Nicotine Bridging: A New Method to Extend Smoke Constituents Biomarker Measurements from Clinical Studies to other Cigarette Mainstream Smoke Constituents

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Introduction:

Philip Morris International (PMI) agrees with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers, and that cigarette smoking is addictive. There is no "safe" cigarette. The best way for smokers to reduce the adverse health consequences of smoking is to quit.

PMI has developed an electrically heated cigarette smoking system (EHCSS) with the goal to reduce exposure to potentially harmful constituents in tobacco smoke. So far, the assessment of the EHCSS-K cigarette shows promising results for substantial reduction of a variety of smoke constituents compared to conventional lit-end cigarettes, based on both chemical analysis of cigarette smoke, and on biomarkers of exposure in clinical studies. There may be numerous smoke constituents (tobacco mainstream smoke contains more that 4700 substances) which are likely not accessible for exposure assessment by measuring their metabolites or measuring them directly in urine, blood, or exhaled breath.

Objective:

Development of a model which can be used to estimate exposures to a large number of smoke constituents on the basis of measured nicotine uptake distributions in smokers.

Methods:

The electrical heated cigarette (EHCSS-K6, 5 mg tar, ISO method) and a marketed conventional lit-end cigarette (Marlboro®, 6 mg tar, ISO method) were smoked using up to 10 different smoking protocols. The purpose was to cover a wide range of human smoking behavior, based on nicotine uptake distributions determined in the clinical study for the two cigarette types. Relationships between nicotine yield and potentially harmful smoke constituents (***nicotine-to-analyte regression analysis***) were used for ***nicotine bridging***, i.e., the estimation of smoke constituents' uptake proportional to measured nicotine uptake distributions.

Discussion

The separation and overlap of uptake distributions were used for examining reduced exposure to potentially harmful smoke constituents. The separation (i.e., change) is based on the modes of the distributions, whereas the overlap depends on both the mode and the standard deviation of the distributions. Both indices (change and overlap) support one another and add significant weight to the comparison of a potentially reduced exposure product to a conventional lit-end benchmark.

Nicotine bridging is complementary to a clinical study and examines potential differences in a laboratory setting that are not amenable to clinical biomarker of exposure determinations. An assumption made for this assessment is that smoke constituents' uptake equals that of nicotine. Nicotine uptake from inhaled mainstream smoke is in the range of 95-99% (1-4), and similarly high deposition rates have been reported for smoke constituents included in this model (5). Smoking behavior is an independent two step process of smoke intake and subsequent inhalation. Whereas intake may vary significantly, the subsequent inhalation pattern has been reported as remaining relatively constant (6). Based on the large variety of structural classes, it seems implausible that all of the more than 4700 different chemical compounds identified in tobacco smoke are equally well absorbed. However, assuming that their uptake is *ipso facto* equivalent to that of nicotine renders the comparative assessment a rather conservative estimation.

References

1: Armitage, A. K., Dollery, C. T., and George, C. F. 1974. Absorption and metabolism of nicotine by man during cigarette smoking. *British Journal of Clinical Pharmacology*, 1 (2).

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3: Isaac, P. F. and Rand, M. J. 1972. Cigarette smoking and plasma levels of nicotine. *Nature*, 236 (5345): 308-310.

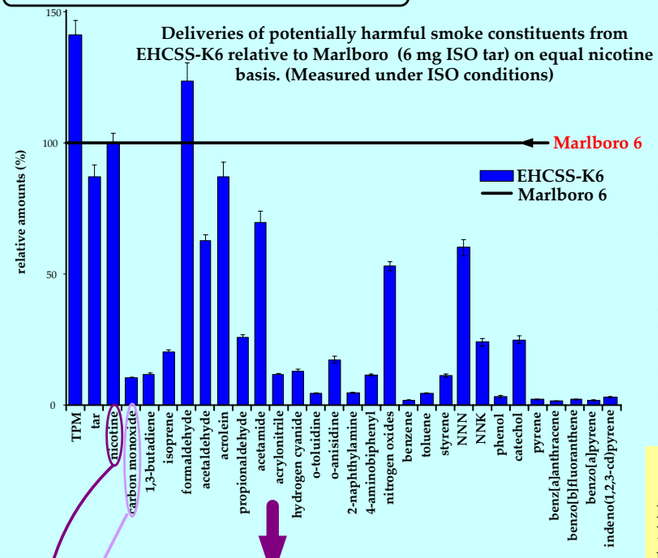
4: Armitage, A. K., Dixon, M., Frost, B. E., Mariner, D. C., and Sinclair, N. M. 2004. The Effect of Inhalation Volume and Breath-Hold Duration on the Retention of Nicotine and Solanesol in the Human Respiratory Tract and on Subsequent Plasma Nicotine Concentrations During Cigarette Smoking. *Beiträge zum Tabakforschung*, 21 (4): 240-249.

5: Baker, R. R. and Dixon, M. 2006. The retention of tobacco smoke constituents in the human respiratory tract. *Inhalation Toxicology*, 17 : 255-94.

6: Rawbone, R. G., Murphy, K., Tate, M. E., and Kane, S. J. 1978. The analysis of smoking parameters: Inhalation and absorption of tobacco smoke in studies of human smoking behaviour. In: Smoking behaviour. Physiological and psychological influences. R.E.Thornton, ed. Edinburgh, Churchill Livingstone. p 171-194.

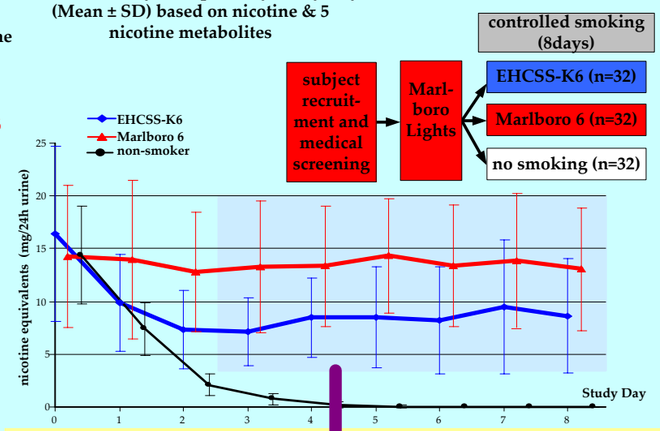
Non-Clinical Data

Deliveries of potentially harmful smoke constituents from EHCSS-K6 relative to Marlboro (6 mg ISO tar) on equal nicotine basis. (Measured under ISO conditions)



Clinical Data

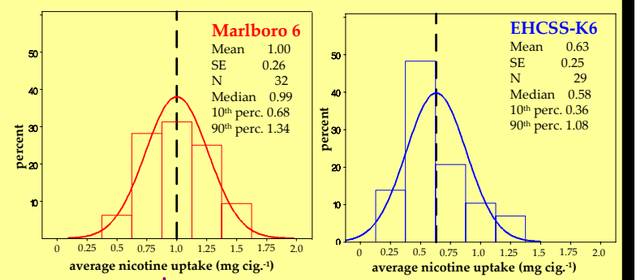
Nicotine Equivalents Excretion (mg nicotine/24 h) by Group and by Study Day (Mean ± SD) based on nicotine & 5 nicotine metabolites



Nicotine Distributions

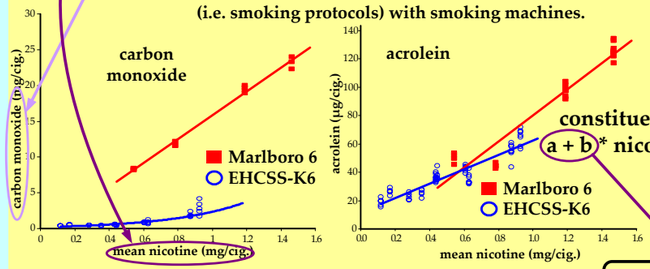
Frequency distributions and fitted normal curves for nicotine uptake of the EHCSS-K6 and the Marlboro 6. (Mean of nicotine equivalents from days 3-8 multiplied by 1.25,

(Schepers, G. and Demetriou, D. 2002. Determination of nicotine and its metabolites in urine by HPLC after DETBA derivatization. 8th Society for Research on Nicotine and Tobacco Meeting, Savannah, GA, February 20-23, 2002.)



Nicotine Regressions

Regressions of potentially harmful smoke constituents against mean nicotine. Yields were measured at different conditions (i.e. smoking protocols) with smoking machines.

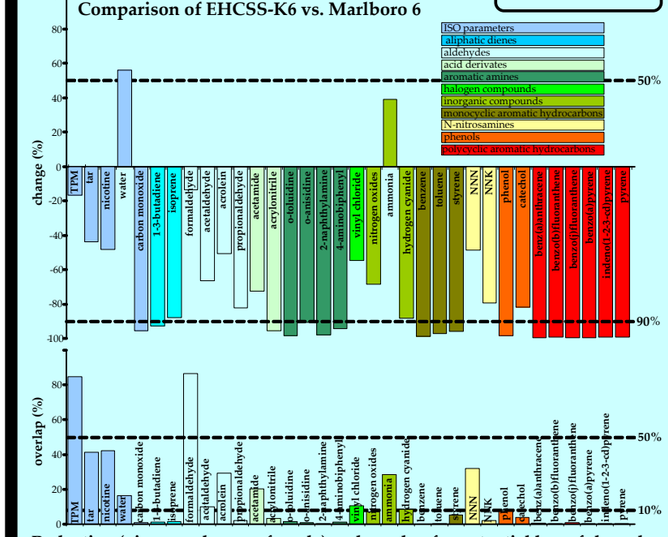


constituent= a + b * nicotine

y= a + b * nicotine uptake

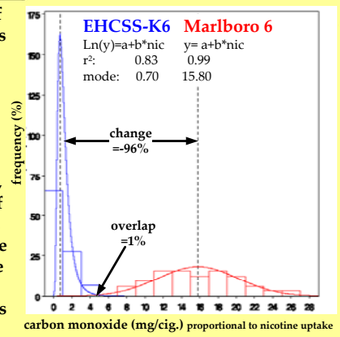
Results

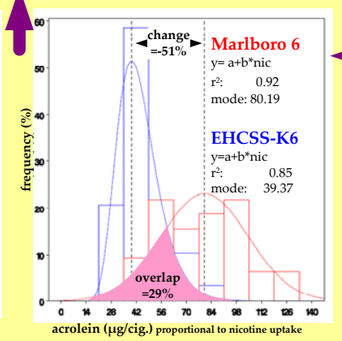
Comparison of EHCSS-K6 vs. Marlboro 6



Reduction (given as change of mode) and overlap for potential harmful smoke constituents of a new electrical cigarette (EHCSS-K6) compared to a conventional cigarette (Marlboro 6)

Overlay graphs of fitted distributions for two smoke constituents proportional to nicotine uptake. The regression model used for nicotine bridging, the r^2, the mode of the distributions, the overlap and the percentage change between two distribution modes is given.





$$change = -1 \bullet \left[\left(1 - \frac{Mode_{EHCSS}}{Mean_{convent}} \right) \bullet 100 \right]$$

Estimation of Change:

Reduction between two cigarettes is measured as percentage change and estimated from the modes of two overlapping distribution curves.

$$overlap = (Area_{EHCSS-K6} + Area_{M6UK}) \bullet 100$$

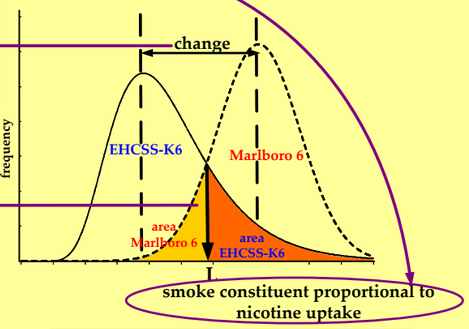
$$Z = Area_{cig.} = \frac{(L - Mean)}{stand.dev.}$$

Estimation of Overlap:

The Z-value of the Z-function corresponds to a certain area of the normal distribution, which can be found in the cumulative Z-table.

The mean and the standard deviation in the Z-function are properties of the normal distribution and "L" was defined as the value of the x-axis of the normal distributions where the frequencies of both normal distributions are equal.

Note: The unit for overlap index is given in percent. However, it is important to keep in mind that this percentage corresponds to the total of the two normal distributions which are compared (i.e. = 200%).



Nicotine Bridging

Conclusions

Nicotine bridging opens new avenues for examining reduced exposure, which could be extended to many smoke constituents as long as the nicotine-to-analyte relationships are known. This approach suggests that smoking the EHCSS-K6 can lead to reduced exposure of certain smoke constituents compared to a conventional lit-end cigarette.

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