PROJECT DESCRIPTION

PROJECT: **Evaluating the Scientific Evidence for Potential Reduced-Risk Tobacco Products ("Reduced Risk Review")**

OBJECTIVE: **To evaluate the science base necessary to determine whether potential reduced-risk tobacco products are likely to reduce risk, develop a detailed research agenda to address gaps in the science base and, if feasible, develop an evaluative process for the scientific assessment of potential reduced-risk tobacco products.**

BACKGROUND:
Although medical, scientific and public health organizations have concluded that the best means to protect individual and public health from tobacco harms are to *achieve abstinence*, *prevent initiation and relapse* and *eliminate environmental tobacco smoke exposure*,[1] consideration is also being given to the concept that reducing adverse impacts on the health of tobacco-users who will not or can not abstain from the use of tobacco products (i.e., "risk reduction") may also be a valuable component of a comprehensive tobacco control program.[2]

The Reduced Risk Review builds on the work done by a Committee of the Institute of Medicine (IOM), which culminated in the report, *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. The IOM study was commissioned in 1999 by the Food and Drug Administration to formulate scientific methods and standards for assessing potential reduced-exposure products (PREPs) (i.e., tobacco-based and pharmaceutical nicotine products). The IOM Committee concluded that "…there can be a successful, scientifically-based harm reduction program that is justifiable and feasible—but only if implemented carefully and effectively…." The specific findings and recommendations of the IOM report serve as the departure points for the LSRO study.

LSRO:
The Life Sciences Research Office (LSRO) is a non-profit organization of biomedical research scientists with headquarters in Bethesda, MD. Established in 1962, LSRO serves to benefit society by independently and objectively evaluating biological information and scientific opinion for the public and private sectors. To meet its mission, LSRO provides scientifically objective, rigorous and complete analyses of critical issues in biology and medicine; convenes expert review committees, workshops and meetings; and conducts peer review of research proposals and programs.

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[1] IOM, 2001. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. National Academy Press: Washington DC, p. 5.

[2] While 70 percent of smokers say they want to quit and 34 percent of smokers attempt to quit each year, only 10 percent of those who try to quit actually break their addiction [to nicotine] and remain tobacco-free for a year. Because many people cannot or will not stop using tobacco and because many adolescents will continue to experiment with things "taboo," there almost certainly will remain a significant population whose health is at risk from smoking. Indeed, it has been predicted that even with the most intensive application of the most effective programs for abstinence and cessation, at least 10 percent to 15 percent of adults in the United States would continue to smoke (IOM, 2001).

PROJECT DIRECTOR:
The Project Director is Dr. Cathy St. Hilaire, an expert with over 20 years experience in the fields of toxicology and risk assessment. Dr. St. Hilaire has been instrumental in the development of risk assessment theory and practice relied upon by US regulatory agencies. In addition, she directed a university-based research program aimed at reducing key uncertainties in risk assessment, with an emphasis on risk assessment of potential human carcinogens and reproductive toxicants. She served as a post-doctoral fellow in the laboratory of Dr. Bruce Ames at UC-Berkeley, received her Ph.D. in microbiology from the Medical College of The Pennsylvania State University and her B.S. in science education from West Virginia University. She was honored by the Society for Risk Analysis in 1987, when she was named a Fellow of the Society.

SPONSOR:
This project has been funded through a contract with Philip Morris USA, Inc. (PM). PM will be responsible for providing: funding, background information about cigarette manufacturing and testing and providing information on studies/programs to date that evaluate potential reduced-risk products. LSRO, as the organization conducting the review, will be responsible for assembling committees of experts, supporting the expert committees with staff and facilities, conducting the necessary studies and reviews, collecting and disbursing public comments, making the data publicly available, conducting an independent review of the literature and supporting evidence, convening an open scientific conference, collecting and analyzing public comment and publishing the final report(s). In order to preserve the third party independence of the review, PM will have no role in the design, conduct, deliberations, or the conclusions of the committees. PM retains limited fiduciary oversight and supplies information on request.. All private communications between PM and LSRO will be restricted to authorized individuals and will be logged. Private communication between PM and members of the Expert Committees is prohibited.

APPROACH:
The Reduced Risk Review will evaluate the science base necessary to assess whether potential 'reduced-risk' tobacco products are likely to reduce the risks of cigarette smoking by identifying and evaluating:

- **Exposure characteristics of potential reduced-risk products.**

  Methods to assess exposures to mainstream, sidestream and environmental tobacco smoke will be evaluated. Although many techniques exist to assess exposure reduction, the IOM committee found that these measures have an unknown predictive power for reduced risk. Thus, a claim of reduced risk will require a demonstration that exposures to critical components of tobacco smoke are significantly reduced to a level that would be anticipated to reduce risk. Thus, emphasis will be placed on the health significance of reduced exposure levels.

- **Specific diseases/adverse health outcomes associated with significant morbidity and mortality caused by smoking.**

  The IOM report identifies a number of diseases and conditions associated with smoking and highlights several diseases or adverse health outcomes as "well-established effects of tobacco use"—including cancer, cardiovascular disease, and chronic obstructive pulmonary disease. These adverse outcomes of tobacco use will serve as the focus for the LSRO study.

- **Surrogate biological markers associated with these diseases.**

  Because short-term indicators of risk reduction will be necessary to assesspotential reduced-risk products, significant attention will be devoted to the assessment of surrogate markers of the adverse outcomes associated with tobacco use. Biological markers reported in *in vitro*, laboratory animal and human clinical studies will be included in this review. As noted by the IOM committee, although a number of disease-specific surrogate markers are currently available, further validation of these markers is needed along with the development of biomarkers that accurately reflect mechanisms of disease.

- **Changes in smoking behavior and/or alternative tobacco use that could adversely impact the potential for risk reduction.**

  The IOM report refers to the phenomenon of compensatory behavior, as was seen with low-yield (e.g., low-tar) cigarettes as follows: "In an effort to maintain adequate exposure to nicotine, smokers who use low-yield products smoke differently (e.g., inhale more deeply) than those who smoke higher-yield products. Thus, exposure to tobacco toxicants from low-yield products is higher than would have been predicted by standardized assays and people who have continued to use these products have not significantly reduced their disease risk by switching to them." Thus, it is necessary to identify any changes in smoking behavior associated with potential reduced-risk tobacco products that will increase exposure and risk, in order to more accurately assess the potential for true risk reduction. In addition, risks associated with smokeless tobacco products offered as potential reduced-risk products will also need to be assessed and compared to the risks associated with smoking.

- **Behavioral/psychological indicators for increased rates of tobacco usage associated with the introduction of reduced-risk products.**

  The IOM Committee also noted that, in the case of low-yield cigarettes, widespread use of these products might have increased harm to the population in the aggregate if smokers who might otherwise have quit did not, if former smokers resumed use, or if some people who would otherwise not have smoked did so because of perceptions that the risk with low-yield products was minimal. Thus, methods to estimate population impacts of potential reduced-risk products will be assessed.

- **Surveillance approaches for reduced-risk tobacco products**

  The IOM Committee developed a set of "Regulatory Principles." One of them addresses post-market 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 post-marketing 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." Surveillance approaches, especially those that would assess biomarkers of exposure and disease risk, as well as smoking behavior, will be evaluated by the Expert Committees. The feasibility of conducting population studies to determine if rates of initiation, cessation and/or relapse of cessation are affected by the availability of reduced-risk products will also be assessed.

PROJECT ORGANIZATION:

TASK 1. Identification and Evaluation of the Scientific Evidence Available to Assess Potential Reduced-Risk Tobacco Products.

There are several critical questions that must be answered prior to the development of pre-market testing guidelines and a framework for peer review. Some examples are:

- What are the appropriate *benchmarks/standards* against which risk reductions will be compared?
- Are there validated and reliable *markers of exposure* to cigarette smoke/tobacco products that could be used to assess the validity of risk-reduction claims?
- Are there validated and reliable *biological markers or surrogate endpoints* for the early detection of tobacco-related toxicity/disease that could be used to assess the validity of reduced-risk claims?
- What are the *critical uncertainties and limitations* in the scientific data supporting the use of biomarkers of exposure and biological effect and what types of scientific studies are needed to reduce the uncertainties?
- Do *individual smoking behaviors* change with the use of reduced-risk products in a way that reduces or eliminates any potential reduction in individual risk?
- Are there *short-term surveillance* approaches that could be relied upon to monitor the effects of the use of reduced-risk products on individual and population risks?

TASK 2. Development of Specific Research Activities to Address Significant Gaps in the Science Reviewed in Task 1.

The purpose of this subtask is to build upon the suggested research activities included in the IOM report, along with research recommendations developed subsequent to the IOM report release[3]. That is, a sufficiently detailed research agenda will be developed as a guide for government and other funding sources, independent investigators and the industry.

TASK 3. Development of a Testing and Peer-Review Process to Assess Potential Reduced-Risk Tobacco Products

Based on the results of the preceding tasks, a process for testing and peer review of the data derived from the prescribed tests will be developed, if feasible. That is, if there are relevant, validated test procedures available to demonstrate the potential for risk-reduction, a framework for the evaluation of these data will be developed. There are several critical questions that must be addressed at this juncture, for example:

- How will *risk reduction* be assessed?
- How will *potential increases in risk* (new toxic constituents of 'smoke'; increases in risk associated with diseases other than the target disease(s) for risk reduction) be considered in the determination of risk-reduction potential?
- Is there an appropriate *level of risk reduction* that should be achieved in order to make a reduced-risk claim (e.g., considering the use/benefit equilibrium)?

[3] For example, Hatsukami et al. 2002. Nicotine & Tobacco Research, S89-S101.

- How should the potential for increased population use of tobacco (and associated increased addiction to nicotine) be considered in the assessment of risk reduction?
- What types of *post-marketing surveillance* would provide reliable information on individual risk reduction and population-wide tobacco product usage patterns?

WORK PLAN:

LSRO is conducting the work of the project through two parallel processes. A Core Committee (http://www.lsro.org/rrrvw/core_committee.html) is providing oversight of the project and is responsible for the completion of Task 3. Three separate State of the Science Review Committees (SSRCs) http://www.lsro.org/rrrvw/committees.html will address critical scientific questions, such as those listed above for Tasks 1 and 2, related to the completion of this project.

OVERSIGHT AND QUALITY ASSURANCE

The LSRO Board of Directors (Board) provides oversight and quality assurance for all LSRO activities. The contract, the selection of members to the Expert Committees, the scope of work and the final report are subject to approval of the Board. The Board reviews each LSRO report for scientific objectivity and fulfillment of contractual obligations.

PROJECT SCHEDULE:

There are five broad phases of work necessary to complete this project. They are presented below along with the proposed timeframes for each:

PHASE 1	**Core Committee Formation and Development of Guidance for SSRCs**	**August 2004-April 2005**
PHASE 2	**Development of SSRCs and Completion of Tasks 1 and 2**	**October 2004-March 2006**
PHASE 3	**Development of SSRC Summaries and Core Committee Completion of Task 3**	**October 2005-May 2006**
PHASE 4	**Development of Draft Final Report(s)**	**January 2006-July 2006**
PHASE 5	**Peer Review and Publication of Final Report(s)**	**July 2006-December 2006**