Application of an Evaluation Process

- Carbon Filter Technology
- EHCSS Technology

Chuck Gaworski, M.S., DABT

Philip Morris USA

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Objective

The objective of this presentation is to illustrate an evaluation process for PREPs using cigarette design technologies currently under development at PM USA.

- Process is dynamic and should be considered flexible
- Contains both non-clinical and clinical endpoints
- Limited data sets shown here are examples selected from a larger set of studies

There is no intention to demonstrate, or imply, reduced exposure/risk claim with this presentation.

Responsible Communication

This presentation is intended for the scientific and 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.

Terminology

- ***Program***
  - The **S**moke **Co**nstituent **R**eduction (SCoR) program explores the use of various technologies for their potential to reduce a smoker's exposure to harmful compounds in cigarette smoke, while maintaining an acceptable smoking experience for adult smokers.
  - The **E**lectrically **H**eated **C**igarette **S**moking **S**ystem (EHCSS) program explores the use of various technologies to heat the tobacco electrically in a special device rather than burning it in an uncontrolled way.
- ***Technology***
  - Carbon filtration is one of several technologies being evaluated.
  - Technologies are being evaluated for filtration with downstream flavor addition
  - An electrical resistance heating element formed from an iron aluminide alloy is an example of a technology.
- ***Prototypes / Products***
  - Prototypes are used for pre-market evaluation of technologies.
  - Products incorporate final attributes.

Reduced Risk Evaluation

Objective:

Addresses IOM Regulatory Principle 4

"Manufacturers should be permitted to market tobacco-related products with exposure-reduction or risk-reduction claims only after prior agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and **(b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects,** as compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that measurable reduction in morbidity and/or mortality (in subsequent clinical or epidemiological studies) would be anticipated, as judged by independent scientific experts."

(Institute of Medicine, 2001, Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction, p. 10., emphasis added)

Evaluation Approaches

Evidence for:

Acceptability	Exposure	Risk	Harm
Non-Clinical	***Non-Clinical***	***Non-Clinical***	***Non-Clinical***
• Smoke chemistry • Mutagenicity • Cytotoxicity • Smoke inhalation	• Smoke chemistry • *In vitro* • *In vivo*	• Animal models of disease • Links to human disease	• Nothing additional
	Human	***Human***	***Human***
	• General / Specific biomarkers of exposure	• Biomarkers of effect	• Long-term health effects −Clinical −Epidemiology • Surveillance

Reduced Risk Evaluation

Analysis of the potential of a design to reduce exposure and provide data supporting anticipation of reduced morbidity / mortality

Knowledge gap!

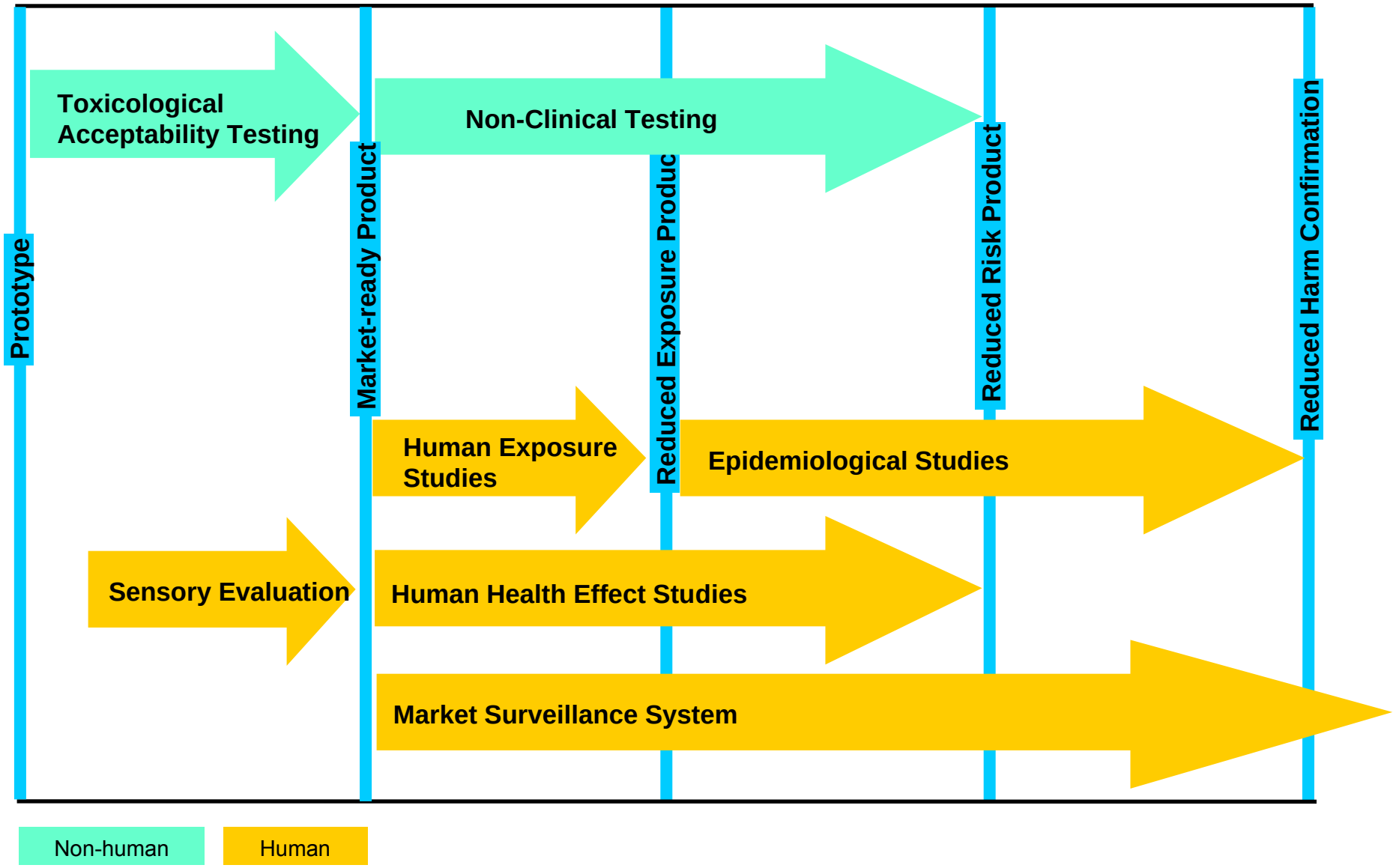
- **What is the current state of disease / risk knowledge?**
  - Known association between smoking and disease but many mechanisms are unknown
  - While the association between disease and smoking in humans is established, few, if any, quantitatively predictable non-clinical models exist (i.e., *in vitro* or *in vivo)*.
- **How can a design be evaluated?**
  - Prototypes vs. final products
  - Robust non-clinical and/or clinical studies
  - Mathematical models vs. direct evidence
  - Biomarkers vs. disease development
- **Who do we talk to and how?**

Examples of our process at work

SCoR Evaluation

SCoR is an acronym for Smoke Constituent Reduction. Through the SCoR program PM USA is exploring the use of various technologies for their potential to reduce a smoker's exposure to harmful compounds in cigarette smoke, while maintaining an acceptable smoking experience for adult smokers.

A Sound and Relevant Harm Reduction Evaluation Process



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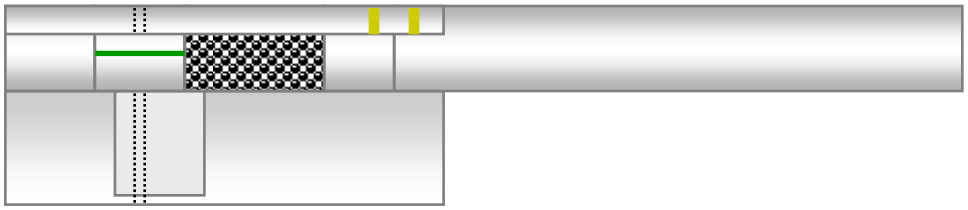
Pre-Market Toxicologic Acceptability Evaluation

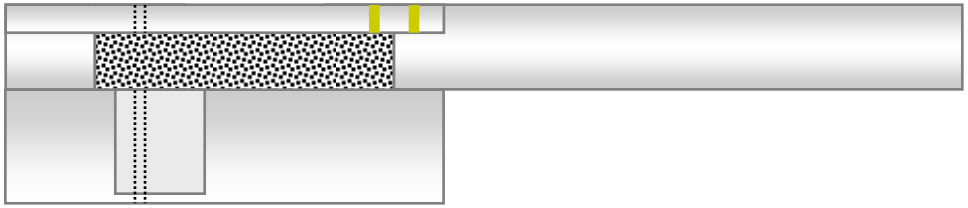
Analysis of the potential of a design to contribute to smoke or increase the toxicity of cigarette smoke as judged by current toxicological testing approaches

- Driven by non-clinical testing approaches & toxicology literature
- Design evaluation - Robust testing using prototypes
- Changes in chemical risk factors - Smoke chemistry
- Non-clinical biological endpoints sensitive to smoke or smoke phases
  - Genotoxicity
  - Cytotoxicity
  - Inhalation

Carbon Filter Prototype Designs - SCoR



Cavity (Plug-Space-Plug)
containing up to 180 mg activated carbon in a cavity configuration



Carbon-on-Tow
containing 45 to 120 mg activated carbon disbursed throughout the filter tow material

Use of SCoR Prototypes and Bridging

Multiple studies conducted with various design prototypes to investigate:

- ***Filter designs***
- ***Carbon type and activity***
- ***Flavor ingredients***
- ***Flavoring methods***
- ***FTC and MDPH smoking conditions.***

Smoke Chemistry, Cytotoxicity, Bacterial Mutagenicity , Mouse Lymphoma, in vivo Micronucleus, 90-day Smoke Inhalation in Rats

Status - SCoR

- Toxicological acceptability testing (pre-market evaluation) of carbon and flavor technologies have been completed allowing test market evaluations.

- Consumer acceptance of taste and flavor in the market is unknown and is the focus of these test markets.

- ***PM USA does not have sufficient evidence that the application of new technologies to these new products warrants a reduced exposure claim. We therefore are not considering making any reduced-exposure claims about these new products at this time.***

EHCSS Evaluations

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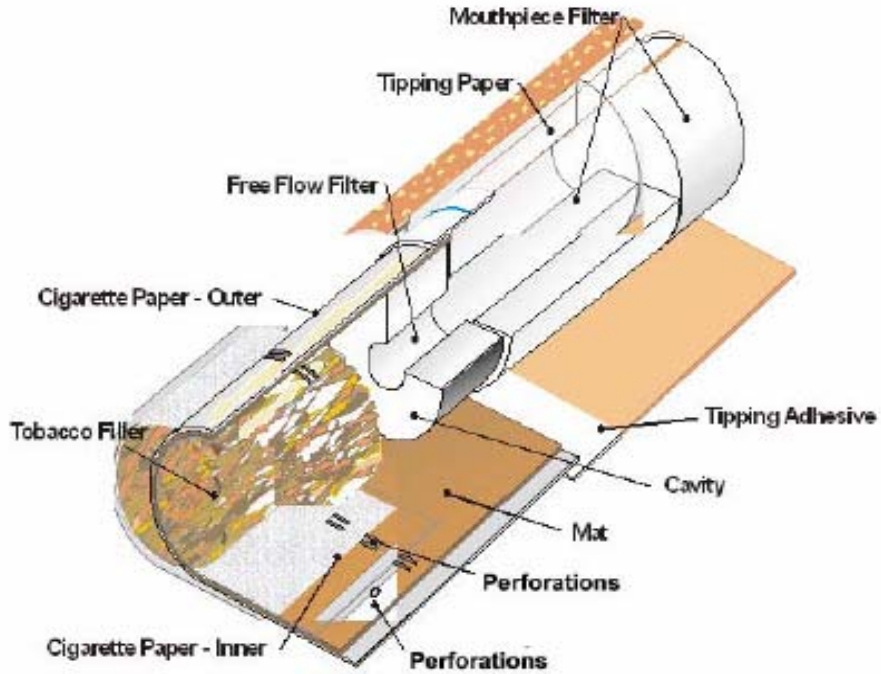
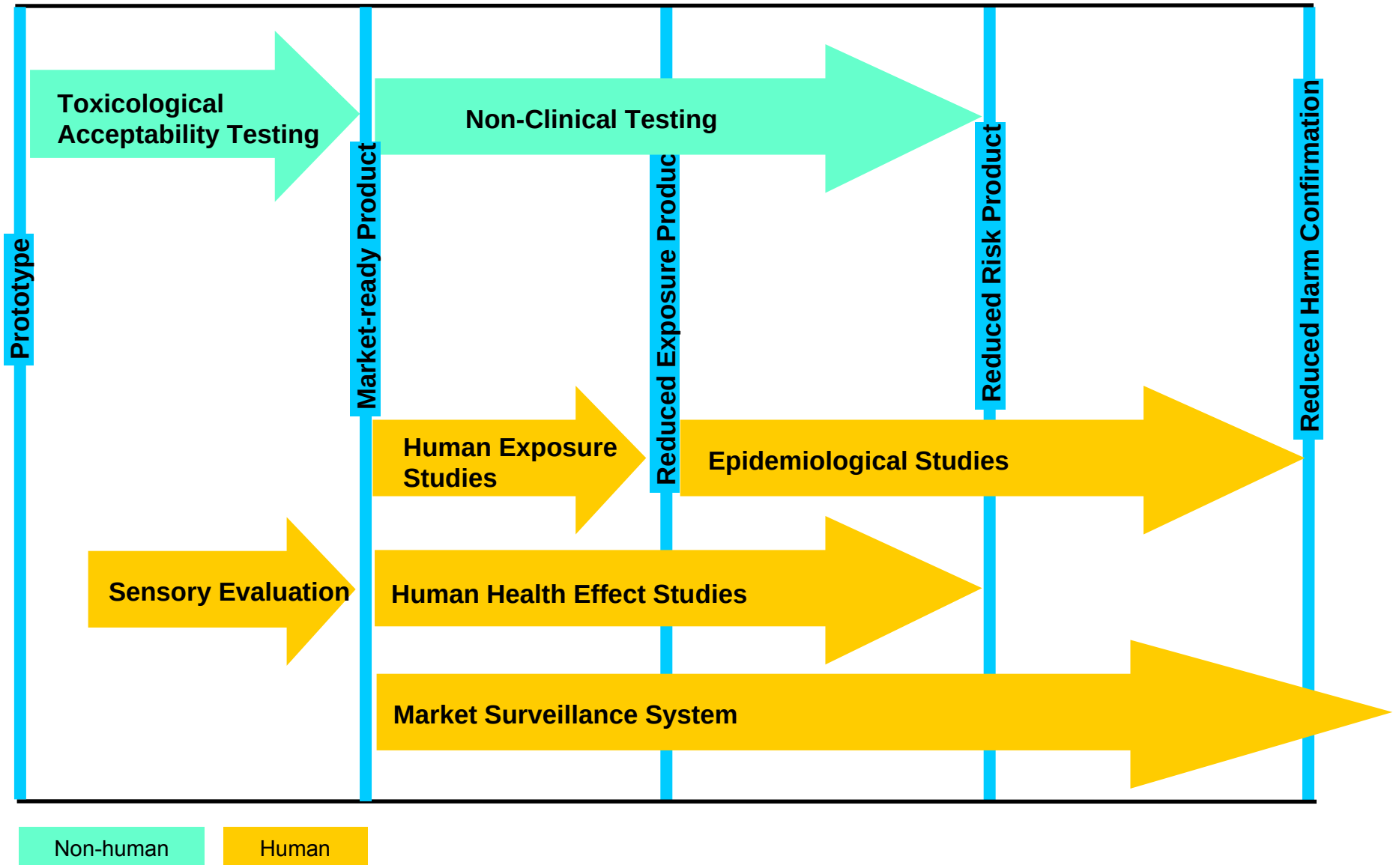


A Sound and Relevant Harm Reduction Evaluation Process



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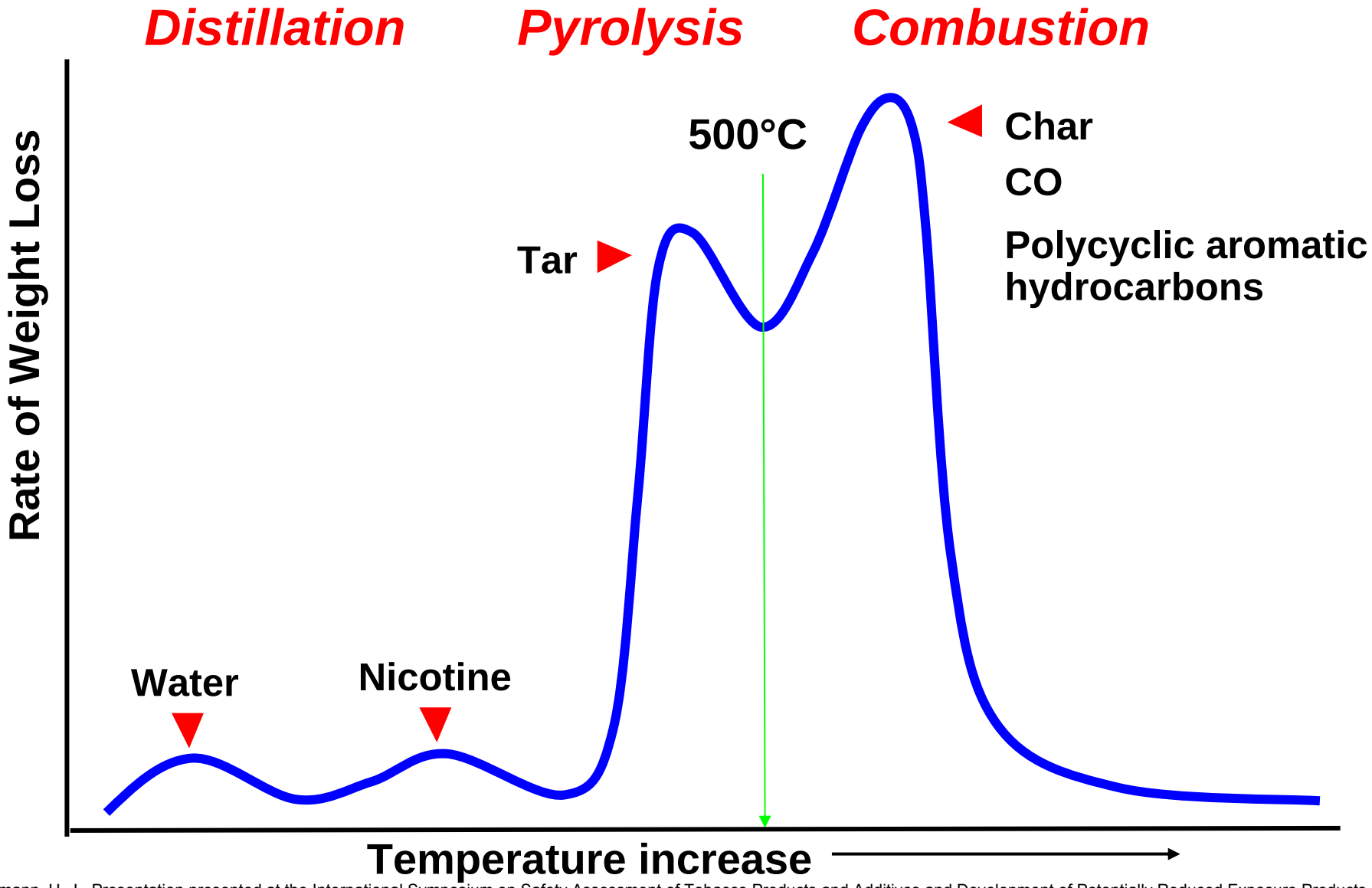
Generation of Smoke Constituents with Increasing Temperatures



Haussmann, H. J., Presentation presented at the International Symposium on Safety Assessment of Tobacco Products and Additives and Development of Potentially Reduced Exposure Products, October 11-12, 2004,Hangzhou, China

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Pre-market Available Data

Publications/presentation on early EHCSS versions:

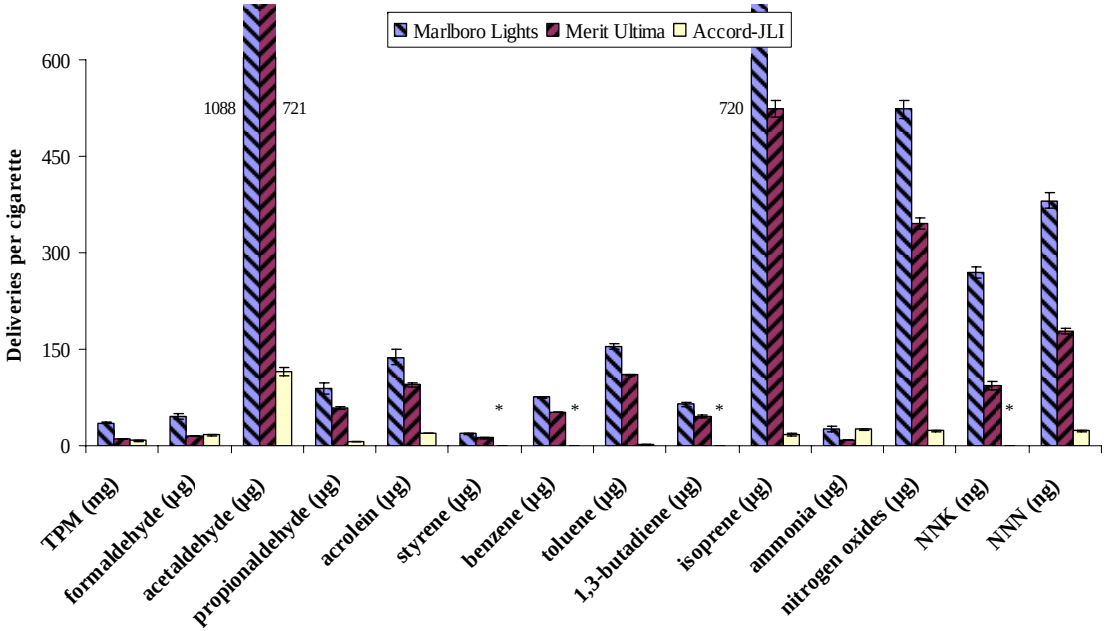
- **Patskan, G. and Reininghaus, W. (2003). Toxicological evaluation of an electrically heated cigarette. Part 1: Overview of technical concepts and summary of findings. *J Appl Toxicol* 23, 323-328.**

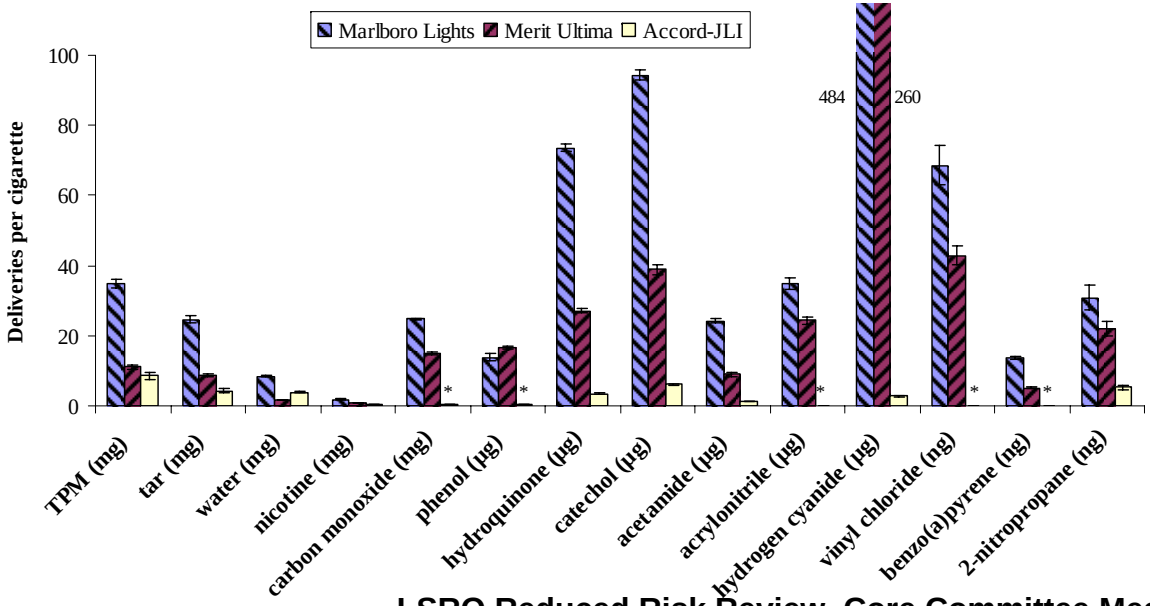
- **Stabbert, R., Voncken, P., Rustemeier, K., Haussmann, H. J., Roemer, E., Schaffernicht, H., and Patskan, G. (2003). Toxicological evaluation of an electrically heated cigarette. Part 2: Chemical composition of mainstream smoke. *J Appl Toxicol* 23, 329-339.**

- **Terpstra, P. M., Teredesai, A., Vanscheeuwijck, P. M., Verbeeck, J., Schepers, G., Radtke, F., Kuhl, P., Gomm, W., Anskeit, E., and Patskan, G. (2003). Toxicological evaluation of an electrically heated cigarette. Part 4: Subchronic inhalation toxicology. *J Appl Toxicol* 23, 349-362.**

- **Tewes, F. J., Meisgen, T. J., Veltel, D. J., Roemer, E., and Patskan, G. (2003). Toxicological evaluation of an electrically heated cigarette. Part 3: Genotoxicity and cytotoxicity of mainstream smoke. *J.Appl.Toxicol.* 23, 341-348.PMRL**

Yield of Smoke Constituents





On a per cigarette basis with machine generated smoke using simulated human smoking profiles, the yield of several toxic constituents of EHCSS-JLI smoke were reduced by > 90% compared to selected market products.

* carbon monoxide delivery 0.28 ± 0 mg/cig; phenol delivery 0.38 ±0.02 µg/cig; acrylonitrile at least one value below quantitative limit, therefore <0.3 µg/cig median value and no SD; vinyl chloride at least one value below quantitative limit, therefore <25 ng/cig median value and no SD; benzo[a]pyrene at least one value below quantitative limit, therefore < 0.12 ng /cig median value and no SD

Non-clinical evaluation of EHCSS-JLI

Test system	Mean change in EHCSS-JLI compared with:		
	FTC Smoking	*Simulated human smoking*[a]	
	1R4F	Marlboro Lights	Merit Ultima
***Salmonella* mutagenicity S9+ particulate phase**	↓ > 98% in TA98 and TA 100	↓ > 98% in TA98 and TA 100	↓ > 98% in TA98 and TA 100
NRU Cytotoxicity: particulate phase gas-vapor phase	↓ 91% 73%	↓ 94% 90%	↓ 85% 84%
90-day rat inhalation:	↓ hyperplasia, squamous metaplasia, atrophy - upper respiratory tract	Not conducted	Not conducted
35-day rat inhalation: Inflammation	↓ neutrophils in BALF[b]	Not conducted	Not conducted

[a] Conditions predicted from measurements collected during clinical trials
[b] BALF = bronchiolar alveolar lavage fluid