EXPOSURE ASSESSMENT IN THE EVALUATION OF 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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Cigarette smoking causes cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer (Centers for Disease Control and Prevention, 2005). Although cigarette smoke contains thousands of constituents that are of biological concern, some of which have been linked to disease development, the components that are most responsible for specific cigarette smoking-related diseases and the exposure thresholds for disease development are unknown.

Tobacco product manufacturers have developed products with modifications intended to reduce exposure to tobacco smoke and/or selected tobacco smoke constituents and, ultimately, disease risk. In 2004, Philip Morris USA, Inc., requested that the Life Sciences Research Office (LSRO) identify the types of scientific information necessary for studying the risk reduction potential of tobacco products; establish criteria to evaluate the scientific information, including identification of comparison products; and define a review process for the scientific information.

LSRO's overall findings and recommendations were published in the report *Scientific Methods to Evaluate Potential Reduced-Risk Tobacco Products* (2007b). LSRO also published the report *Biological Effects Assessment in the Evaluation of Potential Reduced-Risk Tobacco Products* (2007a) which provided an in-depth review of assays, models, and biomarkers of human disease that could be used during premarket evaluation to arrive at scientific conclusions regarding the comparative risks of potential reduced-risk tobacco products (PRRTPs) and conventional cigarettes for smokers who cannot or will not quit. This report, *Exposure Assessment in the Evaluation of Potential Reduced-Risk Tobacco Products*, provides findings, conclusions, and recommendations of the Exposure Assessment (EA) State-of-the-Science Review Committee, which included scientists with the appropriate expertise.

Specific Objectives of the EA Committee

The specific objectives of the EA Committee were to:

- Identify and evaluate methods for assessing exposure of smokers (and other individuals in the smoking environment);
- Identify product characteristics and use behaviors to influence tobacco-product-related exposure; and
- Recommend methods to assess exposure.

The EA Committee was also asked to identify benchmark cigarettes for PRRTP studies and to consider the strengths, limitations, quality, and quantity of the evidence related to exposure assessment methods when evaluating them as tools for assessing PRRTPs. The EA Committee's conclusions and recommendations are provided below. In the rest of the report, the EA

Committee and other Expert Advisory Committees of the Reduced Risk Review Project and LSRO staff will be referred to as *LSRO*.

Conclusions and Recommendations

LSRO concluded that the state-of-the-science is adequate for assessing whether a PRRTP is likely to reduce exposure to tobacco product and smoke toxins compared with exposure received from using conventional cigarettes. LSRO recommended consideration of product characteristics, studies of tobacco product or smoke chemistry, and studies of biomarkers of exposure as critical for assessment of PRRTPs. LSRO took a weight of evidence approach to evaluate the relative usefulness of each assessment method. Biomarker studies were identified as the approach in which LSRO has the most confidence. Other types of studies, such as smoking topography, particle deposition and retention, filter analysis, and microarray studies, can supplement biomarker studies.

Preclinical Studies

Product characterization

LSRO recommends that a PRRTP evaluation begin with an analysis of the differences in composition, design, and function between the PRRTP and conventional cigarettes. The possible effects of these differences should be described and used to guide later studies of PRRTPs. A consideration of the differences between cigarettes is an initial step in determining whether the user of the PRRTP or individuals in the use environment will be exposed to lower levels of tobacco smoke toxins compared to smokers of conventional cigarettes. Smoke chemistry studies should follow the analyses of differences in product characteristics.

Chemistry of tobacco products and tobacco smoke

Differences in product emissions indicate potential differences in exposure between PRRTPs and conventional cigarettes. LSRO recommends conducting broad analytical screens on smoke from cigarette-like PRRTPs and conventional cigarettes to measure as many constituents as possible. LSRO does not recommend using one smoke constituent as representative of a class of compounds, because substances in the same chemical class do not necessarily change in the same direction. Product characteristics should guide prioritization of analytes, and investigators should provide a rationale for selection or exclusion of tobacco smoke constituents for analysis.

LSRO recommends using Kentucky reference cigarettes as analytical controls and at least two conventional cigarettes, each from a separate tar category, as consumer product sample controls. Although no regimen using a cigarette smoking machine can predict actual exposure of smokers to tobacco smoke

constituents, LSRO recommends using the smoking machine regimen of the International Organization for Standardization and the US Federal Trade Commission (see Section II.2.2.1) and at least one other method (*e.g.,* the Massachusetts method or Canadian "intense" smoking method) to assess smoke chemistry profiles of PRRTPs and conventional cigarettes. Utilizing more than one method of smoke generation should provide information about the potential range smoke constituent exposure from PRRTPs.

LSRO recommends using validated non-standard approaches to assess levels of substances in smoke when standardized approaches are unavailable. These new or non-standard methods should be described in adequate detail to allow independent replication and should be published in a peer-reviewed journal. Tobacco product and smoke chemistry studies should guide the clinical studies of tobacco products.

Clinical studies

Clinical studies will play a critical role in comparisons of exposure from PRRTPs and conventional cigarettes. The LSRO report *Biological Effects Assessment in the Evaluation of Potential Reduced-Risk Tobacco Products* (2007a) details guidelines for investigators who conduct such clinical studies. LSRO considers biomarker studies to be the most useful type of clinical studies for PRRTP assessment. LSRO identified biomarkers of exposure[1] used to study tobacco products and ranked them in terms of their usefulness, which was determined by how well they met the following desirable characteristics:

- Tobacco specificity or a substantial difference between smokers and nonsmokers;
- Intra-individual variation that mirrors variation in smoking behavior;
- Existing database on its pharmacokinetics;
- Low analytical method variation;
- Sensitivity and chemical specificity of analytical method(s); and
- Existence of other biomarkers that can confirm the exposure.

LSRO also considered the invasiveness of the sample acquisition technique in ranking biomarkers. Detailed discussions of biomarkers of exposure are found in Chapter III of this report.

LSRO recommends using a battery of biomarkers to assess PRRTPs. Because of nicotine's role in smoking maintenance, all PRRTP evaluations should include measurement of nicotine and at least five of its major metabolites, including cotinine. Investigators should select other biomarkers on the basis of information from product characteristics, smoke chemistry, and other studies. The battery of

[1] A biomarker of exposure is a constituent or metabolite that is measured in a biological fluid or tissue and/or is measured after it has interacted with critical subcellular, cellular, or target tissues.

biomarkers chosen should reflect exposure to both particulate phase and vapor phase smoke components. LSRO identified biomarkers in which it has the most confidence as “Category A” biomarkers. These biomarkers have been sufficiently studied and provide reliable exposure measurements. LSRO also identified “Category B” biomarkers as those in which it has less confidence but for which there are sufficient data to support their use in exposure studies. LSRO would still recommend inclusion of Category B biomarkers in PRRTP evaluations. Other than nicotine and five of its major metabolites, including cotinine, LSRO does not specify a defined set of biomarkers that should be measured for all PRRTP assessments. Categorization of a biomarker as A or B is not meant to be prescriptive (see Section III.4).

LSRO determined that it has the lowest level of confidence in a third group of biomarkers “Category C”, as measures of tobacco product or smoke exposure (see Section III.4). Category C biomarkers are those that are not considered sufficiently reliable for routine use in exposure studies. However, if smoke chemistry or other studies indicate a significant difference in levels of a specific smoke constituent, biomarkers that measure exposure to the constituent of interest should be used in evaluation of the PRRTP regardless of category. Other types of clinical studies, such as smoking topography, filter analysis, and microarray studies, can supplement biomarker studies.

LSRO determined that the state-of-the-science is adequate for studying exposure assessment but acknowledges considerable limitations in the state-of-the-science. For example, additional biomarkers should be identified, validated, and used to compare exposure from PRRTPs with exposure from conventional cigarettes.

LSRO’s recommendations about scientific methods for assessing exposure are limited to what is possible at present. Advancements in the state-of-the-science for exposure assessment will influence recommendations about exposure assessment of PRRTPs. Exposure assessment is an important step in the evaluation of PRRTPs, but ultimately, the biological effects arising from these exposures play the crucial role in determining risk.

Literature Citations

Centers for Disease Control and Prevention. (2005) Annual smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 1997-2001. MMWR Morb Mortal Wkly Rep 54: 625-628.

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