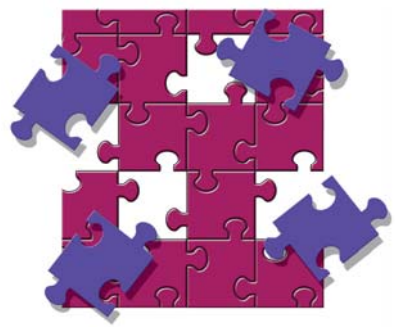
Statement of Work

Individual Exposure Assessment (IEA) Committee

Kara Lewis

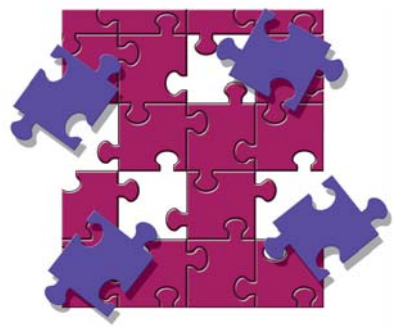
June 14th, 2005

(Slightly modified from version presented)



Clearing the Smoke
Relevant Conclusions

- Conclusion 1: "For many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible."
- Conclusion 4: "Currently available PREPS have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products."

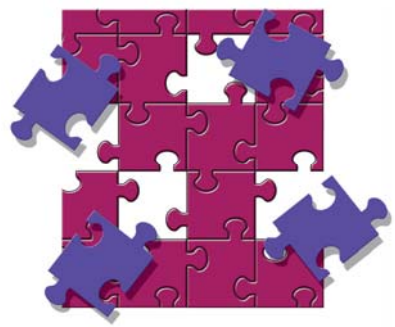


Institute of Medicine (2001)

Clearing the Smoke

Regulatory Principle 2

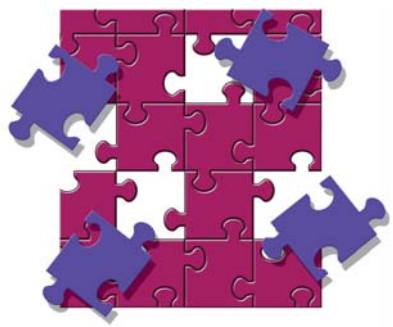
"All tobacco products should be assessed for yield of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various constituents of tobacco smoke should be assessed using appropriate biomarkers…"



Institute of Medicine (2001)

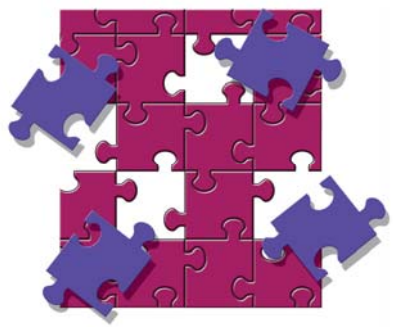
Purpose of the IEA State of the Science Review Committee

- To describe the validity and utility of various individual exposure assessment methods as components of a comparative risk assessment framework.
- To assess the characteristics of potential users, tobacco product use behavior and aspects of product design that have the potential to influence exposure to tobacco product and tobacco smoke constituents.
- To identify relevant research gaps that, if filled, could contribute to an assessment of reduced risk.



Work Products

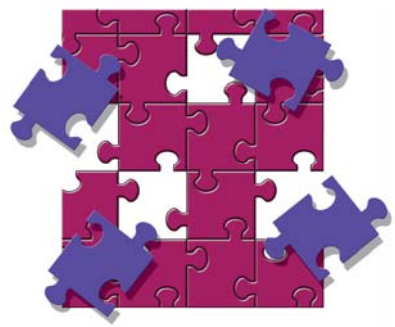
- Summary to the Core Committee at their October 19-20, 2005 meeting.
- Summary chapter in the RRRvw Core Committee Report by April, 2006.
- Formal report by late 2006.



Clearing the Smoke
Four Categories of Measures

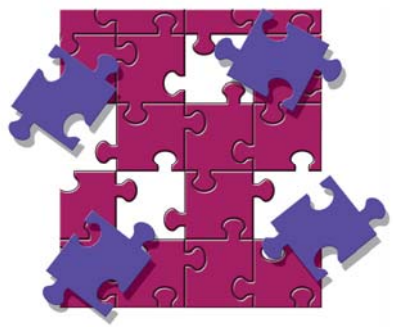
- **External exposure measures**
- **Biomarkers of (internal) exposure**
- Biomarkers of effective dose
- Biomarkers of potential harm

Institute of Medicine (2001)



External Exposure Measures

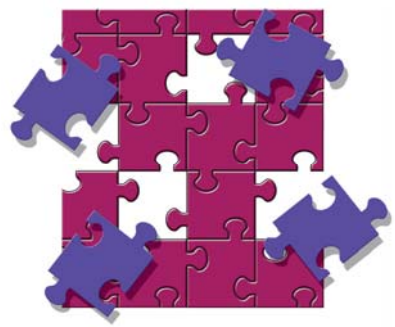
- Cigarette smoking machine yields of substances
- Smoking topography/Cigarette puffing behavior
- Number of cigarettes smoked per day



Biomarkers of (Internal) Exposure

"A tobacco constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose."

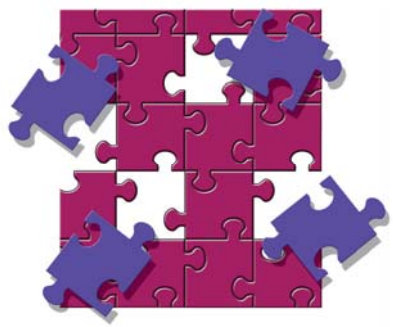
Institute of Medicine (2001)



Potential Influences on Exposure

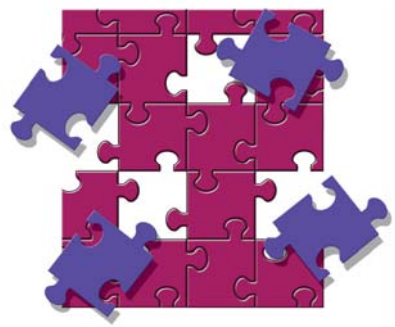
- Product design
- Product use patterns
- Rate of absorption of smoke substances
- Rate of metabolism of smoke substances

Hatsukami et al. (2004)



Tobacco Product and Tobacco Smoke Chemistry

- What techniques are used for generating tobacco smoke?
- What techniques are available for the chemical analysis of tobacco products and tobacco smoke?
- Have they been validated and standardized?
- How relevant are methods for characterizing exposure to actual exposures?
- What methods are in development for the chemical analysis of tobacco products and tobacco smoke?
- What and how much can these analyses contribute to an overall assessment of reduced risk?



Cigarette-Yield Testing Protocols

Federal Trade Commission / International Organization for Standardization : 35 mL puff volume, 2 second puff duration, 60 second inter-puff interval with no ventilation holes blocked.

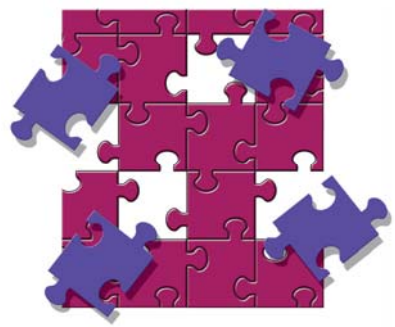
State of Massachusetts Dept. of Public Health : 45 mL puff volume, 2 second puff duration, 30 second inter-puff interval with 50 % of the ventilation holes blocked.

British Columbia – 55 mL puff volume, 2 second puff duration, 30 second inter-puff interval with 100 % blocking of ventilation holes.

Smoke Analytes

- Nicotine, ‘tar’, and carbon monoxide are standard Federal Trade Commission (FTC) measures.

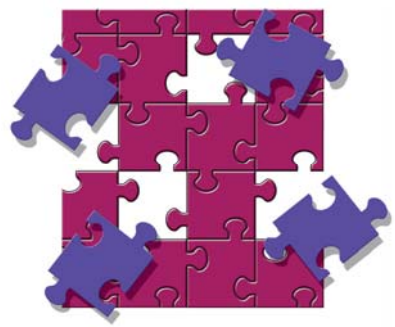
- Other analytes have been identified by organizations, such as the U.S. Consumer Product Safety Commission and the International Agency for Research on Cancer (IARC).



Appropriate Comparison Products

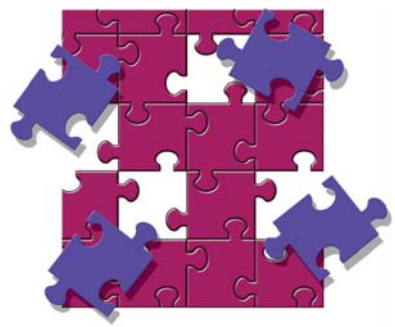
What are the appropriate benchmarks to which potential reduced tobacco products should be compared ?

- Kentucky reference tobacco product?
- The leading product as assessed by market share?
- Each individual smoker's brand at the time of switching to the new product?
- The lowest-risk product currently available?
- Each individual smoker's dominant brand of his or her smoking history?



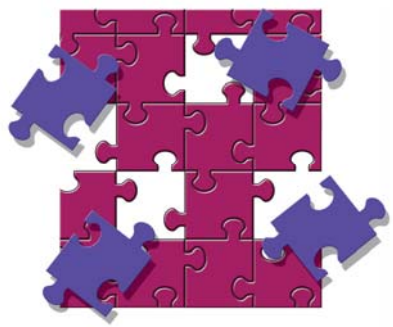
Characteristics of Potential Users

- What user characteristics have the potential to influence the degree of exposure?
- What are the implications on study design?



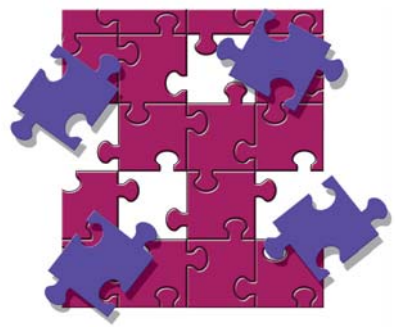
Smoking Behavior (1)

- What measures are used to assess cigarette puffing behavior/smoking topography?
- What other measures are used to assess smoking behavior (*e.g.*, # cigarettes/day, amount of cigarette smoked)?
- What are the appropriate comparison products?
- What are the limitations of using smoking topography and other measures of smoking behavior to estimate tobacco smoke exposure?



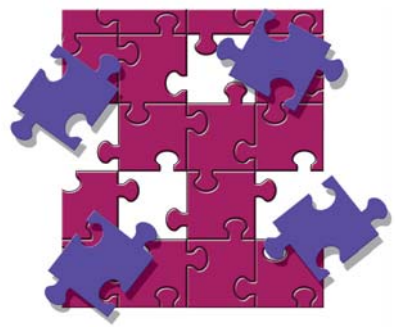
Smoking Behavior (2)

- How do measures of cigarette puffing behavior/smoking topography relate to biomarkers of exposure?
- What and how much can cigarette puffing behavior/smoking topography and other smoking behavior measures contribute to an overall assessment of risk?
- What impact do product characteristics (*e.g.*, elasticity) have on smoking behavior?



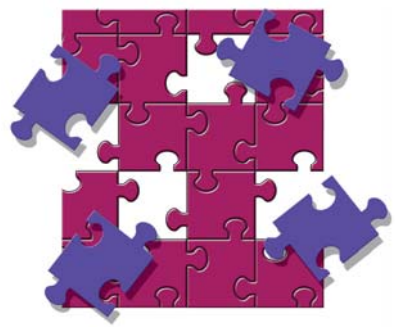
Some Smoking Topography/Cigarette Puffing Behavior Measures

- Puff volume
- Number of puffs
- Puff duration
- Inter-puff interval
- Puff frequency
- Duration of inhalation
- Depth of inhalation
- Inhalation volume



Exposure to Environmental Tobacco Smoke

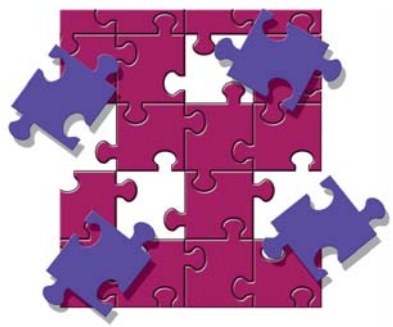
- What methods have been used to acquire information on exposure to environmental tobacco smoke?
- What are the limitations of these methods for estimating exposure to environmental tobacco smoke?
- What is the relationship between biomarkers of exposure/internal dose and other information on exposure to environmental tobacco smoke?
- What can information about exposure to environmental tobacco smoke contribute to an overall assessment of a potential reduced risk product?



Assessment of Environmental Tobacco Smoke Exposure

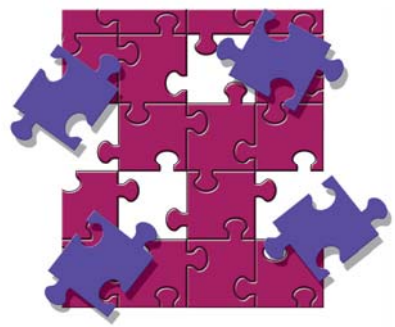
- Using questionnaires or interviews to determine spousal smoking status or to determine the number of hours for which the person is exposed at home, work, or elsewhere
- Measuring biomarkers
- Measuring tracer compounds specific to tobacco smoke

(National Cancer Institute 1999; Douce et al., 2001)



Some Markers of Environmental Tobacco Smoke Exposure

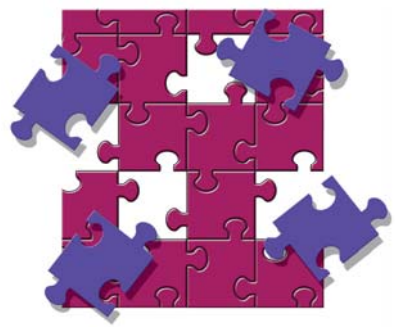
- Nicotine
- Myosmine
- 3 - Ethenylpyridine
- Solanesol
- Scopoletin
- Total respirable suspended particulate matter



Douce et al. (2001)

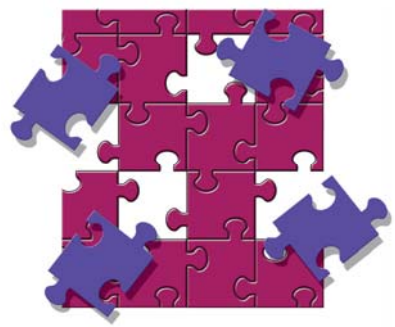
Biomarkers of (Internal) Exposure (1)

- What are the available biomarkers?
- Have available biomarkers been validated?
- How will exposure to substance introduced through product design changes be measured?
- What are the potential confounders and factors that can modify exposure?
- How well do they predict tobacco-related diseases?
- Are there any tobacco product or smoke constituent ratios that are conserved in human measurements?



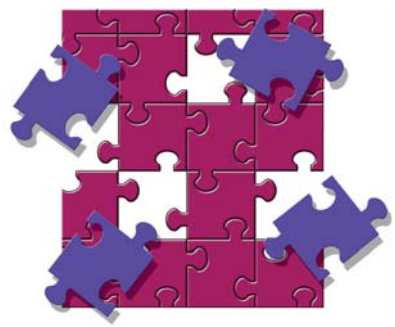
Clinical Study Design

- What clinical study designs have been used to assess exposure/internal dose of tobacco product and tobacco smoke constituents?
- Which are likely to be most useful for evaluating reduced risk products?
- What are the advantages and disadvantages of measuring biomarkers in various biological sample matrices?
- How does the sample population of a clinical study influence the applicability of results?
- What is the appropriate duration for conducting clinical studies on exposure?



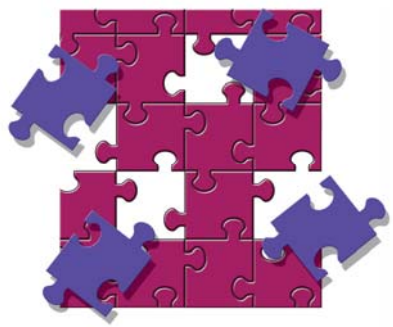
Biomarkers of (Internal) Exposure (2)

- How do current biomarkers of exposure/internal dose fall short and what is required of future biomarkers?
- What are the biomarkers of exposure/internal dose in development?
- What and how much will biomarkers of exposure/internal dose contribute to an overall assessment of reduced risk products?
- How much emphasis should be placed on these kinds of measures?



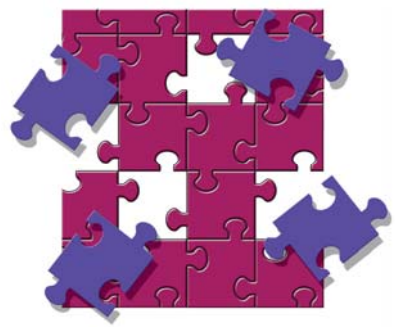
Other Methods of Assessing Exposure

- Microarrays
- Breath Analysis
- Filter Analysis
- Are there other methods that should be considered?



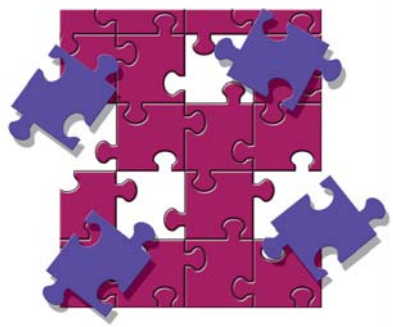
Smokeless Tobacco Use Characteristics

- What methods are used to assess smokeless tobacco product use behaviors?
- What are the limitations of these methods?
- What are the appropriate comparison products?
- What is the relationship between tobacco product use history measures and biomarkers of exposure/internal dose?
- What can information about tobacco product use characteristics contribute to an overall assessment of reduced risk?



Research Needs

- What uncertainties are associated with the described methods?
- What gaps, if filled, could improve individual exposure assessment?
- What are the future directions/requirements for assessing individual exposures?



Conclusions and Recommendations

- What is the relative value of the various approaches used to assess individual exposure for the evaluation of exposure reduction?
- How should the measures used to assess individual exposures to tobacco product and tobacco smoke constituents inform the overall process of evaluating reduced-risk tobacco products?