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An Effective Product Evaluation Strategy for PREP Cigarettes: Recent Advances

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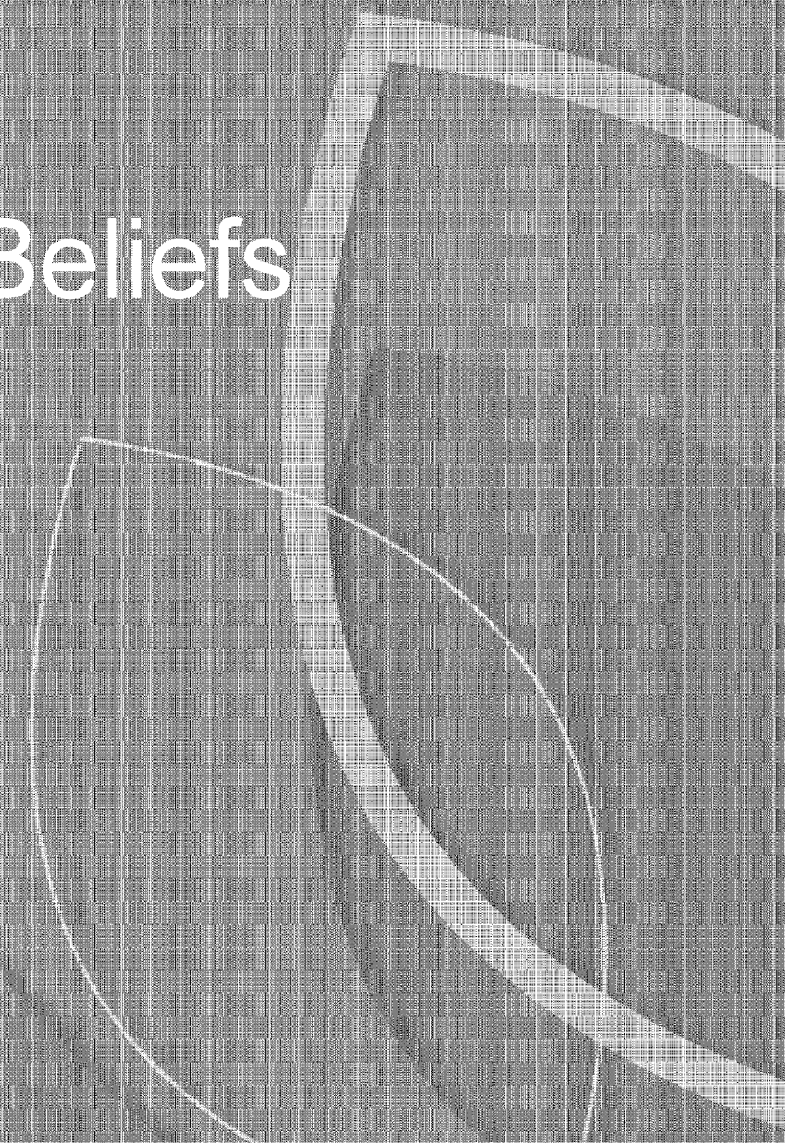
Guiding Principles and Beliefs



Guiding Principles and Beliefs

Smoking causes serious disease.

No tobacco product has been shown to be safe.

The best course of action for tobacco users concerned about their health is to quit.

Guiding Principles and Beliefs

Decreasing the health risks and harm directly associated with the use of tobacco products is in everyone's best interest.

Guiding Principles and Beliefs

Nicotine in tobacco products is addictive but is not considered a significant threat to health.

An individual's level of risk for serious disease is significantly affected by the type of tobacco product used as well as the manner and frequency of use.

Manufacturers, working in conjunction with governments, public health authorities and tobacco producers, should strive to reduce the harm caused by the use of tobacco products.

Guiding Principles and Beliefs

Adult tobacco consumers should have access to a range of tobacco, nicotine and cessation products and should be given information in order to make an informed choice on the relative risks of each product.

Guiding Principles and Beliefs

Public policy should encourage the development of tobacco products that reduce harm or relative risk of serious disease.

Public policy should allow communication of the relative risks of tobacco products and encourage smokers to switch to lower risk products.

Guiding Principles and Beliefs

Public policy should require population- and science-based standards that allow for consistent, accurate and verified communication about reduced harm and the relative risks of tobacco products.

Guiding Principles and Beliefs

Preferential treatment in terms of labeling, adult consumer communication, tax rates and other areas should be given to tobacco products or categories established through scientific evaluation to be significantly less harmful than other available tobacco products or categories.

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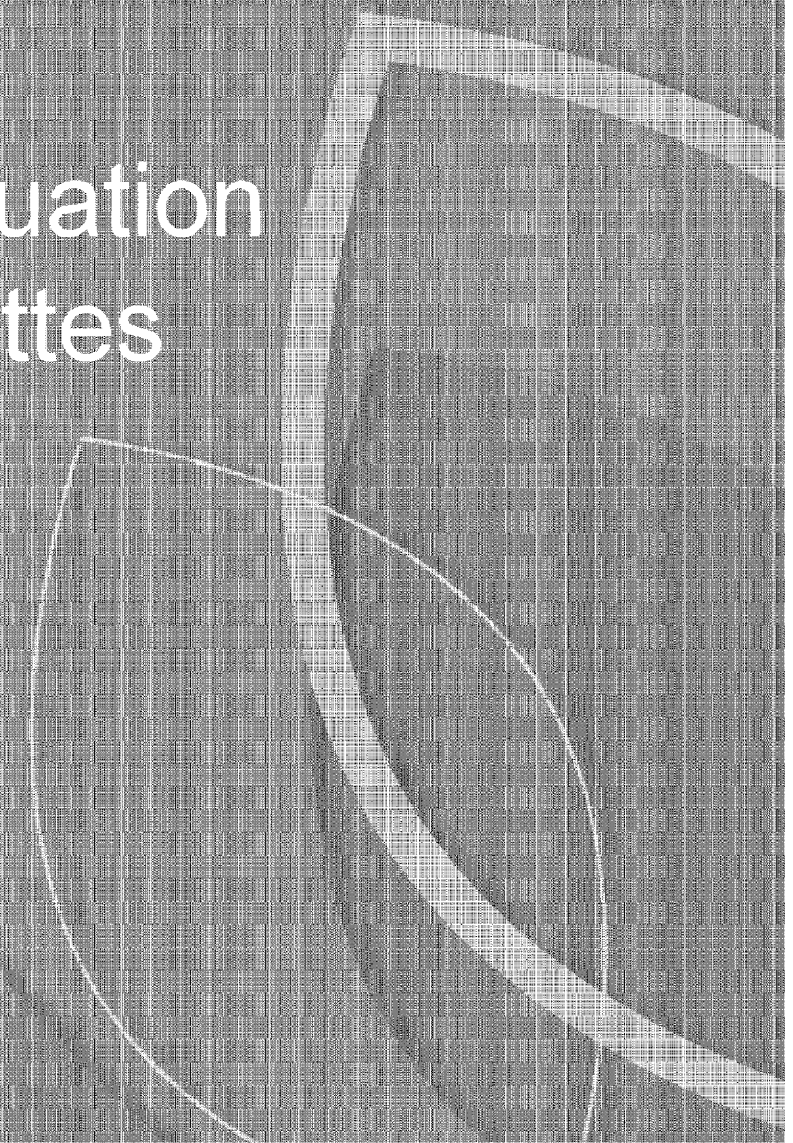
An Effective Product Evaluation Strategy for PREP Cigarettes



Harm Reduction

- *The development of products to address health concerns is termed "harm reduction" and has been reviewed by the Institute of Medicine (IOM)†*
- *IOM coined the term PREP (potentially reduced exposure product) to describe products that have the potential to reduce exposure to one or more toxicants present in smoke.*
- *Harm reduction potential can be assessed when a PREP product has been used by enough consumers for a period of time sufficient to assess the health impact of the product.*

†IOM, 2001: Clearing the Smoke - Assessing the Science Base for Tobacco Harm Reduction.

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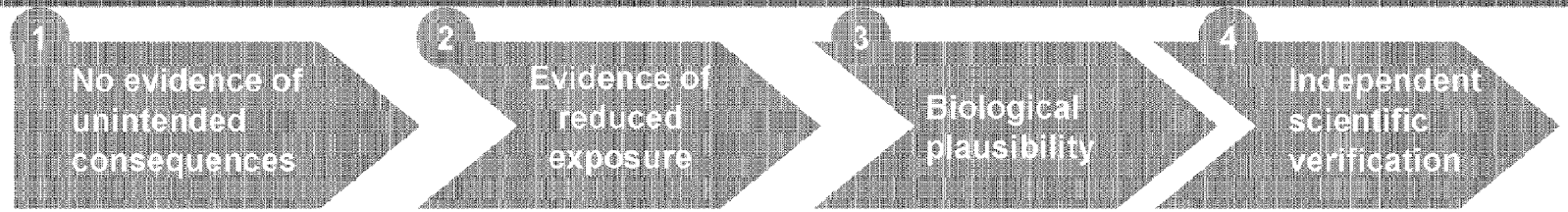
IOM guidelines for a PREP cigarette



Details	*It is essential that manufacturers ensure that product modifications do not increase the biological activity of cigarettes*	*Evidence of reduced exposure may include data from multiple types of studies*	*Sufficiently compelling argument to support the conclusion that a demonstrated reduction in exposure would be anticipated to result in a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies*	*All evidence is verified and validated by an external, preferably government appointed body*
Potential Data	*Smoke Chemistry yield data under multiple machine regimens* *In Vitro Toxicology* *Animal Toxicology*	*Smoke Chemistry yield data under multiple machine regimens* *Biomarker of exposure data in smokers* *Yield-in-use data*	*Comprehensive preclinical toxicology* *Short-term biomarkers of effect data in smokers* *Quantitative risk assessment*	*No evidence of unintended consequences* *Evidence of reduced exposure* *Biological plausibility evidence*

No Single Test Provides the Answer

The specific smoke constituents associated with observed risks are not known with certainty.

There are no *in vitro* or animal models that are direct measures of cigarette smoking related diseases.

Lack of clear mechanisms makes it difficult to focus on specific compound reductions or a single biological endpoint.

RJRT Product Evaluation

The product evaluation strategy used to assess the potential impact of proposed cigarette design modifications at RJRT entails two related and overlapping programs:

- *Product Stewardship*
- *Assessment of Exposure / Risk Reduction*

Product Stewardship Guiding Principles

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The primary objective of the product stewardship program at RJRT is to ensure that product modifications do not increase the biological activity of our cigarettes.

We work to ensure that nothing we do or add to our products will increase the inherent risks associated with smoking.

Exposure / Risk Assessment

1. Chemistry Assessment
2. Pre-clinical Toxicology
3. Smoker Studies
4. External Verification

Reduced Exposure Assessment
Smoke Chemistry

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The risk from smoking results from, among other factors:

- Chemical composition of the smoke
- Degree and nature of the smoker's exposure

Reduced exposure cigarettes:

- Modify the chemical composition of the smoke
- Reduce actual exposure to one or more harmful chemicals in smoke

Reduced Exposure Assessment
Smoke Chemistry

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Standard Smoke Measures

Gross Measures

Aggregate Chemical Measures

Specific Compound Determinations

Reduced Exposure Assessment
Pre-clinical Toxicology

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Specific chemical reductions alone cannot predict reduced toxicity

No single biological assay can directly measure disease risk

A battery of pre-clinical studies must be used:

- To indicate the biological significance of the chemical changes, and
- To demonstrate biologically relevant and significant exposure reductions

Reduced Exposure Assessment
Pre-clinical Toxicology

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In Vitro Studies:

- Mutagenesis (Ames Test)
- Cytogenetics (SCE or Micronucleus Test)
- Cytotoxicity (Neutral Red Assay)

Animal Studies:

- 90 day inhalation study in rats
- 30 week dermal tumor promotion study in mice

Reduced Exposure Assessment Smoker Studies

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Tests in smokers are needed to demonstrate significance and relevance of reduced exposure to toxicants

- Biomarkers of exposure
- Short-term biomarkers of effect

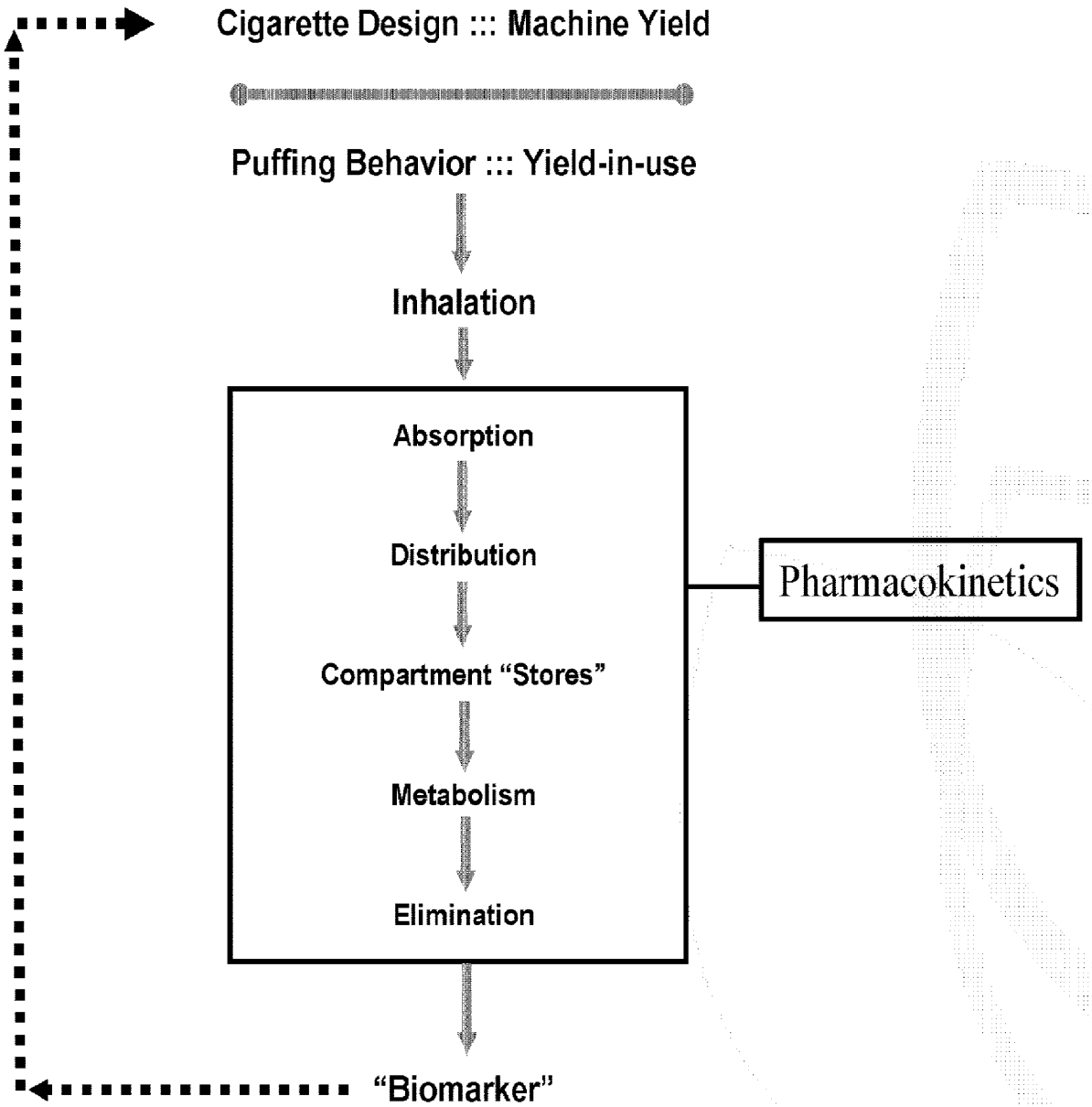
Tests with smokers account for differences in smoking behavior

Terminology

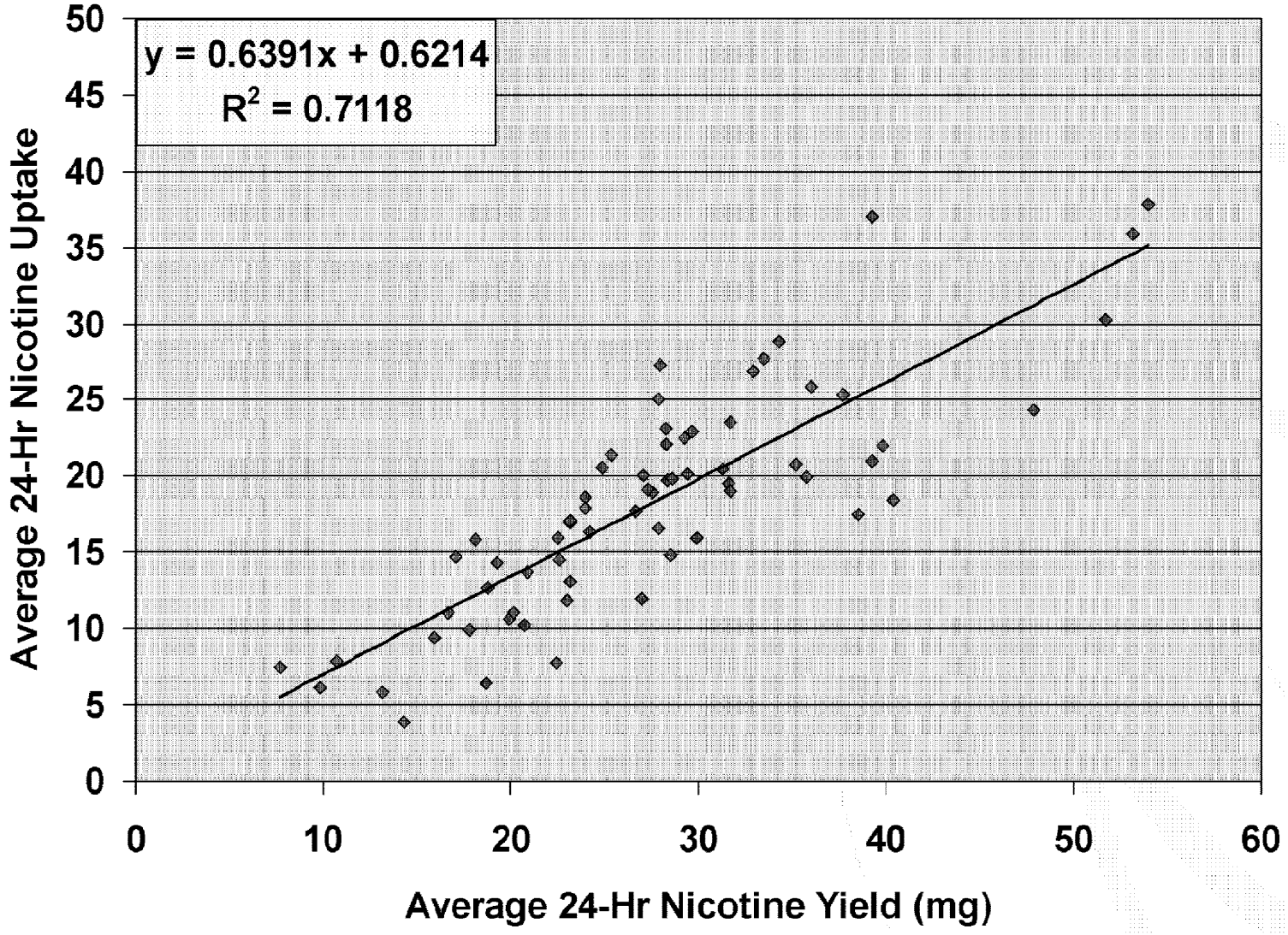
Exposure and Biomarker Assessment Definitions

- *External exposure marker*
  - *Amount of tobacco smoke constituent that enters the mouth*
- *Biomarker of exposure*
  - *tobacco constituent, combustion product, or metabolite measured in a biological fluid or tissue*
  - *has the potential to interact with a biological macromolecule*
  - *sometimes considered a measure of internal dose*
- *Biologically effective dose*
  - *amount that a tobacco constituent, combustion product, or metabolite binds to or alters a biological macromolecule*
- *Biomarker of effect*
  - *measurement of an effect due to exposure*
  - *includes early biological effects and clinical symptoms consistent with harm*

Smoke Uptake



Nicotine Yield vs. Nicotine Uptake



Reduced Exposure Assessment Smoker Studies

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- Biomarkers of Exposure
  - Specific smoke constituents
  - Metabolites
  - Gross Measures (e.g., mutagens)
- Biomarkers of Effect
  - Symptoms
  - Inflammation
  - Macromolecular changes

Methodology

Urinary Biomarkers of Exposure

- *Total Nicotine Uptake*
  - *nicotine, component of tobacco/smoke, plus 9 nicotine metabolites*
- *Urinary Mutagenicity*
  - *non-specific measurement of systemic exposure to mutagens*
- *NNAL*
  - *metabolite of the tobacco-specific nitrosamine NNK*
- *S-phenylmercapturic acid (SPMA)*
  - *metabolite of benzene*
- *3-hydroxypropylmercapturic acid (HPMA)*
  - *metabolite of acrolein*
- *3-hydroxy-1-methylpropyl-mercapturic acid (HMPMA)*
  - *metabolite of crotonaldehyde*
- *1-hydroxypyrene (1-OHP)*
  - *metabolite of pyrene*

Methodology

Urinary Biomarkers of Exposure

- *monohydroxybutenylmercapturic acids (MHBMA) and 1,2-dihydroxybutylmercapturic acid (DHBMA)*
  - *metabolites of 1,3-butadiene*
- *N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine (GAMA) and N-acetyl-S-(2-carbamoylethyl)cysteine (AAMA)*
  - *metabolites of acrylamide*
- *o-toluidine (o-T)*
  - *component of tobacco/smoke*
- *2-aminonaphthalene (2-AN)*
  - *component of tobacco/smoke*
- *4-aminobiphenyl (4-ABP)*
  - *component of tobacco/smoke*

Methodology

Urinary Biomarkers of Effect

- *the isoprostane $iPF_{2\alpha}$-III and its metabolite 2,3-dinor-$iPF_{2\alpha}$-III*
  - *measures of oxidative damage and inflammation*

Methodology

Blood Biomarkers of Biologically Effective Dose

- *4-aminobiphenyl-hemoglobin adducts (4-ABP-Hb)*
  - *measure of aromatic amine uptake + metabolic activation*
- *carboxyhemoglobin (COHb)*
  - *measure of carbon monoxide uptake*

Blood Biomarkers of Effect

- *sister chromatid exchange (SCE) in peripheral lymphocytes*
  - *measure of DNA damage*
- *circulating endothelial precursor cells*
  - *measure of endothelial function*
- *fibrinogen*
  - *measure of hypercoagulable state*

Methodology

Blood Biomarkers of Effect

- *white blood cell count*
  - *measure of inflammation*
- *triglycerides*
  - *lipid marker*
- *red blood cell mass*
  - *measure of hypercoagulable state*
- *hemoglobin A1C*
  - *measure of insulin resistance*
- *HDL cholesterol*
  - *lipid marker*
- *LDL cholesterol*
  - *lipid marker and measure of oxidative stress*

Methodology

Blood Biomarkers of Effect

- *homocysteine*
  - *measure of hypercoagulable state*
- *C-reactive protein*
  - *measure of inflammation*
- *sICAM1 (soluble intercellular adhesion molecule-1)*
  - *measure of inflammation*
- *COPD antibody screen*
  - *potential predictor of pulmonary function*
- *blood pressure*
  - *measure of hemodynamic effects*
- *heart rate*
  - *measure of hemodynamic effects*

Methodology

Respiratory Symptom Questionnaires

- *St. George's Respiratory Questionnaire (SGRQ)*
  - *a disease-specific measure developed to assess patients with mild to severe airway disease*
  - *contains 50 items that measure impact of airway disease on overall health, daily life, and perceived well-being*
  - *has been shown to detect changes in health status following smoking cessation*
  - *has been shown to have potential to detect changes following switch to Eclipse*
- *Leicester Cough Questionnaire (LCQ)*
  - *contains 19 items assessing 3 domains: Physical, Psychological and Social*
  - *has some overlap with the SGRQ but may be more sensitive to changes given the additional levels of health measured*

Methodology

Respiratory Symptom Questionnaires (cont.)

- *Smoking Cessation Quality of Life (SCQoL)*
  - *contains 51 items assessing 15 domains*
  - *uses the Short Form 36 Health Survey (SF-36) as its general health status core measure*

- *American Thoracic Society Division of Lung Disease Questionnaire ATS-DLD-78 (ATS)*
  - *a 96-item respiratory-focused epidemiologic questionnaire*
  - *assesses cough, phlegm, wheezing, breathlessness, illness, and other risk factors*

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Scientific judgment is used to conclude a cigarette is Reduced Exposure

Potential Data for Plausibility	Relevant Data	Details
Comprehensive preclinical toxicology	*At a minimum, a statistically significant decrease in toxicity must be achieved*	➢ *Level of reduction must be biologically meaningful – which means it should be large enough to suggest the observed difference will manifest itself as decreased mortality and morbidity in smokers* ➢ *Should reflect our existing knowledge of relevant epidemiology associated with disease modeled by the pre-clinical assay.*
Biomarkers of exposure in smokers	*At a minimum, a statistically significant decrease in biomarkers of exposure must be achieved*	
Quantitative risk assessment	*At a minimum, a statistically significant decrease in calculated risk must be achieved*	

- ***To establish plausibility there should be directionally consistent data from one or more data types***

  - **Note: It is scientifically unsound to set a specific global reduction in activity level that must be achieved**

Reduced Exposure Assessment Weight of the Evidence Approach

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Data from an array of tests must be used to assess the reduced exposure potential of products.

The patterns of changes in chemistry, pre-clinical toxicology, human exposure and short-term effects in humans must be considered as a whole.

Weight of the evidence approach is the established analytic approach applied.

Experts must weigh the evidence and assess potential for reduced exposure.

RJRT Assessment Methods Continue to Evolve

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Continue to monitor literature to identify new, relevant methods.

RJR will incorporate appropriate new test methods as they become available.

- Must be relevant to tobacco-related disease.
- Must be responsive to cigarette smoke.
- Must be sensitive enough to differentiate between cigarettes.

RJRT Assessment Methods Continue to Evolve

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RJRT will apply significant investment in new methods development.

- Chemical analysis techniques
- In vitro assay methods
- Animal models of diseases and adverse health effects
- Post-market surveillance techniques

Beyond Reduced Exposure Cigarettes: Reduced Risk Products

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Data from the array of tests must be sufficient to establish that the product exhibits biologically meaningful reduced exposure – the basic foundation.

Epidemiologic or other human studies must lead to significant scientific agreement that reduced toxicant intake from use of the reduced exposure product results in a meaningful reduction in a valid measure of chronic disease or a serious adverse health condition associated with tobacco use.

Beyond Reduced Exposure Cigarettes: Reduced Risk Products

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It must also be concluded that the validity of the anticipated reduction in one or more tobacco-related diseases or health conditions associated with use of the reduced risk product is not likely to be reversed by new and evolving science.

Experts must weigh the evidence and assess Reduced Risk potential.

Exposure / Risk Reduction Assessment
External Review and Verification

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RJRT has a panel of 12 outside prominent physicians and scientists with expertise in relevant fields such as:

- Carcinogenesis
- Pulmonology
- Pathology
- Toxicology
- Pharmacology
- Cardiovascular Disease

The outside panel critically reviews and evaluates:

- Test methods applied
- Test results developed for reduced exposure and reduced risk products
- Conclusions reached by RJRT scientists

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