a PRRTTP. Epidemiologic studies of sufficient duration will be required to provide more definitive evidence of population health effects.

LSRO concluded that postmarketing evaluations will be necessary to obtain adequate and reliable data to assess potential increases in population risk.

LSRO reviewed premarketing assessment methods that might be used in the evaluation of potential increased tobacco use/risk in individuals who would otherwise be tobacco free and concluded that currently available methods are not adequate to predict potential adverse effects of PRRTTP use on population risk. While behavioral studies used to assess the potential for increased use of tobacco products can be conducted prior to marketing a PRRTTP, the potential for tobacco-free individuals to use a PRRTTP will depend on a number of factors that will be known only after the product is marketed, such as the physical and sensory properties of the PRRTTP and marketing strategies and imagery used to promote the product.

Therefore, planned postmarketing population assessment studies are necessary to detect unintended public health consequences that may result from the introduction of a PRRTTP.

Summary of LSRO Approach to the Evaluation of PRRTTP

A schematic depiction of pre- and postmarket testing and evaluation approaches recommended by LSRO is presented in Figure 2.

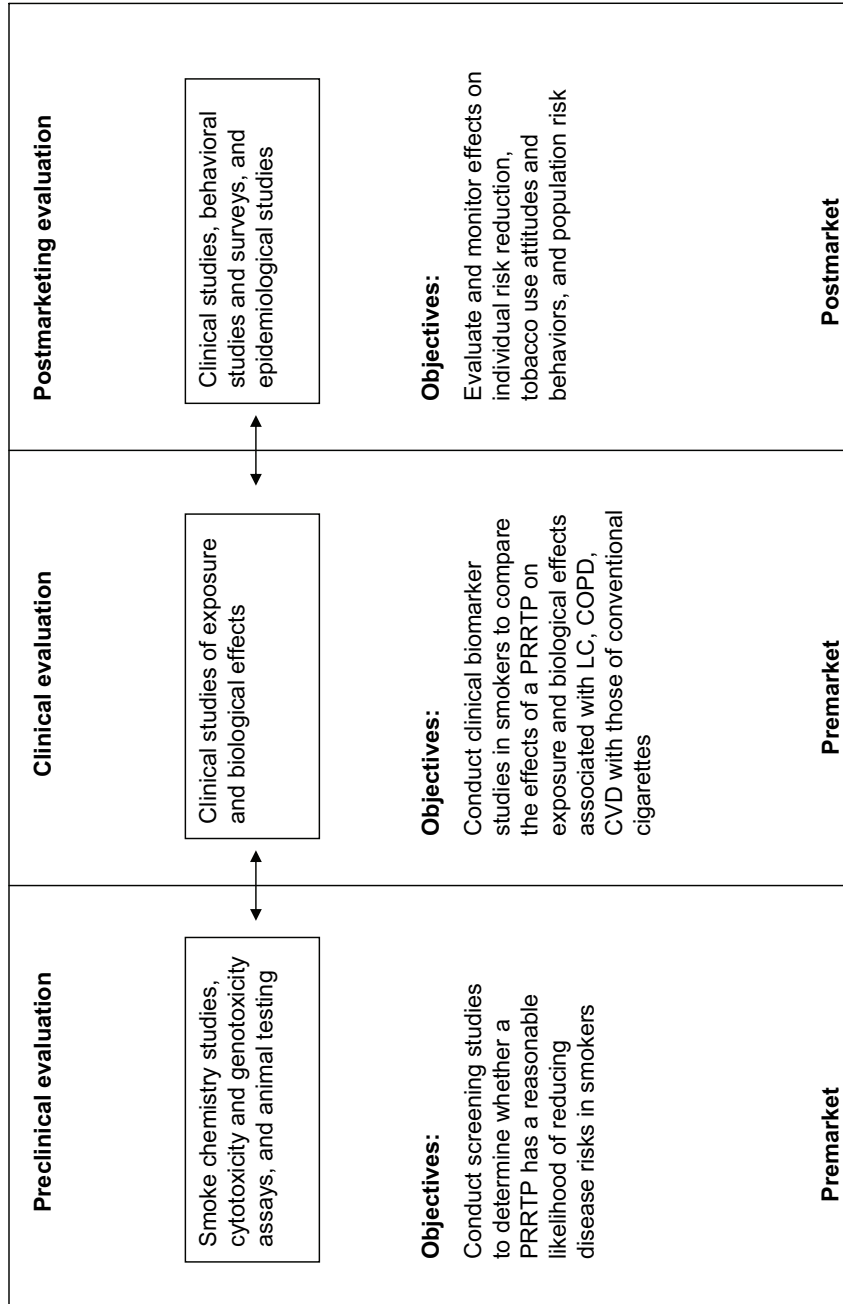


Figure 2. LSRO testing approaches for a potential reduced-risk tobacco product (PR RTP). Copyright 2005 adapted from *Methods to assess potential reduced exposure products* by Hatsukami *et al.* (2005a). Reproduced by permission of Taylor & Francis Group Ltd., <http://www.tandf.co.uk/journals>. **CVD**: cardiovascular disease, **COPD**: chronic obstructive pulmonary disease, **LC**: lung cancer.