

**SYM5C NICOTINE METABOLISM: BEYOND CYP2A6 GENOTYPE**

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Nicotine is primarily metabolized by P450 2A6-catalyzed 5'-oxidation. Genetic variations in this enzyme clearly influence nicotine metabolism and hence its bioavailability. However, CYP2A6 genotype alone is unlikely to explain the large variation in the extent and rate of nicotine metabolism among smokers. In this paper data will be presented exploring the affect of nicotine on its own metabolism and the role of glucuronidation in nicotine metabolism. In vitro, we have demonstrated that the metabolism of nicotine by both P450 2A6 and the extrahepatic enzyme, P450 2A13, results in the time and concentration-dependent inactivation of these enzymes. Recent data support a secondary metabolite of nicotine, a metabolite of the 5'-iminium ion, as the reactive species responsible for the inactivation of P450 2A13 and P450 2A6. It is unclear how nicotine-mediated inactivation may contribute to nicotine bioavailability in smokers. However, it has been reported by Benowitz et al. that the rate of nicotine clearance in smokers is longer than that in non-smokers, and in smokers who have abstained from smoking. In addition to P450 2A6-catalyzed 5'-oxidation, nicotine is metabolized by UGT-catalyzed N-glucuronidation. In smokers nicotine glucuronidation typically accounts for less than 10% of total nicotine metabolism. However, the extent of nicotine glucuronidation varies significantly among individual smokers, and it has been reported that nicotine glucuronidation levels are lower in black smokers compared to white smokers. We have recently confirmed in a study of nicotine patch users, that blacks excreted less nicotine as its N-glucuronide conjugate than did whites. The average percent of the total nicotine excreted as nicotine-N-glucuronide in 24 h urine was  $17.5 \pm 13.0$  (n=47) in blacks and  $31.2 \pm 16.9$  (n=35) in whites. The lower level of nicotine glucuronidation by blacks may contribute to the higher cotinine levels and lower cigarette consumption that has been observed in this ethnic group.

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**SYM5D CIGARETTE YIELDS AND HUMAN EXPOSURE: A COMPARISON OF ALTERNATIVE TESTING REGIMENS**

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There is general agreement that the testing protocol for measuring cigarette smoke emissions — the ISO regime — is an inappropriate mechanism for evaluating human exposure. Alternative smoking regimes have been introduced in Canada and Massachusetts; however, these regimes have not been evaluated against human smoking behaviour and bio-measures of human exposure. Data from this research compare measures of smoke volume and nicotine uptake among human smokers against the puffing parameters and nicotine emissions generated by five different machine smoking regimes: (1) ISO; (2) Massachusetts; (3) Canadian; (4) a "compensatory" regime; and (5) a "human mimic" regime. Measures of smoke volume and puffing behaviour were recorded for 51 smokers who used a portable smoking topography device for 3 one-week trials. Measures of salivary cotinine were taken at the completion of each week. The cigarette brands smoked by participants were then machine-smoked under five testing regimes, including a "human mimic" condition where brands were machine smoked using the puffing behaviour recorded from human smokers. The total volume of smoke collected from each cigarette and the nicotine emissions were recorded. The results indicate that none of the four machine smoking regimes adequately reflected "human mimic" nicotine emissions. In addition, none of the four smoking regimes generated nicotine emissions that were closely associated with actual nicotine uptake in humans. The implication of these results for product testing, the provision of information to consumers, and the use of cigarette emissions will be discussed.

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**SYM6 EXPANSION OF NON-CIGARETTE TOBACCO PRODUCTS: CURRENT RESEARCH AND POLICY IMPLICATIONS**

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The goal of this symposium is to focus scientific and policy attention on non-cigarette tobacco products. This symposium will present research (e.g., prevalence, toxicity/biomarker data, consumer risk perceptions) on various non-cigarette tobacco products, including cigars, smokeless tobacco (SLT) and waterpipes, and the panel will discuss the policy implications stemming from this data as well as identifying key research questions requiring further study that will better inform policy makers', consumers' and treatment professional's responses to non-cigarette tobacco products. Mr. Barry will provide an overview of the key research and policy issues raised by the use of non-cigarette tobacco products, whether the research and policy communities have neglected non-cigarette tobacco products relative to cigarettes, and why these products warrant the attention of scientists and policymakers. Dr. Delnevo will present data on cigar prevalence in the U.S., including little and flavored cigars, and how these products are competing with cigarettes for market share. Dr. Eissenberg will present prevalence and toxicity/biomarker data on waterpipes, including consumer misperceptions of risk associated with waterpipe use. Dr. Hatsukami will present toxicity/biomarker data on SLT, particularly low-nitrosamine SLT, and discuss how these products are viewed in the broader "harm reduction" debate. Ms. Kemper will present focus group data on smoker/consumer perceptions of new SLT products (Camel Snus, Taboka) and the impact of these products and how they are marketed on interest in switching from cigarettes to SLT and on quitting tobacco use. Mr. Mitch Zeller will serve as the discussant to the panel.

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**SYM6A SMOKELESS TOBACCO: HOPE FOR THE FUTURE?**

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The use of oral non-combustible products as a means of reducing harm in cigarette smokers has engendered a great deal of controversy. Most public health officials agree that smokeless tobacco (SLT) use is associated with less disease risk than smoking cigarettes. Furthermore, if smokers completely switched to SLT use, then the relative risk of disease should theoretically reduce dramatically. In Sweden, the increased uptake of SLT, or snus, has been used to explain the decrease in cigarette smoking among men with a consequent decrease in lung cancer mortality. Whether or not this "Swedish experience" will translate to other cultures is unknown and some public health officials believe that it would be unlikely. Concerns over the uptake of SLT among youth and the continued use of tobacco products among adults have been raised, particularly in an unregulated environment. Nonetheless, there are strong advocates for substituting cigarettes for SLT as a method to reduce harm. Unfortunately, the toxicity and addiction potential vary greatly across the tobacco products, along with the risk for disease. The goal of this presentation is to examine the toxicity and nicotine levels across the various brands of oral non-combustible tobacco products, focusing particularly on the new low-nitrosamine products. In addition, studies on the effects of switching from cigarettes to these products will be examined. Finally, the context in which public health community would be willing to endorse the use of SLT as a harm reduction method will be discussed, which include product regulation, control over promotion and advertisement, and strong policies to reduce the prevalence of all tobacco use.

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