

A MULTI-CENTER STUDY TO DETERMINE THE EXPOSURE OF ADULT U.S. SMOKERS TO CIGARETTE SMOKE



(Total Exposure Study)

Barbara Zedler, M.D.

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



Rationale for Assessing Population Exposure

- There are only limited data for population exposure to cigarette smoke.
- Such data can provide valuable context for the assessment of potential reduced exposure products (PREP candidates).
- Smoking machine-derived cigarette yields are not generally predictive for human exposure.
- Therefore, to understand human exposure, clinical studies are required which determine biomarkers of exposure:
 - **Total Exposure Study (TES)**
 - Pilot TES
 - **(Main) TES**
 - Follow-up TES

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



Total Exposure Study (TES): *Purpose*

A **cross-sectional, observational** study to determine the exposure of adult U.S. cigarette smokers to cigarette smoke constituents:

- To include all FTC tar delivery categories
- To generate baseline data for future exposure/ risk/ harm reduction assessments
- To compare selected biomarkers of exposure and biologically effective dose among adult U.S. smokers and non-smokers
- To evaluate smoking behavior as it relates to cigarette smoke exposure
- To investigate the relationship between selected biomarkers of potential harm and cigarette smoke exposure

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Primary Objectives*

- To estimate the exposure of adult U.S. cigarette smokers to cigarette smoke constituents using selected biomarkers of exposure and biologically effective dose
- To investigate the relationship between cigarette smoke exposure of U.S. adult smokers and tar delivery (FTC method)

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Study Design*

- Ambulatory, observational, cross-sectional, multi-center study with **5,000** participants in 5 parallel groups, all FTC tar delivery categories, 2 visits
 - **4,000** adult smokers in 4 groups based on FTC tar delivery categories, representative of adult U.S. population regarding:
 - Age
 - Gender
 - Body Mass Index (BMI)
 - Geographic region
 - Ethnic and racial distribution
 - Socioeconomic status distribution (income and education)
 - **1,000** adult non-smokers

- **41 sites across U.S.**

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Milestones*

- Protocol IRB Approval 3Q 2002
- Clinical conduct 3Q 2002 – 4Q 2003
- Statistical Analysis Plan 4Q 2004
- Bioanalytical data available 1Q 2005
- Statistical database lock 1Q 2005

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Milestones*

Final study reports

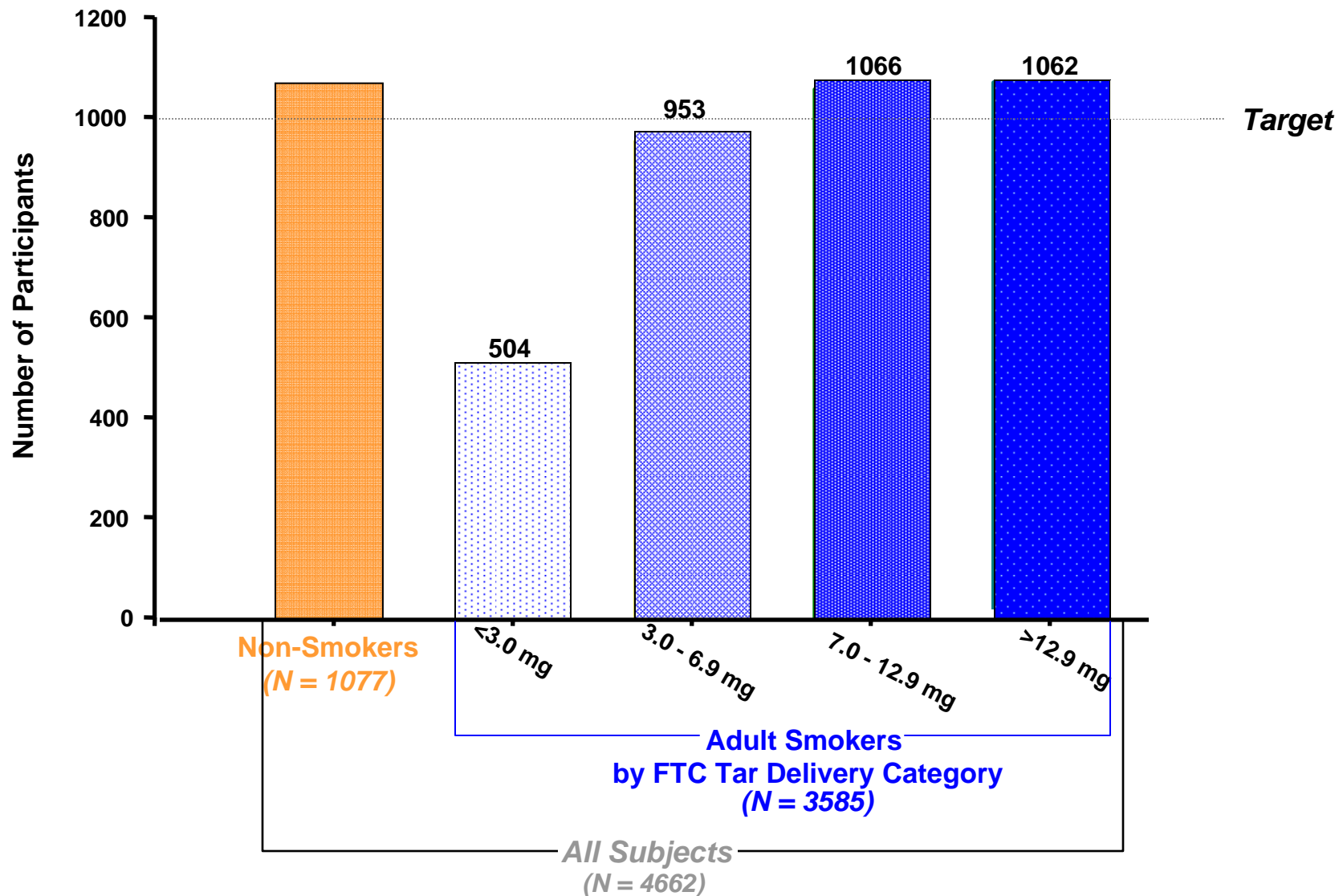
- | | | |
|----|--|---------|
| A. | Demographics, Cig Consumption,
Nicotine Equivalents, COHb | 4Q 2005 |
| B. | Other Biomarkers of Exposure | 1Q 2006 |
| C. | Biomarkers of Potential Harm | 3Q 2006 |
| D. | Model of Adult Smoking | 2Q 2007 |
| E. | Smoking Topography | 3Q 2007 |
| F. | Remaining Regressions | 1Q 2008 |
| G. | Exploratory Analyses | 2Q 2008 |

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Study Population*

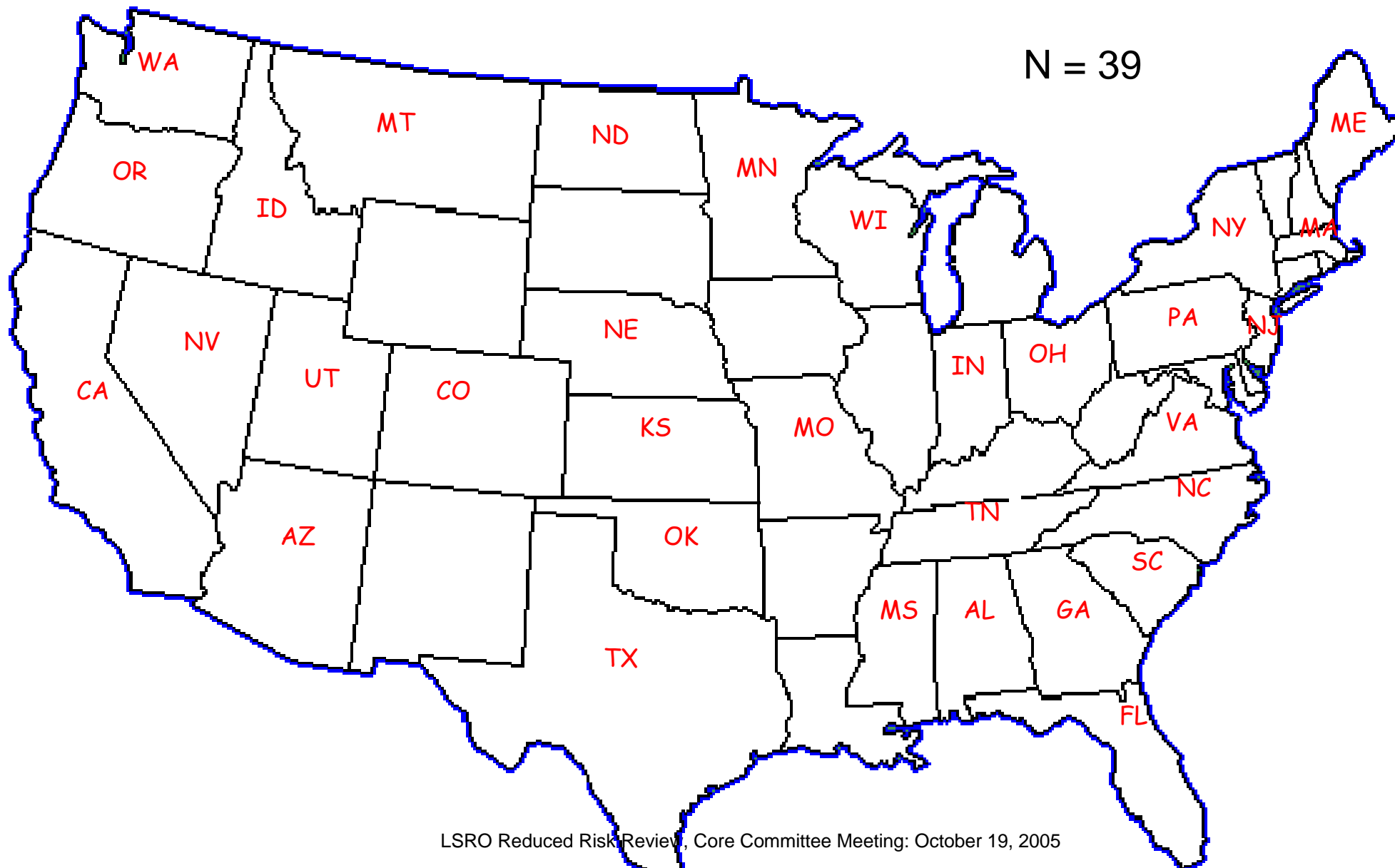


LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Study Sites*



LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Biomarkers of Exposure, Biologically Effective Dose*

Biomarker	Matrix	Smoke Constituent
Nicotine and 5 Major Metabolites <i>(Molar sum expressed as Nicotine Equivalents)</i> <ul style="list-style-type: none">-Nicotine, Nicotine-<i>N</i>-glucuronide-Cotinine, Cotinine-<i>N</i>-glucuronide-<i>trans</i>-3'-Hydroxycotinine,<i>trans</i>-3'-Hydroxycotinine-<i>O</i>-glucuronide	24-hr Urine	Nicotine
Cotinine	Serum	Nicotine
NNAL, NNAL-glucuronides	24-hr Urine	NNK
3-Hydroxypropylmercapturic Acid (3-HPMA)	24-hr Urine	Acrolein
Total 1-Hydroxypyrene (1-OHP)	24-hr Urine	Pyrene <i>(Polycyclic Aromatic Hydrocarbons)</i>
1,3-Butadiene Metabolites <ul style="list-style-type: none">-Monohydroxybutenylmercapturic acid (MHBMA)-Dihydroxybutylmercapturic acid (DHBMA)	24-hr Urine	1,3-Butadiene
Carboxyhemoglobin (COHb)	Whole Blood	Carbon monoxide
4-Aminobiphenyl Hemoglobin (4-ABP-Hb) Adducts	Red Blood Cells	4-Aminobiphenyl

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



TES: *Biomarkers of Potential Harm*

Biomarker	Matrix	Health Effect
HDL- and LDL-Cholesterol	Serum	Atherosclerosis
Triglycerides	Serum	Atherosclerosis
Fibrinogen	Plasma	Cardiovascular disease
hs C-Reactive Protein	Serum	Inflammation
11-Dehydrothromboxane B₂	24-Hour Urine	Platelet activation
von Willebrand Factor Antigen	Plasma	Endothelial cell damage
Microalbumin	24-Hour Urine	Endothelial cell damage
Total Bilirubin	Serum	Depletion of antioxidant capacity
8-<i>epi</i>-Prostaglandin F_{2α}	24-Hour Urine	Lipid peroxidation
FEV₁ and FVC (% of predicted)	N/A	Chronic Obstructive Pulmonary Disease

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.



Pilot TES: *Biomarkers of Potential Harm*

mean (SD)
median

Biomarker	Matrix	Adult Smokers (N=50)	Non-Smokers (N=65)	p-value*
HDL-cholesterol (mg/dL)	blood	47 (11) 46	54 (13) 53	0.003
LDL-cholesterol (mg/dL)	blood	119 (28) 119	111 (29) 109	0.18
hs-CRP (mg/dL)	blood	0.41 (0.46) 0.27	0.28 (0.44) 0.12	0.05
Fibrinogen (mg/dL)	blood	301 (72) 292	253 (58) 248	0.0002
11-Dehydrothromboxane B₂ (pg/mg creatinine)	urine (24-h)	1035 (440) 973	711 (242) 710	<0.0001
8-epi-Prostaglandin F_{2α} (pg/mg creatinine)	urine (24-h)	2058 (827) 1935	1106 (322) 1034	<0.0001

*p-value from Wilcoxon rank-sum test of difference between median values for adult smokers v. non-smokers

LSRO Reduced Risk Review, Core Committee Meeting: October 19, 2005

This presentation is intended for the scientific and the public health community. The information shared with the scientific and public health community is not part of PM USA consumer communications and, if shared with the consumer, has the potential to change the context of the communications intended for the consumer.