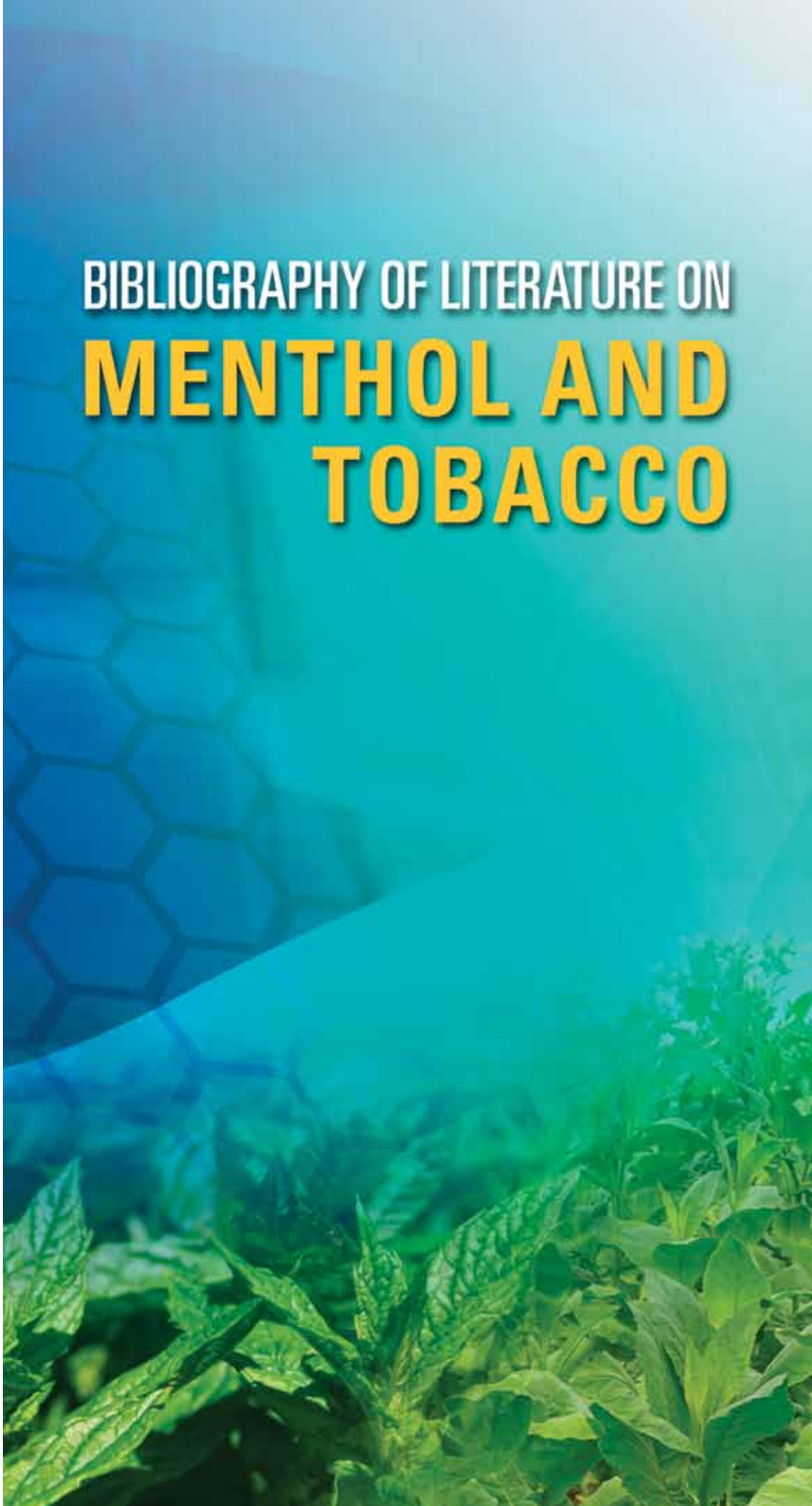
National Cancer Institute

BIBLIOGRAPHY OF LITERATURE ON MENTHOL AND TOBACCO



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Bibliography of Literature on
MENTHOL AND TOBACCO

U.S. Department of Health and Human Services
National Institutes of Health, National Cancer Institute

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Introduction

This bibliography represents a comprehensive review of the scientific literature on menthol and tobacco and the bibliography can be used to help synthesize research findings, identify gaps, guide innovative research and practice, and inform policy.

Using the search terms listed below, 343 research papers published from 1921-2009 were identified in PubMed, Scopus, and ISI Web of Knowledge℠. Abstracts were reviewed to guide the organization of the references into 15 categories outlined in the table of contents. All abstracts directly related to menthol and tobacco and/or nicotine were included. Abstracts that directly or indirectly address potential biological, physiological, and toxicological effects of menthol were also included. Articles not available in English were excluded. All abstracts were organized alphabetically within each category. Some of the abstracts received minor edits to promote consistency throughout the bibliography.

To facilitate access to the source abstracts and journal articles, hyperlinks to each source abstract are included in the bibliography. Please note that direct links to abstracts drawn from the ISI Web of Knowledge℠ database could not be made available; therefore, the hyperlinks provided for these abstracts only provide access to the ISI Web of Knowledge℠ search page. For these abstracts (marked with an *), please use the ISI Web of Knowledge℠ search page and the article title/ author name to obtain the source abstract.

Search Terms: menthol cigarette(s); mentholated cigarette(s); menthol tobacco; mentholated tobacco; menthol smoker(s); menthol AND the following terms: addiction, nicotine, marketing, cancer, biomarkers, asthma, cardiovascular disease, heart disease, vascular disease, chronic obstructive lung disease, respiratory, environmental tobacco smoke, national health, health disparities, minority health

Acknowledgements

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We thank Cathy Backinger, Ph.D., M.P.H., National Cancer Institute, and Bridgette Garrett, Ph.D., Office on Smoking and Health at the Centers for Disease Control and Prevention, for reviewing the bibliography and providing additional guidance and support. We also thank Mirjana Djordevic, Ph.D., National Cancer Institute, for her scientific guidance. Finally, we would like to express our appreciation to the staff at DB Consulting Group, Inc., for designing, formatting, and preparing the document for online posting.

Adult Surveillance and Epidemiology

Allen, B., Jr. and J. B. Unger (2007). "Sociocultural correlates of menthol cigarette smoking among adult African Americans in Los Angeles." Nicotine Tob Res 9(4): 447-51.

Nearly 70% of adult African American smokers smoke menthol cigarettes. More information is needed about the psychological, social, and cultural factors that influence their overwhelming preference for menthol cigarettes. This study examined variables associated with menthol vs. nonmenthol cigarette use among 432 adult African American smokers in Los Angeles, California. Menthol smoking was most prevalent among women, 18-30-year-olds, and employed respondents. Controlling for age and employment, we found that the significant correlates of menthol use among women were parents' menthol smoking, the belief that most African American smokers smoke menthols, and disagreement with the belief that smoking menthol cigarettes is a "Black thing." Among men, the only significant correlate of menthol smoking was the belief that most African American smokers smoke menthols. Results indicate that menthol smoking among adult African Americans is at least partly a consequence of a complex set of social and cultural norms. Further research is needed to understand the reasons why so many African Americans select menthols, as well as the health consequences of these choices.

Clemmey, P., R. Brooner, et al. (1997). "Smoking habits and attitudes in a methadone maintenance treatment population." Drug Alcohol Depend 44(2-3): 123-32.

This study characterized smoking habits and attitudes about quitting in methadone maintenance treatment (MMT) patients, with attention to race and gender differences. Of 179 patients surveyed, 92% (n = 165) were current smokers. These patients reported smoking a mean of 24.8 cigarettes per day. Mean age at smoking initiation was 13.6 years with 53% starting at age 13 or younger. The mean Fagerstrom tolerance questionnaire (FTQ) score was 7.5. Blacks as compared to Whites smoked fewer cigarettes per day (21.6 versus 27.5), had lower expired CO levels (18.8 versus 21.6 ppm), but higher urinary cotinine levels (1812 versus 1419 ng/ml) and were more likely to smoke menthol cigarettes (95 versus 46%). Females scored higher than males on the FTQ measures of nicotine dependence (8.0 versus 7.2), and lower than males on a measure of quit smoking self-efficacy. Subjects in the sample as a whole were well aware of health risks of smoking, as indicated by high scores on health risk perception questions. Sixty-one percent (n = 110) of subjects planned to quit within the next 6 months, 57% were 'very interested' in an on-site quit smoking program and 80% expressed interest in using nicotine replacement products. Overall, these

results indicate high rates of smoking in MMT patients, confirm within a drug abusing population prior findings of racial differences in smoking habits, and suggest that MMT patients are interested in quitting and in using nicotine replacement products. The data support feasibility of implementing smoking cessation treatments with this population in a setting that allows for convenient access to patients and close monitoring of progress.

Crews, K. M. (1994). "Blacks as high-risk smokers." Health Val 18(1): 41-43.

The 1985 National Health Interview Survey found that smoking prevalence is higher for blacks than for whites. Further, more recent reports have revealed that blacks are more often current smokers, quit at a lower rate, smoke fewer cigarettes per day, & prefer menthol cigarettes with high tar & nicotine content. Moreover, smoking-related diseases are the leading cause of death in the black community, tobacco-related cancers are more common among blacks than among whites, & declines in the rate of smoking have been much sharper for whites than for blacks. Smoking cessation programs geared toward the needs of the black community should be emphasized.

Cummings, K. M., A. Hyland, et al. (1997). "Comparison of recent trends in adolescent and adult cigarette smoking behaviour and brand preferences." Tob Control 6 Suppl 2: S31-7.

The objective of this paper was to compare trends in smoking behaviour and use of cigarette brands by adults and adolescents. Data analyzed come from tobacco use surveys of adults and teenagers conducted in 18 communities in the United States, as part of the National Cancer Institute's Community Intervention Trial for Smoking Cessation. Data on adult smoking behaviour were obtained from two cross-sectional telephone surveys, one conducted from January to May 1988 (n = 99348), and the second conducted between August 1993 and January 1994 (n = 79890). Data on adolescent smoking behaviour were obtained from two school-based surveys of ninth-grade students (aged 13-16 years), one conducted in autumn 1990 (n = 7097), and the second conducted in autumn 1992 (n = 7277). Adult cigarette smoking prevalence was estimated as the percentage of adults (18+ years) who were identified either by interview or by proxy as a current smoker. Among adolescents, current smokers were defined as those who reported having smoked on one or more of the 30 days preceding the interview. Cigarette brand use by adults was measured by asking current smokers to report the six digit UPC code on the side of the pack of their current cigarettes. A master list of UPC code numbers was developed so that reported codes could be associated with specific brand names. Among adolescents, cigarette brand use was measured by asking current smokers who reported that they usually buy their own cigarettes: "What brand do you usually buy?" The results indicated that among ninth-grade students, smoking prevalence rates increased between 1990 and 1992 in 13 of the 18 communities. Among adults, smoking rates declined between 1988 and 1993 in 17 out of 18 communities. Within the same communities, cigarette brand use was found to be much more tightly concentrated in adolescent smokers compared with adults, with teenage smokers more likely to report using the most heavily advertised cigarette brands—Marlboro, Newport, and Camel. It was concluded that smoking prevalence rates have increased among teenagers, but have dropped among adults in the same communities. Among adolescents

who smoke, and buy their own cigarettes, the three most heavily advertised brands—Marlboro, Camel, and Newport—have a substantially higher market concentration than among adult smokers.

Giovino, G. A. (2002). "Epidemiology of tobacco use in the United States." Oncogene 21(48): 7326-40.

Efforts to understand trends in and patterns of lung cancer are well served by studies of trends in and patterns of tobacco use. In the United States, the manufactured cigarette emerged as the tobacco product of choice shortly after the turn of the twentieth century. Lung cancer emerged after years of inhalation of cigarette smoke, first among men and then among women. The massive public health education campaign that began after scientists recognized the dangers of cigarette smoking has contributed to large reductions in cigarette use and subsequent smoking-attributable morbidity and mortality. Since 1965, the prevalence of cigarette smoking among US adults has declined by almost half, with positive trends observed among persons in almost all sociodemographic groups and efforts to reduce disparities recognized as an important goal in public health. An epidemiologic approach to understanding and controlling patterns of tobacco use is proposed. The model focuses on the agent (tobacco products), host (consumer or potential consumer), vector (tobacco companies and other users), and environment (with influences from families, social sources, culture, history, politics, law, and media). Accelerating progress in reducing tobacco use will accelerate reductions in tobacco-attributable morbidity and mortality.

Giovino, G. A., S. Sidney, et al. (2004). "Epidemiology of menthol cigarette use." Nicotine Tob Res 6 Suppl 1: S67-81.

Approximately one-fourth of all cigarettes sold in the United States are mentholated. An understanding of the consequences, patterns, and correlates of menthol cigarette use can guide the development and implementation of strategies to reduce smoking prevalence and smoking-attributable morbidity and mortality. This paper summarizes the literature on the health effects of mentholated cigarettes and describes various patterns of use as indicated by consumption and survey data from the United States and other nations. The epidemiological literature on menthol cigarettes and cancer risk is inconclusive regarding whether these cigarettes confer a risk for cancer above that of nonmentholated varieties. Available data indicate that mentholated cigarettes are at least as dangerous as their nonmentholated counterparts. In addition, because mentholation improves the taste of cigarettes for a substantial segment of the smoking population and appears to mask disease symptoms, this additive may facilitate initiation or inhibit quitting. Menthol market share is high in the Philippines (60%), Cameroon (35%-40%), Hong Kong (26%), the United States (26%), and Singapore (22%). Newport has become the leading menthol brand in the United States. Surveys from four nations indicate that menthol use among adult smokers is more common among females than males. Among U.S. smokers, 68.9% of Blacks, 29.2% of Hispanics, and 22.4% of Whites reported smoking a mentholated variety. Research is needed to better explain factors that may influence menthol preference, such as marketing, risk perceptions, brand formulation, and taste preferences. Such research would guide the development of potentially more effective programs and policies.

Haas, A. L., J. L. Sorensen, et al. (2008). "Cigarette smoking in opioid-using patients presenting for hospital-based medical services." Am J Addict 17(1): 65-9.

Little is known about cigarette smoking among opioid users who are not in substance abuse treatment. The study examined cigarette smoking in out-of-treatment opioid users presenting at a hospital who participated in drug abuse research. Participants exhibited a high rate of smoking (92%) at baseline that remained unchanged at one year and were moderately nicotine-dependent. Nineteen percent preferred unfiltered cigarettes. Women were more likely to smoke menthol cigarettes; men were more likely to smoke unfiltered cigarettes. Caucasians tended to smoke more than other ethnicities and exhibited greater dependence. Out-of-treatment drug users continue to be at high risk for continued smoking.

Hymowitz, N., D. Corle, et al. (1995). "Smokers' baseline characteristics in the COMMIT trial." Prev Med 24(5): 503-8.

Baseline telephone survey data from 10 COMMIT sites were submitted to statistical analyses to compare the smoking characteristics of non-Hispanic white (white), non-Hispanic black (black), Mexican-origin (Mexican), and Puerto Rican-origin (Puerto Rican) smokers. Survey results indicated white men and women were more likely to be classified as "heavy smokers" than members of other racial/ethnic groups, although black and Puerto Rican smokers were more likely than whites to increase their smoking rates on weekends. Whites were less likely to report stopping smoking in the past. White and Mexican smokers were most likely to smoke light or ultralight brands and least likely to smoke menthol cigarettes. Blacks were most likely to report smoking their first cigarette of the day within 10 min of waking. Based on these results, it was concluded that the differences and similarities among different groups of smokers may have important implications for understanding patterns of tobacco-related disease in smokers from different racial/ethnic and sex groups.

Hymowitz, N., C. Mouton, and H. Edkholdt. (1995). "Menthol cigarette smoking in African Americans and Whites." Tob Control 4: 194-195.

No abstract available.

Kabat, G. C., A. Morabia, et al. (1991). "Comparison of smoking habits of Blacks and Whites in a case-control study." Am J Public Health 1(11): 1483-1486.

Information from Blacks and Whites interviewed in a case-control study of tobacco-related diseases was analyzed to identify explanatory factors for racial differences in smoking habits. Blacks were three times more likely to be light vs heavy smokers. This association did not differ according to such variables as cigarette preference, degree of inhalation, or quitting. The association of race and light smoking was present in both current and ex-smokers. Sociodemographic or smoking-related characteristics do not appear to explain racial differences in smoking habits. Future studies should focus on cultural factors influencing smoking behavior.

Muscat, J. E., J. P. Richie, Jr., et al. (2002). "Mentholated cigarettes and smoking habits in whites and blacks." Tob Control 11(4): 368-71.

The objective of this study was to determine if cigarette mentholation is associated with the frequency of smoking and with quitting, and whether mentholation explains racial differences in these two smoking behaviours. A cross-sectional analysis of case-control data on smoking and lung cancer was conducted on 19 545 current and former cigarette smokers. The main outcome measures included smoking > 20 cigarettes per day (cpd) versus < or = 20 cpd and continued smoking versus quit smoking. The results indicated that among blacks, the prevalence odds ratio (POR) of heavy smoking (> or = 21 cpd) associated with mentholated cigarettes versus non-mentholated cigarettes was 0.7 (95% confidence interval (CI) 0.5 to 0.9) in current smokers and 0.6 (95% CI 0.4 to 0.9) in former smokers. Among whites, the corresponding POR were 0.9 (95% CI 0.8 to 1.0) and 0.9 (95% CI 0.8 to 1.0). Blacks were less likely to have been heavy smokers than whites, but the difference was unrelated to cigarette mentholation. The POR of continued smoking versus quitting, associated with mentholated cigarettes was 1.1 (95% CI 1.0 to 1.2) for both blacks and whites. Based on these results, it was concluded that smoking > 20 cpd was independently associated with whites. Among blacks, smoking < or = 20 cpd was independently associated with mentholated cigarettes. The risk of quitting was not associated with cigarette menthol flavour.

Mwenifumbo, J. C., E. M. Sellers, et al. (2008). "Socioeconomic and drug use determinants of smoking status in an urban adult population of Black African descent." Nicotine Tob Res 10(8): 1319-25.

We examined the influence of socioeconomics and drug use on current smokers (N = 137) and nonsmokers (N = 143) from an urban adult population of Black African descent. Median participant age was 33 years (range = 20-59). Smokers consumed a median of eight cigarettes/day (range = 0-35). Interestingly, 86% smoked fewer than 15 cigarettes/day and only 8% smoked menthol cigarettes. Socioeconomic and drug use variables significantly associated with smoking status in univariate analyses were included in a multiple logistic regression model that controlled for gender and age. Compared with nonsmokers, smokers were less likely to be university educated, more likely to be divorced, separated, or widowed, more likely to be current alcohol users, and more likely to be current marijuana users. Unexpectedly, household income and employment status were not associated with smoking status. Among current alcohol users, smokers consumed three times the number of drinks per month that nonsmokers consumed ($p<.001$). Among current marijuana users, smokers consumed more than five times the number of joints per month that nonsmokers consumed ($p<.001$). Overall, lower education levels, divorce, and alcohol and marijuana use were significantly associated with increased likelihood of smoking among this population.

Orleans, C. T., V. J. Schoenbach, et al. (1989). "A survey of smoking and quitting patterns among black Americans." Am J Public Health 79(2): 176-81.

A sample of adult Black policyholders of the nation's largest Black-owned life insurance company was surveyed in 1986 to add to limited data on smoking and quitting patterns among Black Americans, and to provide direction for cessation initiatives targeted to Black

smokers. Forty per cent of 2,958 age-eligible policyholders for whom current addresses were available returned a completed questionnaire. Population estimates for smoking status agree closely with national estimates for Blacks age 21-60 years: 50 per cent never-smokers; 36 per cent current smokers; 14 per cent ex-smokers. Current and ex-smokers reported a modal low-rate/high nicotine menthol smoking pattern. Current smokers reported a mean of 3.8 serious quit attempts, a strong desire and intention to quit smoking, and limited past use of effective quit smoking treatments and self-help resources. Correlates of motivation to quit smoking were similar to those found among smokers in the general population, including smoking-related illnesses and medical advice to quit smoking, previous quit attempts, beliefs in smoking-related health harms/quitting benefits, and expected social support for quitting. Methodological limitations and implications for the design of needed Black-focused quit smoking initiatives are discussed.

Richardson, T. (1996). "Menthol cigarette use in African Americans." Hosp Pract (Minneap) 31(8): 22H-22I.

No abstract available.

Sidney, S., I. Tekawa, et al. (1989). "Mentholated cigarette use among multiphasic examinees, 1979-86." Am J Public Health 79(10): 1415-6.

Mentholated cigarette use was studied in relation to age and race in 29,037 current smokers who were Kaiser Permanente Medical Care Program members. The percentages of mentholated cigarette users were much higher in Blacks and Asians than in Whites, especially in the younger age groups. A marked inverse relationship between mentholated cigarette use and age was present in Blacks and Asians; mentholated cigarette use showed little difference with age in Whites.

Simon, W. and R. J. Lucero (1960). "Consumption of mentholated cigarettes by alcoholics." Dis Nerv Syst 21: 213-4.

No abstract is available.

Youth Surveillance and Epidemiology

Appleyard, J., P. Messeri, et al. (2001). "Smoking among Asian American and Hawaiian/Pacific Islander youth: data from the 2000 National Youth Tobacco Survey." Asian Am Pac Isl J Health 9(1): 5-14.

One of the first steps to reducing the disproportionate burden of tobacco on racial and ethnic minorities is to understand how tobacco differentially affects these populations. This paper, based on a nationally representative sample of Asian American youth and a smaller sample of Hawaiian/Pacific Islander youth, provides the tobacco control community with important information about the smoking behavior of these youth. The National Youth Tobacco Survey, conducted during the spring of 2000 (NYTS 2000), provides recent national estimates of smoking behavior among Asian American youth. The data also permit a limited exploration of possible differences between self-described Asians and Hawaiian/Pacific Islander youth, two groups that have been combined into a single racial/ethnic category in earlier national studies. The report's findings provide estimates and 95 percent confidence intervals for current smoking, age of smoking initiation, use of menthol cigarettes and tobacco brand preferences. NYTS 2000 data indicate that during the last year of high school, one third of Asian American youth are smokers. Of these youth, 60% report that their usual brand of cigarettes is a menthol brand. Among female Hawaiian/Pacific Islander youth in middle school, more than 25% report having smoked during the past month.

Cummings, K. M., A. Hyland, et al. (1997). "Comparison of recent trends in adolescent and adult cigarette smoking behaviour and brand preferences." Tob Control 6 Suppl 2: S31-7.

The objective of this paper was to compare trends in smoking behaviour and use of cigarette brands by adults and adolescents. Data analysed in this paper come from tobacco use surveys of adults and teenagers conducted in 18 communities in the United States, as part of the National Cancer Institute's Community Intervention Trial for Smoking Cessation. Data on adult smoking behaviour were obtained from two cross-sectional telephone surveys, one conducted from January to May 1988 (n = 99348), and the second conducted between August 1993 and January 1994 (n = 79890). Data on adolescent smoking behaviour were obtained from two school-based surveys of ninth-grade students (aged 13-16 years), one conducted in autumn 1990 (n = 7097), and the second conducted in autumn 1992 (n = 7277). Adult cigarette smoking prevalence was estimated as the percentage of adults (18+ years) who were identified either by interview or by proxy as a current smoker. Among adolescents, current smokers were defined as those who reported having smoked

on one or more of the 30 days preceding the interview. Cigarette brand use by adults was measured by asking current smokers to report the six digit UPC code on the side of the pack of their current cigarettes. A master list of UPC code numbers was developed so that reported codes could be associated with specific brand names. Among adolescents, cigarette brand use was measured by asking current smokers who reported that they usually buy their own cigarettes: "What brand do you usually buy?" The results indicated that among ninth-grade students, smoking prevalence rates increased between 1990 and 1992 in 13 of the 18 communities. Among adults, smoking rates declined between 1988 and 1993 in 17 out of 18 communities. Within the same communities, cigarette brand use was found to be much more tightly concentrated in adolescent smokers compared with adults, with teenage smokers more likely to report using the most heavily advertised cigarette brands—Marlboro, Newport, and Camel. It was concluded that smoking prevalence rates have increased among teenagers, but have dropped among adults in the same communities. Among adolescents who smoke, and buy their own cigarettes, the three most heavily advertised brands—Marlboro, Camel, and Newport—have a substantially higher market concentration than among adult smokers.

Hersey, J. C., S. W. Ng, et al. (2006). "Are menthol cigarettes a starter product for youth?" Nicotine Tob Res 8(3): 403-13.

This study assessed the relationship between menthol use and nicotine dependence. Data from the National Youth Tobacco Survey indicated that menthol cigarette use was significantly more common among newer, younger smokers. Additionally, youth who smoked menthol cigarettes had significantly higher scores on a scale of nicotine dependence compared with nonmenthol smokers, controlling for demographic background and the length, frequency, and level of smoking. The study suggests that menthol cigarettes are a starter product that may be associated with smoking uptake by youth.

Kaufman, N. J., B. C. Castrucci, et al. (2004). "Changes in adolescent cigarette-brand preference, 1989 to 1996." Am J Health Behav 28(1): 54-62.

The objective of the study was to understand changes in cigarette-brand choice by adolescents in the context of demographic differences and advertising. Data from 3 nationally representative cross-sectional surveys of adolescents were analyzed. The results indicated that Marlboro, Camel, and Newport brand cigarettes accounted for over 80% of the cigarettes usually bought by adolescents in 1989, 1993, and 1996. Between 1989 and 1996, Marlboro and Camel market shares changed little, whereas preference for Newport doubled among white and Hispanic adolescents. It was concluded that brand preference among adolescents has been steadily concentrated among 3 brands. More attention may need to be focused on mentholated brands given the increase in Newport's market share.

Moolchan, E. T. (2004). "Adolescent menthol smokers: will they be a harder target for cessation?" Nicotine Tob Res 6 Suppl 1: S93-5.

Menthol smoking may influence the development of tobacco addiction and related health consequences, yet limited data on menthol smoking by youth are available. We assessed

usual brand menthol preference by Baltimore-area teenage smokers applying to a smoking cessation study between September 1999 and December 2002. Of a biethnic (Black and White) sample of 593 youths (mean age=15.5+/-1.4 years, 51% female, 45% African American), the overwhelming majority (93%) were menthol smokers. Menthol preference rates were highest among African American girls and lowest among White boys. Overall, a statistically significant association was found between ethnicity and menthol preference, chi2 (df=1)=19.4, p<.001. This association also was observed separately for girls, chi2 (df=1)=9.21, p=.0024, and for boys, chi2 (df=1)=9.59, p=.0020. Menthol smoking did not vary with age in either ethnic group. These findings of overwhelming menthol preference in a treatment-seeking sample of adolescents warrant further research on the developmental trajectory, cessation, and health-related impact of menthol smoking by youth.

Muilenburg, J. L. and J. S. Legge, Jr. (2008). "African American adolescents and menthol cigarettes: smoking behavior among secondary school students." J Adolesc Health 43(6): 570-5.

The purpose of this paper was to examine the impact of smoking menthol cigarettes among secondary students, primarily African Americans, across five measures of smoking behavior. Data were gathered from a 2006 survey of six secondary schools in a large urban area in the southeastern United States. Ordered logit analysis is employed to estimate race and menthol effects on cigarette consumption. The results indicated that African American youth smoke at lower rates than white adolescents and menthol smokers consume cigarettes at higher rates irrespective of race. Most importantly, findings showed a strong interaction effect with black menthol smokers demonstrating the highest levels of cigarette consumption. Based on these results, it was concluded that there is a need to provide adolescent and adult African Americans with accurate information on the dangers of menthol cigarettes. Any proposed legislation should consider the special problems of menthol and its relationship to high cigarette consumption, especially for African American adolescents.

Osaki, Y., T. Tanihata, et al. (2006). "Adolescent smoking behaviour and cigarette brand preference in Japan." Tob Control 15(3): 172-80.

As part of efforts to develop a smoking control strategy for Japanese adolescents, the results of two nationwide surveys on adolescent smoking behaviour were compared. A descriptive study on smoking behaviour among high school students was conducted. Self-reporting anonymous questionnaires were administered to 115,814 students in 1996 and 106,297 in 2000 in randomly sampled junior and senior high schools throughout Japan. The main outcome measures were smoking prevalence, proportion of smokers by usual sources of cigarettes, national estimated cigarettes consumed by minors, and share of cigarette brands smoked by high school students. The results indicated that the experiment rate among junior high school boys decreased in 2000 compared with that in 1996, whereas current and daily smoking rates did not. Although prevalence among Japanese girls was much lower than that among boys, prevalence among girls increased in 2000. The main source of cigarettes among high school smokers was vending machines. The proportion of smokers who usually purchased cigarettes from vending machines increased in 2000, in spite of the 1998 introduction of restrictions on night-time operations. Japanese adolescents

were more likely than adults to smoke American cigarette brands, and the adolescent market share of American brands has increased rapidly, especially for menthol brands. This survey revealed the seriousness of the problem of smoking behaviour among Japanese high school students and suggested that this behaviour may be influenced by social environmental factors, including the marketing strategies of the tobacco industry. It was concluded that action should be taken to reduce the prevalence and impact of pro-tobacco marketing messages and to abolish cigarette vending machines.

Richter, P. A., L. L. Pederson, et al. (2006). "Young adult smoker risk perceptions of traditional cigarettes and nontraditional tobacco products." Am J Health Behav 30(3): 302-12.

The objective of this study was to explore risk perceptions of traditional and nontraditional tobacco products (NTPs) among young adult smokers. Focus groups were conducted with African Americans, non-Hispanic whites, and Hispanics. Risk ratings of light, regular, and menthol cigarettes and of NTPs and marijuana and cigarettes were compared. The results indicated that participants tended to view light cigarettes as safer than regular cigarettes. Shisha and herbal products were rated as safer than traditional cigarettes, but there were differences in ratings by race/ethnicity related to preferred cigarette variety. It was concluded that health communication messages about the use of cigarettes and NTPs should consider risk perceptions about the products and racial/ethnic differences.

Psychosocial, Cultural, and Environmental Factors

Castro, F. G. (2004). "Physiological, psychological, social, and cultural influences on the use of menthol cigarettes among Blacks and Hispanics." Nicotine Tob Res 6 Suppl 1: S29-41.

Patterns of menthol cigarette consumption among Blacks and Hispanics are likely a product of the interactive effects of several factors: the physiological and pharmacological sensory effects of menthol, the "cool" psychological identity of being menthol smokers, the promotional marketing of menthol cigarettes, and the cultural effects of health-related beliefs and subjective culture norms. This article presents two conceptual frameworks—a moderation logic model and a mediation logic model—for organizing the disparate literature on factors affecting the consumption of menthol cigarettes among Blacks and Hispanics. Three factor domains are examined as direct effect predictors of menthol cigarette smoking: (a) physiological and pharmacological, (b) psychological, and (c) social and environmental. In addition, a fourth domain of cultural variables is presented as a class of moderator or mediator variables that can interact with these physiological, psychological, and social factors as determinants of menthol cigarette use. These cultural variables are examined as mediating or moderating factors that influence the use of menthol cigarettes by Black and Hispanic consumers. Recommendations are offered for future research to further understand the influence of cultural and other factors as determinants of menthol cigarette smoking among Blacks and Hispanics.

Farrelly, M. C., B. R. Loomis, et al. (2007). "Do increases in cigarette prices lead to increases in sales of cigarettes with high tar and nicotine yields?" Nicotine Tob Res 9(10): 1015-20.

We used scanner data on cigarette prices and sales collected from supermarkets across the United States from 1994 to 2004 to test the hypothesis that cigarette prices are positively correlated with sales of cigarettes with higher tar and nicotine content. During this period the average inflation-adjusted price for menthol cigarettes increased 55.8%. Price elasticities from multivariate regression models suggest that this price increase led to an increase of 1.73% in sales-weighted average tar yields and a 1.28% increase in sales-weighted average nicotine yields for menthol cigarettes. The 50.5% price increase of nonmenthol varieties over the same period yielded an estimated increase of 1% in tar per cigarette but no statistically significant increase in nicotine yields. An ordered probit model of the impact of cigarette prices on cigarette strength (ultra-light, light, full flavor, unfiltered) offers an

explanation: As cigarette prices increase, the probability that stronger cigarette types will be sold increases. This effect is larger for menthol than for nonmenthol cigarettes. Our results are consistent with earlier population-based cross-sectional and longitudinal studies showing that higher cigarette prices and taxes are associated with increasing consumption of higher-yield cigarettes by smokers.

Fernander, A., M. Schumacher, et al. (2008). "Smoking risk and the likelihood of quitting among African-American female light and heavy smokers." J Natl Med Assoc 100(10): 1199-206.

While African-American females are more likely to be light smokers compared to their counterparts of other racially classified social groups (RCSGs), they are more likely to carry a heavier burden of smoking-related morbidity and mortality. Thus, it is critical that African-American female light smokers are targeted to engage in smoking cessation. Research has revealed that African-American women are less likely to have a successful quit attempt following a cessation intervention than females from other RCSGs. It has been postulated that the low smoking cessation rates among African-American female light smokers may be due to the lack of appropriate psychosocioculturally tailored cessation interventions that address issues of stress and coping that explain why they smoke and continue to smoke that may differ from their heavy smoker counterparts. The purpose of this study was to ascertain whether African-American female light smokers differed from their heavy smoker counterparts on psychosociocultural stress and coping factors. Findings revealed no differences in the sociodemographic variables of age, income, education and BMI; in the psychosociocultural measures of acculturative stress, race-related stress and coping; or in the smoking characteristics of menthol smoking status, cotinine level and CYP2A6 metabolic functioning between light and heavy smokers. However, the study found that African-American female light smokers take longer to smoke their first cigarette of the day, have a lower smoking risk, are more likely to quit, and exhibit lower carbon monoxide levels than African-American female heavy smokers. The current study suggests that other than the obvious factors of greater likelihood of quitting, lower smoking risk, longer latency to smoke and lower carbon monoxide levels, specific smoking cessation programs may not need to be differentially psychosocio-culturally tailored for African-American female light smokers compared to their heavy-smoking counterparts.

Fernander, A. F., C. A. Patten, et al. (2005). "Exploring the association of John Henry active coping and education on smoking behavior and nicotine dependence among Blacks in the USA." Soc Sci Med 60(3): 491-500.

Although smoking is used as a coping tool in response to stress and Blacks have been found to report smoking more in response to stress than Whites, little research exists that has examined ethno-culturally specific constructs of stress and coping as they relate to smoking behavior and nicotine dependence among Blacks in the USA. This study explored the association between the ethno-culturally interactively defined construct of John Henryism, as well as the individual contributions of John Henry active coping and education on smoking behavior and nicotine dependence in a relatively urban-Midwestern

Black population. Self-identified Black patients (n = 146) who had previously received a clinical intervention for nicotine dependence were followed to assess smoking status and John Henry active coping. Results revealed that patients with low levels of education who had low levels of John Henry active coping reported higher nicotine dependence scores than any other education by John Henry active coping group. Furthermore, low levels of John Henry active coping were associated with the use of menthol cigarettes and lower-educational level was associated with smoking greater than 20 cigarettes per day. Further community-based studies examining this construct among Black smokers in various socio-cultural contexts are needed to clarify the association between John Henry active coping and socioeconomic status on smoking behavior and nicotine dependence among Blacks.

Hymowitz, N., Mouton, C., Edkholdt, H. (1995). "Menthol cigarette smoking in African Americans and Whites." Tob Control 4: 194-195.

No abstract available.

Richter, P., D. Beistle, et al. (2008). "Small-group discussions on menthol cigarettes: listening to adult African American smokers in Atlanta, Georgia." Ethn Health 13(2): 171-82.

In 2002, the First Conference on Menthol Cigarettes brought together researchers from diverse backgrounds to summarize what is known about menthol cigarettes and the people who smoke them and to identify areas of needed research on menthol cigarettes. Since the conference, PubMed reports 24 articles, including the conference proceedings, on menthol cigarettes and African Americans. Many of the articles address epidemiological or biomedical topics. While there has been some focus on social influences and marketing issues, more research and a greater focus on this topic are needed. To stimulate research on a population disproportionately burdened by the health effects of smoking, we conducted small-group discussions in 2005 with adult African American smokers in Atlanta, Georgia. Each group discussion focused on a different topic: smoking behavior and preferences, perceptions of social influences, health effects and perceived harmfulness of menthol, quitting menthol cigarette smoking, or the influence of marketing and advertising of menthol cigarettes. Themes emerged from the discussions: (1) emulation of black culture by white youth and racial integration of neighborhoods and communities may have modified the perception that African Americans smoke menthol cigarettes and whites smoke non-menthol cigarettes; (2) non-menthol cigarette smokers were thought to be 'hardcore' smokers with less interest in quitting; (3) switching to non-menthol cigarettes was discussed as a way of quitting cigarettes for habitual menthol smokers; and, (4) smoking menthol cigarettes was thought to lead to fewer negative health effects. It was concluded that some topics suggested by the participants warrant further investigation and more research is needed to assess the pervasiveness of these beliefs and their potential utility for smoking cessation interventions.

Richter, P. A., L. L. Pederson, et al. (2006). "Young adult smoker risk perceptions of traditional cigarettes and nontraditional tobacco products." Am J Health Behav 30(3): 302-12.

The objective of this study was to explore risk perceptions of traditional and nontraditional tobacco products (NTPs) among young adult smokers. Focus groups with African Americans, non-Hispanic whites, and Hispanics were conducted. Risk ratings of light, regular, and menthol cigarettes and of NTPs and marijuana and cigarettes were compared. The results indicated that participants tended to view light cigarettes as safer than regular cigarettes. Shisha and herbal products were rated as safer than traditional cigarettes, but there were differences in ratings by race/ethnicity, related to preferred cigarette variety. It was concluded that health communication messages about the use of cigarettes and NTPs should consider risk perceptions about the products and racial/ethnic differences.

Marketing to and Industry Targeting of Adults

Altman, D. G., N. Schooler, et al. (1991). "Alcohol and cigarette advertising on billboards." Health Educ Res 6(4): 487-490.

We report an analysis of 901 billboards in San Francisco, California. Using neighborhood census data, we assessed how billboard advertising of tobacco and alcohol products differed in Asian, black, Hispanic and white neighborhoods. The data illustrate that: (1) across all billboard advertising of products and services, tobacco (19%) and alcohol (17%) were most heavily advertised; (2) black neighborhoods had the highest rate of billboards per 1000 population; (3) black and Hispanic neighborhoods had proportionately more tobacco and alcohol billboards than white or Asian neighborhoods; (4) black neighborhoods were proportionately more likely than other neighborhoods to have billboard advertising of menthol cigarettes and malt liquor while advertising of beer/wine was proportionately higher in Hispanic neighborhoods.

Assunta, M. and S. Chapman (2004). "A "clean cigarette" for a clean nation: a case study of Salem Pianissimo in Japan." Tob Control 13 Suppl 2: ii58-62.

The objective of this study was to illustrate, through internal industry documents, how RJ Reynolds exploited the concerns of the Japanese society about cleanliness to market the concept of cleaner, implicitly healthier cigarettes in Japan. These documents were obtained using systematic keyword and opportunistic Website searches of formerly private internal industry documents, which showed that RJ Reynolds developed marketing plans based upon their cultural assumptions of Japanese people as fastidious about hygiene and manners and having relatively high penchants to try new products. RJ Reynolds found there was also a growing concern for health and the environment, and smokers were conscious about annoying others. Deodorised consumer products were one of Japan's biggest trends. These characteristics presented RJ Reynolds with a profitable formula for marketing Salem Pianissimo, a clean cigarette with less smell and smoke. Salem Pianissimo, a 100 mm cigarette claiming to contain 1 mg tar and 0.1 mg nicotine, was targeted to women since menthol cigarettes were popular among 18-24 year old female smokers, although Japan's law prohibited those below 20 years to smoke and the tobacco industry had a voluntary code disallowing advertising to women and youth. RJ Reynolds successfully launched its clean cigarette, Salem Pianissimo, in Japan by exploiting perceived cultural characteristics such as a penchant for cleanliness and social harmony and an eagerness to try new products.

Balbach, E. D., R. J. Gasior, et al. (2003). "R.J. Reynolds' targeting of African Americans: 1988-2000." Am J Public Health 93(5): 822-7.

The purpose of this study was to describe RJ Reynolds (RJR) Tobacco Company's strategy for targeting African Americans, as revealed in tobacco industry documents and magazine advertisements. The authors searched industry documents to determine RJR's strategies and analyzed magazine advertising during 2 periods: the time of the launch of the company's Uptown cigarette (1989-1990) and a decade later (1999-2000). RJR's efforts to target the African American market segment existed before and after Uptown, and the company's strategy was largely implemented via other RJR brands. Advertisements featured mentholated cigarettes, fantasy/escape, expensive objects, and nightlife. The study concluded that to help all populations become tobacco-free, tobacco control practitioners must understand and counter tobacco industry strategies.

Castro, F. G. (2004). "Physiological, psychological, social, and cultural influences on the use of menthol cigarettes among Blacks and Hispanics." Nicotine Tob Res 6 Suppl 1: S29-41.

Patterns of menthol cigarette consumption among Blacks and Hispanics are likely a product of the interactive effects of several factors: the physiological and pharmacological sensory effects of menthol, the "cool" psychological identity of being menthol smokers, the promotional marketing of menthol cigarettes, and the cultural effects of health-related beliefs and subjective culture norms. This article presents two conceptual frameworks—a moderation logic model and a mediation logic model—for organizing the disparate literature on factors affecting the consumption of menthol cigarettes among Blacks and Hispanics. Three factor domains are examined as direct effect predictors of menthol cigarette smoking: (a) physiological and pharmacological, (b) psychological, and (c) social and environmental. In addition, a fourth domain of cultural variables is presented as a class of moderator or mediator variables that can interact with these physiological, psychological, and social factors as determinants of menthol cigarette use. These cultural variables are examined as mediating or moderating factors that influence the use of menthol cigarettes by Black and Hispanic consumers. Recommendations are offered for future research to further understand the influence of cultural and other factors as determinants of menthol cigarette smoking among Blacks and Hispanics.

Cummings, K. M., G. Giovino, et al. (1987). "Cigarette advertising and black-white differences in brand preference." Public Health Rep 102(6): 698-701.

Anecdotal evidence indicates that the cigarette industry is targeting the sale of specific brands, notably menthol cigarettes, to black consumers. This paper presents data on the types of cigarettes smoked by white and black smokers. The cigarette brand preferences of two populations of smokers were examined. The first comprised 70 white and 365 black adult smokers seen at the Deaconness Family Medicine Center located in Buffalo, NY. The second population included 1,070 white and 92 black smokers who called a Stop Smoking Hotline in Buffalo. The results showed that, in both populations, blacks were twice as likely to smoke mentholated cigarettes compared with whites. In an attempt to evaluate the

targeting of cigarette ads to black smokers as a possible explanation for black-white differences in brand preferences, cigarette ads appearing in magazines targeted to predominantly white or black readers were compared. Cigarette ads appearing in seven magazines were reviewed, four directed to predominantly white readers (Newsweek, Time, People, Mademoiselle) and three with wide circulation among black audiences (Jet, Ebony, Essence). The results showed that the magazines targeted to black readers contained significantly more cigarette ads and more ads for menthol brand cigarettes than magazines similar in content but targeted to white readers. The observation that a higher percentage of blacks smoke menthol cigarettes than do whites is consistent with the findings regarding differences in the type of cigarette ads appearing in magazines intended for black or white readers. However, it is not possible to determine from this study whether cigarette advertising is the cause of the differences in preference of cigarette brands between white and black smokers. Future research focusing on understanding the reasons for cigarette brand preferences may provide ideas for anti smoking campaigns aimed at specific target groups.

Gardiner, P. S. (2004). "The African Americanization of menthol cigarette use in the United States." Nicotine Tob Res 6 Suppl 1: S55-65.

Today, over 70% of African American smokers prefer menthol cigarettes, compared with 30% of White smokers. This unique social phenomenon was principally occasioned by the tobacco industry's masterful manipulation of the burgeoning Black, urban, segregated, consumer market in the 1960s. Through the use of television and other advertising media, coupled with culturally tailored images and messages, the tobacco industry "African Americanized" menthol cigarettes. The tobacco industry successfully positioned mentholated products, especially Kool, as young, hip, new, and healthy. During the time that menthols were gaining a large market share in the African American community, the tobacco industry donated funds to African American organizations hoping to blunt the attack on their products. Many of the findings in this article are drawn from the tobacco industry documents disclosed following the Master Settlement Agreement in 1998. After a short review of the origins and growth of menthols, this article examines some key social factors that, when considered together, led to disproportionate use of mentholated cigarettes by African Americans compared with other Americans. Unfortunately, the long-term impact of the industry's practice in this community may be partly responsible for the disproportionately high tobacco-related disease and mortality among African Americans generally and African American males particularly.

Kreslake, J. M., G. F. Wayne, et al. (2008). "The menthol smoker: tobacco industry research on consumer sensory perception of menthol cigarettes and its role in smoking behavior." Nicotine Tob Res 10(4): 705-15.

The use of menthol in cigarettes is actively promoted by the tobacco industry for its perceived sensory benefits, and smokers of menthol cigarettes commonly differ from nonmenthol smokers in markers of smoking behavior and addiction. In this study, we analyzed internal tobacco industry documents to describe the relationships between sensory perception and the attitudes, preferences, and patterns of cigarette use among menthol smokers. Two unique types of menthol smokers emerged from this analysis: those who cannot tolerate

the harshness and irritation associated with smoking nonmenthol cigarettes, and those who seek out the specific menthol flavor and associated physical sensation. Among the first segment of menthol smokers, menthol reduces negative sensory characteristics associated with smoking. This segment of smokers may include a large proportion of occasional smokers or young people, as well as smokers who have "traded down" to a less strong cigarette because of perceived harshness or negative health effects. Some established menthol smokers, on the other hand, appear to be tolerant of and even actively seek stronger sensory attributes, including higher menthol levels. Smokers of these "stronger" menthols have traditionally been disproportionately Black and male. Some beginning or occasional smokers may adopt menthols for their mild properties and to cover up the taste of tobacco, but then develop a stronger desire for the menthol taste over time. Future research measuring smoking behavior and evaluating cessation outcomes of menthol smokers should consider the duration of menthol use and differentiate smokers according to their reasons for using menthols.

Lakhani, H. (1979). "Empirical implications of mathematical functions used to analyze market penetration of new products-Cigarettes case study." Technol Forecast Soc 15(2): 147-156.

Three types of S-shaped growth curves-the logistic, the lognormal, and the Gompertz-are widespread in the literature on analysis of market penetration of new products/processes. This article discusses the mathematical properties of these function in the light of their empirical implications, such as location of the point of maximum growth rate, the symmetry/asymmetry of the growth rates around that inflection point, and the ease of estimation (linear and nonlinear regressions). The empirical economic expectations cannot specify these phenomena a priori so that a less restrictive function should be preferred. Such a function is the Gompertz function. It is, therefore, applied to the study of market penetration of filtered and menthol cigarettes and shown that the empirical verification vindicates the theoretical postulates of that function. The empirical estimates are also closer to actual estimates of growth rates of adoption.

Landrine, H., E. A. Klonoff, et al. (2005). "Cigarette advertising in Black, Latino, and White magazines, 1998-2002: an exploratory investigation." Ethn Dis 15(1): 63-7.

The number, type (menthol vs non-menthol), brand (Black, White, women's, other), and size of cigarette ads in Black, Latino, and White magazines were examined, and digital photographs of 274 cigarette ads appearing in Ebony (Black), People (White), and People in Spanish (Latino) for the 4.5-year period of January 1998 to August 2002 were analyzed. The results indicated that Black magazines were 9.8 times and Latino magazines 2.6 times more likely than White magazines to contain ads for menthol cigarettes. Black and Latino magazines also contained significantly more ads for brands (Virginia Slims) that target women. It was concluded that the tobacco industry, which continues to target Blacks with menthol cigarette ads, appears now to be targeting Latinos similarly and targets Black and Latino women with additional, tailored cigarette ads.

Laws, M. B., J. Whitman, et al. (2002). "Tobacco availability and point of sale marketing in demographically contrasting districts of Massachusetts." Tob Control 11 Suppl 2: ii71-3.

The objective of this study was to assess the prevalence and characteristics of tobacco sales and point-of-sale promotions and advertising in predominantly Latino business districts and in comparison districts and to evaluate the economic importance of tobacco sales and marketing to Latino owned small businesses. Observational surveys of retail establishments and interviews with store managers were conducted in demographically contrasting business districts of eastern Massachusetts. The main outcome measures were the percentage of businesses selling tobacco, numbers and characteristics of exterior and interior tobacco advertisements per store, and merchant reports of promotional allowances received from tobacco distributors. The results indicated that the proportion of businesses selling tobacco, hence having storefront tobacco advertising, is strongly negatively correlated with per capita income in the census tracts where businesses are located (Spearman's rho = -0.794, p = 0.006). Mentholated brands are marketed disproportionately in low income, urban communities. Latino merchants are highly dependent on tobacco sales, but would require relatively modest compensation to forego tobacco promotional allowances. It was concluded that storefront tobacco advertising is far more prevalent in predominantly minority, low-income communities than in non-minority, higher-income communities. Principally, this is due to the differing mix of kinds of businesses in the two types of communities and the greater prevalence of tobacco vendors in lower income neighborhoods. Tobacco companies obtain this advertising at little cost.

Mackay, J. and A. Amos (2003). "Women and tobacco." Respirology 8(2): 123-30.

Smoking prevalence is lower among women than men in most countries, yet there are about 200 million women in the world who smoke, and in addition, there are millions more who chew tobacco. Approximately 22% of women in developed countries and 9% of women in developing countries smoke, but because most women live in developing countries, there are numerically more women smokers in developing countries. Unless effective, comprehensive and sustained initiatives are implemented to reduce smoking uptake among young women and increase cessation rates among women, the prevalence of female smoking in developed and developing countries is likely to rise to 20% by 2025. This would mean that by 2025 there could be 532 million women smokers. Even if prevalence levels do not rise, the number of women who smoke will increase because the population of women in the world is predicted to rise from the current 3.1 billion to 4.2 billion by 2025. Thus, while the epidemic of tobacco use among men is in slow decline, the epidemic among women will not reach its peak until well into the 21st century. This will have enormous consequences not only for women's health and economic wellbeing but also for that of their families. The health effects of smoking for women are more serious than for men. In addition to the general health problems common to both genders, women face additional hazards in pregnancy, female-specific cancers such as cancer of the cervix, and exposure to passive smoking. In Asia, although there are currently lower levels of tobacco use among women, smoking among girls is already on the rise in some areas. The spending power of girls and women is increasing so that cigarettes are becoming more affordable. The social

and cultural constraints that previously prevented many women from smoking are weakening; and women-specific health education and quitting programmes are rare. Furthermore, evidence suggests that women find it harder to quit smoking. The tobacco companies are targeting women by marketing light, mild, and menthol cigarettes, and introducing advertising directed at women. The greatest challenge and opportunity in primary preventive health in Asia and in other developing areas is to avert the predicted rise in smoking among women.

Mazis, M. B., D. J. Ringold, et al. (1992). "Perceived age and attractiveness of models in cigarette advertisements." J Marketing* 56(1): 22-37.

A sample of 561 persons judged the age and attractiveness of the models in 50 cigarette ads. Seventeen percent of the models were perceived, on average, to be significantly younger than 25 years of age, an apparent violation of the tobacco industry's voluntary advertising code. Cigarette ads with young persons were found to appear more often in magazines with younger audiences and for menthol brands. Regardless of viewer age, younger models were judged as more attractive than older models.

McDaniel, P. A. and R. E. Malone (2007). ""I always thought they were all pure tobacco": American smokers' perceptions of "natural" cigarettes and tobacco industry advertising strategies." Tob Control 16(6): e7.

The objective of this study was to examine how the US tobacco industry markets cigarettes as "natural" and American smokers' views of the "naturalness" (or unnaturalness) of cigarettes. Internal tobacco industry documents, the Pollay 20th Century Tobacco Ad Collection, and newspaper sources were reviewed; themes and strategies were categorized; and the findings were summarized. Cigarette advertisements have used the term "natural" since at least 1910, but it was not until the 1950s that "natural" referred to a core element of brand identity used to describe specific product attributes (filter, menthol, tobacco leaf). The term "additive-free", introduced in the 1980s, is now commonly used to define natural cigarettes. Tobacco company market research, available from 1970 to 1998, consistently revealed that within focus group sessions, smokers initially had difficulty interpreting the term "natural" in relation to cigarettes; however, after discussion of cigarette ingredients, smokers viewed "natural" cigarettes as healthier. Tobacco companies regarded the implied health benefits of natural cigarettes as their key selling point, but hesitated to market them because doing so might raise doubts about the composition of their highly profitable "regular" brands. Although our findings support the idea advanced by some tobacco control advocates that informing smokers of conventional cigarettes' chemical ingredients could promote cessation, they also suggest that such a measure could increase the ubiquity and popularity of "natural" cigarettes. A more effective approach may be to "denaturalize" smoking.

O'Keefe, A. M. and R. W. Pollay (1996). "Deadly targeting of women in promoting cigarettes." J Am Med Women Assoc 51(1-2): 67-69.

The history of tobacco marketing portrays a strong relationship between cigarette advertising targeted to women and the rise in the prevalence of women smoking. This article describes how tobacco companies crafted their marketing strategies to obfuscate the growing evidence of the health hazards of tobacco and to circumvent attempts to regulate cigarette advertising. It shows how the tobacco industry understood and capitalized on the women's liberation movement to sell cigarettes as symbols of freedom and emancipation, tracing the creation and promotion of Virginia Slims as a case study. And it documents the unfortunate success of these marketing strategies as reflected in the trends of tobacco use, especially among underage girls, and the commensurate increase in tobacco-related disease and death among women.

Peace, J., N. Wilson, et al. (2008). "Recent changes in cigarette packaging in New Zealand may continue to mislead smokers." New Zeal Med J 121(1268).

No abstract available.

Pollay, R. W. and T. Dewhirst (2002). "The dark side of marketing seemingly "Light" cigarettes: successful images and failed fact." Tob Control 11 Suppl 1: I18-31.

The objective of this study was to understand the development, intent, and consequences of US tobacco industry advertising for low machine yield cigarettes. Analysis of trade sources and internal US tobacco company documents, now available on various web sites created by corporations, litigation, or public health bodies, shows that when introducing low-yield products, cigarette manufacturers were concerned about maintaining products with acceptable taste/flavour and feared consumers might become weaned from smoking. Several tactics were employed by cigarette manufacturers, leading consumers to perceive filtered and low machine yield brands as safer relative to other brands. These tactics include using cosmetic (that is, ineffective) filters, loosening filters over time, using medicinal menthol, using high-tech imagery, using virtuous brand names and descriptors, adding a virtuous variant to a brand's product line, and generating misleading data on tar and nicotine yields. It was concluded that advertisements of filtered and low tar cigarettes were intended to reassure smokers concerned about the health risks of smoking and present the respective products as an alternative to quitting. Promotional efforts were successful in getting smokers to adopt filtered and low yield cigarette brands. Corporate documents demonstrate that cigarette manufacturers recognised the inherent deceptiveness of cigarette brands described as "Light"or "Ultra-Light" because of low machine measured yields.

Pollay, R. W., J. S. Lee, et al. (1992). "Separate, but not equal - racial segmentation in cigarette advertising." J Advertising* 21(1): 45-57.

The ethnic segmentation of the cigarette market is currently controversial, but not a new phenomenon. A census of 540 cigarette ads from 1950-1965 Ebony magazines, compared to a matched sample from Life, reveals segmented and segregated advertising toward black

consumers. The ads in Ebony eventually featured black models almost exclusively, primarily professional athletes. Despite endorsements from black athletes and musicians also famous to white audiences, none of these appeared in the Life ads. On average, the segregated advertising was two to three years tardy in offering filtered products to black consumers, suggesting that appeals to black pride were not without prejudice. Potential reasons for these historical results are discussed, as are current practices.

Samji, H. A. and R. K. Jackler (2008). ""Not one single case of throat irritation": misuse of the image of the otolaryngologist in cigarette advertising." Laryngoscope 118(3): 415-27.

Early in the last century, when questions about the health effects of smoking became a topic of widespread discussion, tobacco companies undertook a multi-faceted campaign to allay the public's fears. As terms like "smoker's cough" and "coffin nails" (referring to cigarettes) began to appear in the popular vernacular, tobacco marketers recognized the need to counter this threat to their livelihood. One strategy was to use endorsements by healthy and vigorous-appearing singers, radio stars, and actors. Another was to raise fears over weight gain: "Reach for a Lucky instead of a sweet." Among the more reprehensible tactics was the utilization of the image of the noble and caring physician to sell cigarettes: doctors were depicted both as satisfied and enthusiastic partakers of the smoking habit (e.g., "More doctors smoke Camels"). Images of medical men (and a few token women) appeared under warm reassurances of the safety of smoking. Frequently, images appeared of a head-mirrored "throat doctor," smiling benignly, while indicating that the company's product would do no harm. Indeed, many cigarette ads, especially for menthol brands, suggested a therapeutic soothing benefit from smoking. Liberal use was also made of pseudo-scientific medical reports and surveys. Our intention is to tell, principally through advertising images-the story of how, between the late 1920s and the early 1950s, tobacco companies used deceptive and often patently false claims in an effort to reassure the public of the safety of their products.

Sutton, C. D. and R. G. Robinson (2004). "The marketing of menthol cigarettes in the United States: populations, messages, and channels." Nicotine Tob Res 6 Suppl 1: S83-91.

This commentary looks at the marketing menthol cigarettes to various targeted populations--women, middle school youth and Asian/Pacific Islander immigrants as well as African Americans. The authors take the position that "ethnic awareness" as evidenced in the advertising of menthol cigarette brands to African Americans is just one of four distinct messages that tobacco marketers have used for what they have termed the "coolness" category. The other messages are: healthy/medicinal; fresh/refreshing/cool/clean/crisp; and youthfulness/silliness and fun. The commentary poses three questions: (a) Are new population segments being steered toward menthol cigarettes using marketing approaches that are similar to what has occurred with African Americans and women? (b) What exactly is the relationship between the marketing of menthol cigarettes and subsequent use of menthol tobacco products by specific population subgroups? (c) Are there lessons to be learned from the marketing of menthol cigarettes that can be used to improve the public health and medical communities' smoking cessation and tobacco use prevention communications efforts?

Wayne, G. F., G. N. Connolly, et al. (2004). "Assessing internal tobacco industry knowledge of the neurobiology of tobacco dependence." Nicotine Tob Res 6(6): 927-940.

The recent availability of internal tobacco industry documents provides a significant resource for evaluating industry understanding of the pharmacological, psychosocial, and behavioral mechanisms underlying tobacco dependence. In this study, we catalog the range of efforts undertaken by tobacco manufacturers seeking knowledge of these mechanisms. Some areas of industry research, such as cellular and molecular studies of nicotine and its effects, are widely available in the open literature. Of greater interest are internal research projects that have demonstrated direct influence on product development. These include studies of smoker psychology and behavior, evoked-response studies of tobacco-delivered nicotine, the effects of sensory perception, dose-related effects, and the development of nicotine analogs and synergists. Our findings suggest extensive industry knowledge of mechanisms that determine smoker perception and behavior, and application of this knowledge in product development, including control of sensory response, uptake of nicotine, and product effects. Independent research recently has begun to consider the contributions of tobacco product ingredients and design factors to the determination of risk, severity, and prevalence of addiction. However, the application of these findings to cessation and treatment efforts is still quite limited. We conclude that clinical research would greatly benefit from further examination of the decades of knowledge accumulated by tobacco manufacturers.

White, V. M., M. M. White, et al. (2006). "Cigarette promotional offers: who takes advantage?" Am J Prev Med 30(3): 225-31.

Promotional offers on cigarettes (e.g., dollar-off, multipack discounts) composed the largest share of tobacco industry marketing expenditures, totaling $8.9 billion, or 72% of the total budget in 2002. Internal industry documents indicate that young adults, potential quitters, and other price-sensitive groups are the targets of these marketing tactics. However, the effectiveness of these tactics in actually reaching the targeted groups in the general population of smokers has not yet been investigated. Data were analyzed from 4618 current smokers responding to the large, random-digit-dialed population-based 2002 California Tobacco Survey. The characteristics identified were of smokers who reported that they used these offers "every time I see one." The results indicated that 35 percent of smokers used promotional offers every time they saw one. Multivariate analyses identified young adults, women, African Americans, those with higher daily cigarette consumption, and those worried about cigarette costs as more likely to use promotional offers at every opportunity. Smokers most committed to quitting were no more likely to use promotional offers than those with no intention to quit. Because cigarette brand was highly correlated with age and race/ethnicity, it was not included in the multivariate analysis. Those who smoked menthol cigarettes and Camels, more often young adults and African Americans, were much more likely than those who smoked other brands to use promotional offers. It was concluded that with the exception of smokers intending to quit, cigarette promotional offers are effectively reaching most industry-targeted groups and, more importantly, young adults, who have the greatest long-term customer potential, are responding.

Yerger, V. B., J. Przewoznik, et al. (2007). "Racialized geography, corporate activity, and health disparities: tobacco industry targeting of inner cities."
J Health Care Poor Underserved 18 (4 Suppl): 10-38.

Industry has played a complex role in the rise of tobacco-related diseases in the United States. The tobacco industry's activities, including targeted marketing, are arguably among the most powerful corporate influences on health and health policy. We analyzed over 400 internal tobacco industry documents to explore how, during the past several decades, the industry targeted inner cities populated predominantly by low-income African American residents with highly concentrated menthol cigarette marketing. We study how major tobacco companies competed against one another in menthol wars fought within these urban cores. Little previous work has analyzed the way in which the inner city's complex geography of race, class, and place shaped the avenues used by tobacco corporations to increase tobacco use in low-income, predominantly African American urban cores in the 1970s-1990s. Our analysis shows how the industry's activities contributed to the racialized geography of today's tobacco-related health disparities.

Marketing to and Industry Targeting of Youth

Glanz, K., N. M. Sutton, et al. (2006). "Operation storefront Hawaii: tobacco advertising and promotion in Hawaii stores." J Health Commun* 11(7): 699-707.

Our objective was to explore the nature and location of tobacco product advertising and promotion in retail stores in Hawaii. We performed a cross-sectional study of tobacco product store-based advertisements, including the number, location (indoor/outdoor; proximity to candy, toys, school), size, and brand of the ads. Trained youth (ages 12-19 years) collected data on 3,151 advertisements and promotions among 184 stores. We found that most ads appeared indoors, and the most heavily advertised brand was Kool. Kool is also the most heavily smoked brand among youth in Hawaii. This study underscores the high visibility of retail store advertising and promotions (both indoor and outdoor) in places that attract the attention of youth.

Johnson, D. M., L. A. Wine, et al. (2008). "Designing a tobacco counter-marketing campaign for African American youth." Tob Induc Dis 4(1): 7.

The objectives of this qualitative study were to: a) identify common marketing themes and tactics used by the tobacco industry to entice African Americans (AA's) and youth to initiate and maintain smoking behavior, especially smoking mentholated brands of cigarettes, and b) determine AA youths' knowledge, attitudes, intentions, and beliefs about smoking and the tobacco industry. Together, these activities could aid in the development of effective tobacco counter-marketing campaigns for AA youth. Using publicly available tobacco industry documents, computerized searches using standardized keywords were run and results were cataloged and analyzed thematically. Subsequently, 5 focus groups were conducted with n = 28 AA middle school-aged youth. Results suggest that the tobacco industry consistently recruited new AA smokers through a variety of means, including social and behavioral marketing studies and targeted media and promotional campaigns in predominantly AA, urban, and low income areas. AA youth interviewed in this study were largely unaware of these tactics, and reacted negatively against the industry upon learning of them. Youth tended to externalize control over tobacco, especially within the AA community. In designing a counter-marketing campaign for this population, partnering knowledge of tobacco industry practices with youth needs and community resources will likely increase their effectiveness.

Kaufman, N. J., B. C. Castrucci, et al. (2004). "Changes in adolescent cigarette-brand preference, 1989 to 1996." Am J Health Behav 28(1): 54-62.

The objective of the study was to understand changes in cigarette-brand choice by adolescents in the context of demographic differences and advertising. Data from 3 nationally representative cross-sectional surveys of adolescents were analyzed. The results indicated that Marlboro, Camel, and Newport brand cigarettes accounted for over 80% of the cigarettes usually bought by adolescents in 1989, 1993, and 1996. Between 1989 and 1996, Marlboro and Camel market shares changed little, whereas preference for Newport doubled among white and Hispanic adolescents. It was concluded that brand preference among adolescents has been steadily concentrated among 3 brands. More attention may need to be focused on mentholated brands given the increase in Newport's market share.

Kreslake, J. M., G. F. Wayne, et al. (2008). "Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults." Am J Public Health 98(9): 1685-92.

We examined whether tobacco manufacturers manipulate the menthol content of cigarettes in an effort to target adolescents and young adults by analyzing data from tobacco industry documents describing menthol product development, results of laboratory testing of US menthol brands, market research reports, and the 2006 National Survey on Drug Use and Health. The results indicated that the tobacco industry attracted new smokers by promoting cigarettes with lower menthol content, which were popular with adolescents and young adults, and provided cigarettes with higher menthol content to long-term smokers. Menthol cigarette sales remained stable from 2000 to 2005 in the United States, despite a 22% decline in overall packs sold. It was concluded that tobacco companies manipulate the sensory characteristics of cigarettes, including menthol content, thereby facilitating smoking initiation and nicotine dependence. Menthol brands that have used this strategy have been the most successful in attracting youth and young adult smokers and have grown in popularity.

Mazis, M. B., D. J. Ringold, et al. (1992). "Perceived age and attractiveness of models in cigarette advertisements." J Marketing* 56(1): 22-37.

A sample of 561 persons judged the age and attractiveness of the models in 50 cigarette ads. Seventeen percent of the models were perceived, on average, to be significantly younger than 25 years of age, an apparent violation of the tobacco industry's voluntary advertising code. Cigarette ads with young persons were found to appear more often in magazines with younger audiences and for menthol brands. Regardless of viewer age, younger models were judged as more attractive than older models.

Cessation Interventions and Quitting Behaviors Among Adults

Ahluwalia, J. S., K. J. Harris, et al. (2002). "Sustained-release bupropion smoking cessation in African Americans - A randomized controlled trial." J Amer Medl Assoc 288(4): 468-474.

African Americans disproportionately experience greater smoking attributable morbidity and mortality. Few clinical trials for smoking cessation in African Americans have been conducted, despite a different profile of both smoking and quitting patterns. The objective of this study was to compare a sustained-release form of bupropion hydrochloride (bupropion SR) with a placebo for smoking cessation among African Americans. A randomized, double-blind, placebo-controlled trial was conducted among 600 African American adults treated at a community-based health care center from February 11, 1999, to December 8, 2000. Volunteers who smoked 10 or more cigarettes per day were recruited by targeted media and health care professionals. Participants were randomly assigned to receive 150 mg of bupropion SR (n=300) or a placebo (n=300) twice daily for 7 weeks. Brief motivational counseling was provided in person at baseline, quit day, weeks I and 3, end of treatment (week 6), and by telephone at day 3 and weeks 5 and 7. The main outcome measure was biochemically confirmed 7-day point prevalence abstinence at weeks 6 and 26 following quit day. Using intention-to-treat procedures, confirmed abstinence rates at the end of 7 weeks of treatment were 36.0% in the bupropion SR group and 19.0% in the placebo group (17.0 percentage point difference; 95% confidence interval, 9.7-24.4; P<.001). At 26 weeks the quit rates were 21.0% in the treatment and 13.7% in the placebo groups (7.3 percentage point difference; 95% confidence interval, 1.0-13.7; P=.02). Those taking bupropion SR experienced a greater mean reduction in depression symptoms at week 6 (2.96 [9.45] vs 1.13 [8.84]) than those taking the placebo, and after controlling for continuous abstinence, those taking bupropion SR also gained less weight than those taking the placebo. It was concluded that bupropion SR was effective for smoking cessation among African Americans and may be useful in reducing the health disparities associated with smoking.

Benowitz, N. L. (2002). "Smoking cessation trials targeted to racial and economic minority groups." J Amer Med 288(4): 497-499.

No abstract available.

Fu, S. S., M. M. Kodl, et al. (2008). "Racial/ethnic disparities in the use of nicotine replacement therapy and quit ratios in lifetime smokers ages 25 to 44 years." Cancer Epidem Biomar 17(7): 1640-1647.

We examined racial/ethnic variations in the use of nicotine replacement therapy (NRT) and quit ratios among Caucasian, African American, Asian, and Latino lifetime smokers ages 25 to 44 years. We conducted cross-sectional analyses using data from individuals (n = 27,031) screened for enrollment in the Collaborative Study of the Genetics of Nicotine Dependence. Participants were randomly sampled from three Midwestern metropolitan areas using Health Maintenance Organization membership lists in Detroit, MI and Minneapolis, MN and a driver's license registry in St. Louis, MO from March 2003 to August 2005. A telephone survey collected information on smoking history, previous quit attempts, and sociodemographic characteristics. Among lifetime smokers (n = 9,216), univariate analysis indicated that African Americans (22%) and Latinos (22%) were significantly less likely to report having ever used NRT for smoking cessation than Caucasians (31%). Asians (22%) also reported lower rates of using NRT than Caucasians, but this difference was marginally significant (P = 0.06). These disparities persisted in multivariate analysis for African Americans [adjusted odds ratio (OR), 0.76; 95% confidence interval (95% Cl), 0.63-0.91; P < 0.01] but not for Latinos (adjusted OR, 0.76; 95% Cl, 0.54-1.06; P = 0.11) or Asians (adjusted OR, 0.98; 95% CI, 0.60-1.60; P = 0.95). As measured by the quit ratio, African Americans (35%) were less likely to have quit smoking than Caucasians (52%). This disparity persisted in multivariate logistic regression (adjusted OR, 0.66; 95% Cl, 0.56-0.78; P < 0.001). Asian and Latino smokers were as likely as Caucasians to report smoking cessation. Future prospective studies are needed to assess whether lower utilization of cessation treatments such as NRT contribute to the observed disparity in quit ratios for African Americans.

Fu, S. S., K. S. Okuyemi, et al. (2008). "Menthol cigarettes and smoking cessation during an aided quit attempt." Nicotine Tob Res 10(3): 457-62.

Menthol may make cigarettes more addictive and rates of menthol cigarette smoking are disproportionately higher among Black. However, few studies have examined the association between menthol cigarette smoking and cessation, and the studies to date have produced conflicting findings. The present study examines the effect of menthol cigarette smoking on cessation among a multi-ethnic sample of smokers making a pharmacotherapy-aided quit attempt. We hypothesized that menthol cigarette smoking would be associated with lower smoking abstinence rates and conducted a secondary analysis of data from a multi-site randomized controlled trial of an intervention designed to facilitate repeat tobacco cessation treatment (N = 1,343). The intervention consisted of a patient phone call and a computerized provider prompt. The primary outcome for this analysis was 7-day point prevalence smoking abstinence. The average age of the sample was 56 years old. Overall, 25% of the sample smoked menthol cigarettes: 19% of Whites, 62% of Blacks, and 25% of other ethnicity (p<.001). We observed no significant effects for menthol cigarette smoking or ethnicity on smoking abstinence rates. In conclusion, combined with findings from previous research, this study suggests that smoking menthol cigarettes does not decrease smoking cessation among older smokers during a quit attempt aided with pharmacotherapy.

Gandhi, K. K., J. Foulds, et al. (2009). "Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic." Int J Clin Pract 63(3): 360-7.

Lower rates of smoking cessation and higher rates of lung cancer in African American (AA) smokers may be linked to their preference for mentholated cigarettes. This study assessed the relationship between menthol smoking, race/ethnicity and smoking cessation among a diverse cohort of 1688 patients attending a specialist smoking cessation service. The results indicated that 46% of the patients smoked mentholated cigarettes, but significantly more AA (81%) and Latino (66%) patients than Whites (32%) smoked menthols. AA and Latino menthol smokers smoked significantly fewer cigarettes per day (CPD) than non-menthol smokers (15.7 vs. 20.3 for AA and 17.0 vs. 22.1 for Latinos), with no differences among White menthol and non-menthol smokers. At the 4-week follow up, AA, Latino and White non-menthol smokers had similar quit rates (54%, 50% and 50% respectively). In contrast, among menthol smokers, AAs and Latinos had lower quit rates (30% and 23% respectively) compared with Whites (43%, $p < 0.001$). AA and Latino menthol smokers had significantly lower odds of quitting [odds ratio (OR) = 0.34; 95% CI = 0.17, 0.69 for AA, and OR = 0.32; 95% CI = 0.16, 0.62 for Latinos] than their non-menthol counterparts. At the 6-month follow up, a similar trend was observed for the race/ethnicity subgroups, with AA menthol smokers having half the odds of being abstinent compared with AA non-menthol smokers (OR = 0.48; 95% CI = 0.25, 0.9). It was concluded that despite smoking fewer CPD, AA and Latino menthol smokers experience reduced success in quitting as compared with non-menthol smokers within the same ethnic/racial groups.

Harris, K. J., K. S. Okuyemi, et al. (2004). "Predictors of smoking cessation among African-Americans enrolled in a randomized controlled trial of bupropion." Prev Med 38(4): 498-502.

The identification of individual characteristics that predict successful smoking cessation treatment has been limited to studies with mostly white participants. This study identifies factors that predict successful quitting among African-Americans participating in a smoking cessation trial. Twenty-one baseline variables were analyzed as potential predictors from a double-blind placebo-controlled, randomized trial that used bupropion SR for smoking cessation among 600 African-American smokers. Chi-square tests, two sample t tests, and multiple logistic regression procedures were employed to identify predictors of 7-day abstinence among the 535 participants who completed the 7-week medication phase. The results indicated that univariate predictors of cessation were receiving bupropion ($P < 0.0001$), not smoking menthol cigarettes ($P = 0.0062$), smoking after 30 min of waking ($P < 0.0001$), older age ($P = 0.0085$), smoking fewer cigarettes per day ($P = 0.0038$), and lower cotinine levels ($P = 0.0002$). Logistic regression identified three significant independent predictors. Participants who received bupropion treatment were more than twice as likely to quit smoking at the end of treatment compared to participants who received a placebo (OR = 2.62; 95% CI = 1.77-3.88, $P < 0.0001$), smoked within 30 min of waking (OR = 0.40; 95% CI = 0.25-0.62, $P < 0.0001$) and had higher salivary cotinine levels at baseline (OR = 0.799; 95% CI = 0.629-0.922, $P < 0.0001$). The study is the first to identify predictors of smoking cessation among African-Americans participating in a clinical trial

and indicates that, aside from bupropion treatment, various indicators of addiction were the strongest predictors. While this is similar to findings among white smokers, thresholds of addiction may need to be adjusted for African-American smoking patterns. Additional studies focused on diverse populations are needed to improve treatment approaches and to identify population-specific factors that are important for treatment-matching approaches.

Hebert, J. R., H. M. Brandt, et al. (2009). "Interdisciplinary, translational, and community-based participatory research: Finding a common language to improve cancer research." Cancer Epidem Biomar 18(4): 1213-1217.

Preventing cancer, downstaging disease at diagnosis, and reducing mortality require that relevant research findings be translated across scientific disciplines and into clinical and public health practice. Interdisciplinary research focuses on using the languages of different scientific disciplines to share techniques and philosophical perspectives to enhance discovery and development of innovations; (i.e., from the "left end" of the research continuum). Community-based participatory research (CBPR), whose relevance often is relegated to the "right end" (i.e., delivery and dissemination) of the research continuum, represents an important means for understanding how many cancers are caused as well as for ensuring that basic science research findings affect cancer outcomes in materially important ways. Effective interdisciplinary research and CBPR both require an ability to communicate effectively across groups that often start out neither understanding each other's worldviews nor even speaking the same language. Both demand an ability and willingness to treat individuals from other communities with respect and understanding. We describe the similarities between CBPR and both translational and interdisciplinary research, and then illustrate our points using squamous cell carcinoma of the esophagus as an example of how to deepen understanding and increase relevance by applying techniques of CBPR and interdisciplinary engagement.

Hyland, A., S. Garten, et al. (2002). "Mentholated cigarettes and smoking cessation: findings from COMMIT. Community Intervention Trial for Smoking Cessation." Tob Control 11(2): 135-9.

The majority of African American smokers smoke mentholated cigarettes. Some evidence suggests that African Americans may be more nicotine dependent than whites. One theory is that menthol in cigarettes is responsible for enhancing the dependence producing capacity of cigarettes; however, few studies have prospectively examined the association between menthol use and indicators of nicotine dependence. The objective of this study was to examine the association between the use of menthol cigarettes and smoking cessation, amount smoked, and time to first cigarette in the morning. Baseline smokers from the Community Intervention Trial for Smoking Cessation (COMMIT) completed a telephone tobacco use survey in 1988 and were re-interviewed in 1993. Use of mentholated cigarettes was assessed by self report at baseline. Indicators of dependence examined were six month cessation in 1993, amount smoked among continuing smokers in 1993, and time to first cigarette in the morning in 1988. Multivariate regression techniques were used to assess the association of baseline menthol use with these outcomes while controlling for other factors related to dependence. The results indicated that, overall, 24% of the sample smoked a

mentholated brand in 1988. No consistent associations were observed for menthol use and indicators of dependence in both overall and race specific analyses. Factors significantly associated with increased menthol use were female sex, age 25-34 years, African American and Asian race/ethnicity, greater education, greater than 60 minutes to the first cigarette in the morning, two or more past quit attempts, and use of premium brand cigarettes. Canadian respondents and those who smoked 15-24 cigarettes per day had lower rates of menthol use. Use of mentholated cigarettes was not associated with quitting, amount smoked, or time to first cigarette in the morning. It was concluded that future work is needed to clarify the physiological and sociocultural mechanisms involved in mentholated cigarette smoking.

Okuyemi, K. S., J. S. Ahluwalia, et al. (2003). "Does menthol attenuate the effect of bupropion among African American smokers?" Addiction 98(10): 1387-93.

African Americans have higher tobacco-related morbidity and mortality and are more likely to smoke menthol cigarettes than their white counterparts. This study examined differences in smoking characteristics and cessation between African American menthol and non-menthol smokers. The study sample consisted of 600 African American smokers enrolled in a clinical trial that assessed the efficacy of sustained-release bupropion for smoking cessation. The smoking-related characteristics and abstinence rates of menthol (n = 471) and non-menthol (n = 129) smokers were compared at 6 weeks and 6 months. The results indicated that menthol smokers were younger (41.2 versus 52.9 years), more likely to be female (73.7% versus 56.6%) and more likely to smoke their first cigarette within 30 minutes of waking up (81.7% versus 69.8%) than non-menthol smokers (all $P < 0.01$). Cigarette taste (50% versus 40%, $P = 0.054$) was rated non-significantly higher by menthol smokers. Seven-day point-prevalence abstinence from smoking at 6 weeks were 28% and 42% ($P = 0.006$) and at 6 months were 21% and 27% ($P = 0.21$) for menthol and non-menthol smokers, respectively. At 6 weeks follow-up, stepwise logistic regression revealed that among those younger than 50 years, non-menthol smokers were more likely to quit smoking (odds ratio = 2.0; 95% CI = 1.03-3.95) as were those who received bupropion (odds ratio = 2.12; 95% CI = 1.32-3.39). The conclusion was that African American menthol smokers had lower smoking cessation rates after 6 weeks of treatment with bupropion-SR, thereby putting them at greater risk of the health effects of smoking. Lower overall cessation rates among African Americans menthol smokers may partially explain ethnic differences in smoking-related disease risks.

Okuyemi, K. S., M. Ebersole-Robinson, et al. (2004). "African-American menthol and nonmenthol smokers: differences in smoking and cessation experiences." J Natl Med Assoc 96(9): 1208-11.

Despite smoking fewer cigarettes per day, African Americans have lower cessation rates and experience disproportionately higher rates of smoking-related health consequences. It has been suggested that the high preference for menthol cigarettes may contribute to the excessive smoking-related morbidity African Americans experience.. Smoking menthol cigarettes could increase African Americans' health risks from smoking if smokers of menthol cigarettes have lower cessation rates, thereby, experiencing longer durations of smoking, than smokers of nonmentholated cigarettes. Few studies have examined the associations

between smoking of mentholated cigarettes and smoking cessation among African Americans. This study examined the smoking patterns of menthol cigarette smokers and their smoking cessation experiences. A cross-sectional survey of 480 African-American smokers at an inner-city health center examined sociodemographics, smoking characteristics, and smoking cessation experiences of menthol smokers (n = 407) and compared them to those of nonmenthol smokers (n = 73). The results indicated that menthol smokers were younger and more likely to smoke cigarettes with longer rod length, filters, and high in nicotine and tar. Although both groups did not differ by number of past quit attempts, time since most recent quit attempt was shorter for menthol smokers. The durations of most recent and longest-ever quit attempts were nonsignificantly shorter for menthol compared to nonmenthol smokers. These data suggest that African-American menthol smokers are less successful with smoking cessation. Prospective studies are needed to confirm these findings and examine mechanisms underlying such differences.

Okuyemi, K. S., B. Faseru, et al. (2007). "Relationship between menthol cigarettes and smoking cessation among African American light smokers." Addiction 102(12): 1979-86.

The study's aim was to determine whether African American light smokers who smoked menthol cigarettes had lower cessation when treated with nicotine replacement therapy and counseling. Data were derived from a clinical trial that assessed the efficacy of 2 mg nicotine gum (versus placebo) and counseling (motivational interviewing counseling versus health education) for smoking cessation among African American light smokers (smoked < or = 10 cigarettes per day). Study participants consisted of 755 African American light smokers. The primary outcome variable was verified 7-day point-prevalence smoking cessation at 26 weeks follow-up and by salivary cotinine. The findings indicated that compared to non-menthol smokers, menthol smokers were younger and less confident to quit smoking (P = 0.023). At 26 weeks post-randomization, 7-day verified abstinence rate was significantly lower for menthol smokers (11.2% versus 18.8% for non-menthol, P = 0.015). It was concluded that among African American light smokers, use of menthol cigarettes is associated with lower smoking cessation rates. Because the majority of African American smokers use menthol cigarettes, a better understanding of the mechanism for this lower quit rate is needed.

Pletcher, M. J., B. J. Hulley, et al. (2006). "Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function: the Coronary Artery Risk Development in Young Adults (CARDIA) Study." Arch Intern Med 166(17): 1915-22.

African American smokers are more likely to experience tobacco-related morbidity and mortality than European American smokers, and higher rates of menthol cigarette smoking may contribute to these disparities. We prospectively measured cumulative exposure to menthol and nonmenthol cigarettes and smoking cessation behavior (1985-2000), coronary calcification (2000), and 10-year change in pulmonary function (1985-1995) in African American and European American smokers recruited in 1985 for the Coronary Artery Risk Development in Young Adults Study. We identified 1535 smokers in 1985 (972 menthol and 563 nonmenthol); 89% of African Americans preferred menthol vs 29% of European Americans (P<.001). After adjustment for ethnicity, demographics, and social factors, we

found nonsignificant trends in menthol smokers toward lower cessation (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.49-1.02; P = .06) and recent quit attempt (OR, 0.77; 95% CI, 0.56-1.06; P = .11) rates and a significant increase in the risk of relapse (OR, 1.89; 95% CI, 1.17-3.05; P = .009). Per pack-year of exposure, however, we found no differences in tobacco-related coronary calcification (adjusted OR, 1.27; 95% CI, 1.01-1.60 from menthol cigarettes and 1.33; 95% CI, 1.06-1.68 for nonmenthol cigarettes per 10-pack-year increase; P = .75 for comparison) or 10-year pulmonary function decline (adjusted excess decline in forced expiratory volume in 1 second, 84 mL; 95% CI, 32-137 for menthol cigarettes and 80 mL; 95% CI, 30-129 for nonmenthol cigarettes, per 10-pack-year increase; P = .88 for comparison). It was concluded that menthol and nonmenthol cigarettes seem to be equally harmful per cigarette smoked in terms of atherosclerosis and pulmonary function decline, but menthol cigarettes may be harder to quit smoking.

Pletsch, P. K. and A. T. Kratz (2004). "Why do women stop smoking during pregnancy? Cigarettes taste and smell bad." Health Care Women Int 25(7): 671-9.

There are high rates of cigarette smoking resumption among women who have quit smoking while pregnant, and the reasons for this are poorly understood. Our purpose in this study was to obtain an in-depth description of the context surrounding smoking behaviors during pregnancy and the first 3 months after women give birth in order to gain insight into the reasons women resume smoking. We used a longitudinal qualitative descriptive approach with in-depth interviews conducted early in pregnancy, at 36 weeks of pregnancy, and 3 months postpartum. Our purposive sample consisted of 15 pregnant women who had stopped smoking without assistance by their first prenatal visit. All women smoked mentholated cigarettes prior to pregnancy and 40% were primiparas. A thematic content analysis of 43 interviews revealed that the majority of women experienced an aversion to the taste or smell of tobacco smoke while pregnant and attributed these sensation changes to being pregnant. The taste and smell of tobacco smoke returned to prepregnancy states postpartum, and by 3 months postpartum 73% of the women had resumed smoking. This physiologic change can be conceptualized as a pregnancy-specific motivation for smoking cessation that can inform our efforts toward relapse prevention.

Pollak, K. I., B. Taiwo, et al. (2002). "Reported cessation advice given to African Americans by health care providers in a community health clinic." J Community Health 27(6): 381-93.

Physician smoking cessation advice has been shown to be effective in encouraging patients to attempt cessation. Few studies have examined factors associated with patient-reported physician advice in an inner city community health clinic. Smokers identified via chart review and provider referral met with a study "smoking specialist." Eligible participants self-identified as African American, smoked at least 1 cigarette per day in the prior 7 days, were 18 or older, had access to a telephone, and agreed to consider blood testing for genetic susceptibility to lung cancer. Of the 869 smokers identified, 487 were eligible and completed a brief in-person and a more extensive follow-up telephone survey within one week after their visit. Patient reports of smoking cessation advice by providers were regressed on patient demographic, smoking, health, and social support variables. Seventy percent of

participants reported that they had been advised to quit smoking. Smokers who were older, did not smoke menthol cigarettes, were in poorer health, and who had a regular health care provider were most likely to report having received advice. Patients in this community health setting reported high rates of provider advice to quit smoking. Yet, even in this optimal condition, young healthy smokers did not report receiving advice, even when they were ready to quit smoking. Providers may need additional training and prompting to counsel young healthy smokers about the importance of cessation.

Robles, G. I., D. Singh-Franco, et al. (2008). "A review of the efficacy of smoking-cessation pharmacotherapies in nonwhite populations." Clin Ther 30(5): 800-12.

Cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States. Research suggests that behavioral support strategies and pharmacotherapy can improve abstinence rates. However, both approaches, especially pharmacotherapy, have been understudied in nonwhite US populations. The aim of this review was to evaluate the efficacy of smoking-cessation pharmacotherapy in nonwhite US populations. To identify English-language studies that evaluated the use of smoking-cessation pharmacotherapies in nonwhite patients, a literature search using the following search terms, smoking cessation, nicotine replacement therapy, bupropion SR, varenicline, minority, ethnicity, African American, black, Hispanic, American Indian, and Alaska Native, was conducted in MEDLINE (1966\2-December 2007), International Pharmaceutical Abstracts (1980\2-January 2008), Database of Abstracts of Reviews of Effectiveness (1990\2-December 2007), and EMBASE Drugs & Pharmacology (1991\2-third quarter 2007). Nine studies were identified and assessed: 6 looked at smoking-cessation pharmacotherapy in black smokers, 1 in Hispanic smokers, 1 in Native American smokers, and 1 in white and nonwhite smokers. Among black smokers (N = 410; mean cigarettes per day [cpd], 20.4) who received the nicotine patch versus placebo, the 30-day self-reported abstinence rates were 21.5% versus 13.7% (P = 0.03) at 10 weeks and 17.1% versus 11.7% (P = NS) at 6 months. Among black smokers (N = 600; mean [SD] cpd, 16.1 [7.5]) who received sustained-release (SR) bupropion 150 mg BID versus placebo for 7 weeks, the 7-day biochemically verified abstinence rates at weeks 6 and 26 were 36.0% versus 19.0% (Delta, 17%; 95% CI, 9.7\2-24.4; P < 0.001) and 21.0% versus 13.7% (Delta, 7.3%; 95% CI, 1.0\2-13.7; P = 0.02). Predictors of smoking cessation included use of bupropion SR (abstinence rate, 41.5% vs 21.1%; P<0.001); smoking nonmentholated cigarettes (abstinence rate, 28.3% in mentholated smokers [n = 417] vs 41.5% in nonmentholated smokers [n = 118]; P = 0.006); not smoking within 30 minutes of awakening (abstinence rate, 26.4% [n = 420] in those who did vs 48.7% [n = 115] in those who did not; P < 0.001); and lower baseline salivary cotinine levels (256.8 [137.0] ng/mL in those who became abstinent vs 305.6 [143.4] ng/mL in those who remained smokers; P < 0.001). Among black light (<or=10 cpd) smokers (N = 753) who received 2 mg nicotine gum, the biochemically verified 7-day abstinence rates at weeks 8 and 26 in mentholated versus nonmentholated smokers were 22.6% versus 26.8% (P = NS) and 11.2% versus 18.8% (P = 0.015), respectively; at week 26, the abstinence rates in those who received gum + mentholated cigarettes (n = 309) versus gum + nonmentholated cigarettes (n = 67) were 14% versus 24% (P = 0.031). In Hispanic smokers (N = 108; mean [SD] cpd, 18.8 [10.2]) who received nicotine patch versus placebo for 10 weeks, 46% versus 26% (chi(2) = 4.01;

P = 0.05) were abstinent from weeks 2 to 10 (completed all doses of patch); patients who were more acculturated and received active treatment had a higher abstinence rate than less acculturated patients (63% vs 47%; P value not provided). Among Native American smokers (N = 252; cpd not provided) who received nicotine patch + counseling and were followed up at 3, 6, 9, and 12 months, self reported abstinence rates were 31% (49/156), 30% (21/71), 24% (13/55), and 21% (4/19), respectively (P values not provided). In a 6-month study of white (n = 191) and nonwhite (n = 108) smokers (mean [SD] cpd, 21 [11]) randomized to receive a nicotine patch (n = 144) versus nasal spray (n = 155) for 8 weeks, the carbon monoxide\2-verified 7-day abstinence rates were 34.7% versus 29.0%; at 6 months, these rates were 18.1% versus 15.5% (P = NS). Among nonwhite patients, logistic regression analysis at 6 months found that a higher proportion of patients randomized to receive nasal spray did not smoke for >or=7 consecutive days (odds ratio, 0.20; 95% CI, 0.05-0.77; P = 0.02). Data from the studies in this review support the use of smoking-cessation pharmacotherapy (nicotine patch and bupropion SR) among nonwhite patients. Black patients, who smoked within 30 minutes of awakening, smoked mentholated cigarettes, and had high salivary cotinine levels may have difficulty quitting regardless of the number of cigarettes smoked per day. Determining the type of cigarettes smoked (mentholated vs nonmentholated) and salivary cotinine levels may be helpful in assessing the severity of smoking addiction and guide pharmacotherapy (eg, starting at higher doses of nicotine-replacement therapy in a light smoker). Other than smoking-cessation behavioral studies, there is a lack of congruent smoking-cessation pharmacotherapy studies in American Indian/Alaska Native, Hispanic, and other ethnic populations.

Rose, J. E. and F. M. Behm (2004). "Extinguishing the rewarding value of smoke cues: pharmacological and behavioral treatments." Nicotine Tob Res 6(3): 523-32.

The present study examined several pharmacological and behavioral treatments designed to promote extinction of the responses to rewarding cigarette smoke cues. Pharmacological treatments comprised nicotine skin patches (21 mg/24 hr) and the nicotinic acetylcholine receptor antagonist mecamylamine (10 mg/day), administered separately or in combination. Behavioral manipulations included switching to denicotinized cigarettes, to cigarettes having different menthol flavor, or to ventilated-filter (low tar and nicotine) cigarettes. Smokers were assigned to the various treatments for 2 weeks before they quit smoking. During weekly test sessions, subjects rated the rewarding effects of their usual brands of cigarettes or cigarettes with different menthol content (mentholated vs. nonmentholated). Over the 2-week treatment period, all pharmacological treatments reduced ratings of reward for the usual-brand test cigarettes. Switching to smoking denicotinized cigarettes for 2 weeks similarly decreased rewarding effects of the usual-brand test cigarettes. Subjects also strongly preferred cigarettes with the same menthol content to which they were accustomed. However, manipulating the menthol content of the cigarettes smoked during the 2 weeks of treatment had different effects, depending on whether smokers habitually smoked mentholated or nonmentholated cigarettes. For menthol smokers, removal of the menthol cue hampered extinction of reward ratings for the usual-brand (mentholated) test cigarette. For nonmenthol smokers, addition of the menthol cue did not affect the progress of extinction of nonmenthol smoke cues. These findings demonstrate the importance of sensory cues in

determining subjective reward and show that the reward value of these cues can be altered by removal of nicotine from tobacco or by pharmacological manipulations that interfere with the reinforcing effects of nicotine.

Royce, J. M., N. Hymowitz, et al. (1993). "Smoking cessation factors among African Americans and whites. COMMIT Research Group." Am J Public Health 83(2): 220-6.

This study was undertaken to explore smoking patterns and attitudes that influence smoking cessation and relapse among African Americans. Baseline data from eight Community Intervention Trial for Smoking Cessation (COMMIT) sites were analyzed. Compared with Whites, African Americans who smoke less than 25 cigarettes per day were 1.6 times more likely to smoke within 10 minutes of awakening (a behavioral indicator of nicotine dependence), adjusting for education, age, and gender (OR = 1.2 for heavier smokers). African Americans reported a stronger desire to quit smoking and reported serious quit attempts in the past year. African Americans favored tobacco restrictions (they were 1.8 times more likely than Whites to view smoking as a serious community problem, 1.7 times more likely to favor restrictions on cigarette vending machines, and 2.1 times more likely to prohibit smoking in their car). African Americans were lighter/moderate, menthol smokers. It was concluded that African Americans find smoking socially unacceptable and are strongly motivated to quit; however, their "wake-up" smoking may indicate high nicotine dependence, making abstinence difficult even for lighter smokers.

Schneider, N. G., R. E. Olmstead, et al. (2001). "The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments." Clin Pharmacokinet 40(9): 661-84.

Nicotine inhaled in smoke is the most rapid form of delivery of the drug. With smoking, arterial boli and high venous blood nicotine concentrations are produced within seconds and minutes, respectively. The potency of nicotine as the primary reinforcement in tobacco addiction is attributed to this rapid rate of delivery. By design, nicotine treatments reduce the rate and extent of drug delivery for weaning from nicotine during smoking cessation. Theoretically, they prevent relapse by reducing withdrawal and craving associated with the abrupt cessation of cigarettes. The nicotine inhaler treats the complexity of smoking through weaning both from the drug and from the sensory/ritual components associated with smoking. The inhaler is 'puffed' but not lit and there is considerable 'puffing' required to achieve slower rising and lower nicotine concentrations. These factors allow it to be used as a nicotine reduction treatment. One inhaler contains 10 mg of nicotine (and 1 mg of menthol) of which 4 mg of nicotine can be extracted and 2mg are systemically available. Shallow or deep 'puffing' results in similar nicotine absorption. Nicotine is delivered mainly to the oral cavity, throat and upper respiratory tract with a minor fraction reaching the lungs. This was confirmed with positron emission tomography and by assessment of arterial concentrations. A single inhaler can be used for one 20-minute period of continuous puffing or periodic use of up to 400 puffs per inhaler. With controlled puffing in laboratory testing, venous plasma nicotine concentrations from a single inhaler puffed 80 times over 20 minutes averaged 8.1 microg/L at 30 minutes. Lower concentrations of 6.4 to 6.9 microg/L have been reported for self-administration under clinical conditions. The time to

peak plasma concentrations varies but is always significantly longer than with cigarette delivery. Estimates of nicotine intake from cotinine concentrations were higher than expected (60 to 70% of baseline smoking concentrations). This elevation may be due to the swallowing of nicotine and subsequent first-pass biotransformation to cotinine. In general, venous blood nicotine concentrations are considerably lower than with smoking and are within the range observed for other nicotine reduction therapies. Efficacy trials show consistent superiority of the inhaler over placebo. Despite the 'cigarette-like' appearance of the inhaler and the associated sensory/ritual elements, little treatment dependence or abuse has been reported. This is attributed to the slow rise time and low nicotine blood concentrations. The inhaler is a valuable addition to treatment of tobacco dependence and can be used alone or with other treatments.

Westman, E. C., F. M. Behm, et al. (1996). "Airway sensory replacement as a treatment for smoking cessation." Drug Develop Res 38(3-4): 257-262.

Although nicotine may be a necessary component of the smoking addiction, it is obvious even to the non-expert that there is far more to smoking than the delivery of nicotine alone. Among the many aspects of smoking that smokers find pleasurable, 60% of smokers report liking of the feeling of cigarette smoke in the throat and chest. This paper summarizes several studies that strongly suggest that the airway sensations of smoking are important for at least the short-term satisfaction and craving reduction of cigarette smoking, and that these sensations can be reproduced by several other substances than cigarette smoke. Airway sensory replacement, especially in combination with nicotine replacement, may fill one of the many gaps that currently exist in smoking cessation treatment.

Cessation Interventions and Quitting Behaviors Among Youth

Fagan, P., E. Augustson, et al. (2007). "Quit attempts and intention to quit cigarette smoking among young adults in United States." Am J Public Health 97(8): 1412-1420.

We investigated variables associated with quitting behaviors among current, daily, and nondaily young adult smokers in the United States. Data from the national 2003 Tobacco Use Special Cessation Supplement to the Current Population Survey were analyzed to identify factors associated with quit attempts and serious intention to quit among young adult smokers aged 18 to 30 years (n =7912). Daily smokers who smoked 20 or more cigarettes per day, had their first cigarette within 30 minutes of waking, and smoked no usual type were less likely than were their comparison groups to have 1 more or quit attempts. Nondaily smokers who were male, Hispanic, and smoked no usual type of cigarette were also less likely than were their comparison groups to report 1 or more quit attempts. Although unemployed nondaily smokers were more likely than were the employed to report intention to quit, nondaily smokers with an annual family income of $25000 to $49000 were less likely than were higher-income families to report intention to quit. It was concluded that nicotine dependence measures were significantly associated with quitting and intention to quit among daily smokers, but sociodemographics were associated with quitting and intention to quit among nondaily smokers.

Measurement of Menthol Content and Yields

Angeyo, K. H., J. P. Patel, et al. (1998). "Measurement of trace element levels in Kenyan cigarettes with the energy dispersive X-ray fluorescence spectroscopy technique." J Trace Microprobe T* 16(2): 233-246.

Cd-109 radioisotope-excited Energy Dispersive X-ray Fluorescence (EDXRF) spectroscopy was optimized for light element matrix analysis and utilized to quantify the major, minor and particularly trace elements in a total of 35 intermediate thickness samples representing the five main brands of cigarettes manufactured and widely consumed in Kenya. An elemental profile differential analysis performed on Sportsman, Rosta, Champion, Sweet Menthol and Crownbird cigarette tobaccos and their ashes has constituted a procedure to study and correct for the organic dark matrix background and scattering intensity contributions from cellulose on the elemental sensitivities. 17 elements (K, Ca, Ti, Mn, Fe, Ni, Cu, Zn, As, Se, Pb, Br, Rb, Sr, Zr, Nb and Ga) were detected in the cigarette samples to as low as I mu g/g (Nb). Analysis of the cigarette ashes indicated that an average of 1.7 mu g of Se, 3.4 mu g/g of Ga and 3.1 mu g/g of As are completely ingested during smoking. These elemental profiles together with the 225 mu g/g of the detected Sr, might play some toxic role in the carcinogenic tendencies normally associated with tobacco consumption.

Bestmann, H. J., K. Haberkorn, et al. (1996). "GC profiles of volatile constituents from human urine obtained by closed loop stripping, purge and trap technique and simultaneous stem distillation-extraction." Z Naturforsch [C] 51(11-12): 849-52.

Different techniques like "closed loop stripping" [CLSA], "purge and trap" [PTI], and continuous steam distillation extraction [SDE] were used to establish GC profiles of major histocompatibility complex-associated volatile constituents of human urine and statistically evaluated for reliability. Of the three methods investigated, PTI appeared to be superior for the detection of very volatile substances, whereas SDE was the most efficient one with respect to yield. A number of short to medium-chain ketones, 4-hydroxy-3-methoxy-styrene, menthol and nicotine were identified in preliminary analyses.

Byrd, G. D., K. W. Fowler, et al. (1990). "Isotope dilution gas chromatography-mass spectrometry in the determination of benzene, toluene, styrene and acrylonitrile in mainstream cigarette smoke." J Chromatogr 503(2): 359-68.

A cryogenic trapping method with isotope dilution gas chromatography-mass spectrometry analysis has been developed for the determination of benzene, toluene, styrene and acrylonitrile in mainstream vapor phase cigarette smoke. The method is simple, direct, and quantitative. Vapor phase samples are collected cryogenically in a series of four traps following removal of the particulate phase with a Cambridge filter pad. For all four analytes, 75-85% of the total amounts recovered were found in the initial trap and less than 1% in the final trap. Assessment of instrumental precision by multiple injections of a sample gave relative standard deviations of less than 2%. Linear calibration for all analytes over the analysis range gave an r2 value greater than 0.99 with average relative standard deviations at the mean ranging from 1.4 to 8.2%. The cigarettes analyzed include a reference cigarette (Kentucky 1R4F), a commercial ultra-low "tar" mentholated cigarette, and two cigarettes that heat but do not burn tobacco. The values determined for the four analytes in the 1R4F samples are comparable to reported values of similar cigarettes. The cigarettes which heat rather than burn tobacco yield less of all four analytes compared to the other cigarettes in the study.

Celebucki, C. C., G. F. Wayne, et al. (2005). "Characterization of measured menthol in 48 U.S. cigarette sub-brands." Nicotine Tob Res 7(4): 523-31.

More than 25% of cigarettes sold in the United States are branded as mentholated, and these cigarettes are smoked disproportionately among populations with disparate tobacco-related health outcomes. This study is the first (independent of the tobacco industry) to report menthol for 48 popular commercially available mentholated cigarette sub-brands. The dependent variable "menthol per cigarette" was obtained by gas chromatography-mass spectrometer assay, whereas average per-cigarette milligram weight of tobacco filler ("tobacco per cigarette") was determined gravimetrically. Pearson's correlations assessed associations among continuous variables. Analyses of variance assessed mean differences on the independent variables of interest: manufacturer, brand family, industry descriptors of length (100 mm and King [85 mm]) and label (ultralight, light, medium/mild, and regular/full flavor), and a category constructed by the authors of exclusively menthol brand families (those without a non-menthol offering; Kool, Newport, and Salem) versus others (GPC, Camel, and Marlboro). Results showed menthol per cigarette and menthol per tobacco (i.e., milligrams of menthol per gram of tobacco filler) to be significantly greater in cigarettes labeled with industry descriptors of ultralight or light, belying the common consumer perception that "light" means less. Menthol per cigarette and tobacco per cigarette were significantly greater in 100-mm compared with 85-mm cigarettes. The study results are consistent with prior research that suggests menthol may be used to offset reductions in smoke delivery or impact and to facilitate compensatory smoke inhalation behaviors in smokers of cigarettes with reduced machine-measured smoke delivery. Tobacco manufacturers should be required by federal or other regulatory agencies to report the amount of menthol added to cigarettes.

Charles, S. M., C. Jia, et al. (2008). "VOC and particulate emissions from commercial cigarettes: analysis of 2,5-DMF as an ETS tracer." Environ Sci Technol 42(4): 1324-31.

Emissions of particulate matter (PM) and a broad suite of target volatile organic compounds (VOCs) in total, main-stream (MS) and side-stream (SS) smoke emissions are measured for six types of commercial cigarettes. The suitability of 2,5-dimethyl furan (DMF) as a tracer for environmental tobacco smoke (ETS) is investigated using laboratory results and a field study of 47 residences. Over 30 VOCs were characterized in cigarette smoke, including several that have not been reported previously. "regular tar", "low tar", menthol, and nonmenthol cigarettes showed only minor differences in PM and VOC emissions. When total emissions are considered, PM emissions averaged 18 +/- 2 mg cigarette(-1) and VOC emissions averaged 3644 +/- 160 mg cigarette(-1). DMF appears to satisfy all requirements for a tracer, namely, uniqueness, detectability, similar emission factors across tobacco products (211 +/- 16 microg cigarette(-1)), consistent proportions to other ETS compounds, and behavior similar to other ETS components in relevant environments. On the basis of field study results, DMF more reliably indicated smoking status than occupant-completed questionnaires, and cigarette smoking was responsible for significant fractions of benzene (50%), styrene (49%), and other VOCs in the smoker's homes.

Clark, T. J. and J. E. Bunch (1997). "Qualitative and quantitative analysis of flavor additives on tobacco products using SPME-GC mass spectroscopy." J Agr Food Chem* 45(3): 844-849.

Headspace solid-phase microextraction-gas chromatography-mass spectroscopy (HS-SPME-GC-MS) has been used for both qualitative and quantitative analysis of flavor additives to tobacco. Sampling conditions for the 100 mu m methyl silicone fiber, 65 mu m polyacrylate fiber, 65 mu m methyl silicone/divinylbenzene fiber, and 65 mu m Carbowax/divinylbenzene fiber were investigated. Menthol, anethole, benzaldehyde, and tetramethylpyrazine were quantitated on spiked Kentucky Reference 1R1 tobacco. Major components in mandarin orange oil, nutmeg oil, and sweet fennel oil exhibited linear relationships with concentration of the essential oil. Limits of detection for 31 typical tobacco flavors have been determined.

Coleman III, W. M., T. A. Perfetti, et al. (1998). "Quantitative analysis of menthol isomer distributions in selected samples." J Chromatogr Sci 36(6): 318-321.

Menthol occurs naturally in oils of the Mentha species in the (1R, 3R, 4S)-(-) form (l-menthol), whereas synthetic menthol is available either in the same form or as a racemic mixture (d- and l-menthol). Quantitative analysis of the presence of the (1S, 35, 4R)-(+)-form (d-menthol) is achieved by using gas chromatographic analysis on a chiral capillary column with selective ion monitoring detection. Detection of the presence of as little as 0.01% d-menthol in the total menthol concentration is possible with relative standard deviation values averaging around 7%. Minimal sample preparation with short sample analysis times of 30 min provide for a rapid sample turn around. This method should be applicable to the speciation of menthol in a wide variety of menthol-containing products, including cigarettes.

Connolly, G. N., H. R. Alpert, et al. (2007). "Trends in nicotine yield in smoke and its relationship with design characteristics among popular US cigarette brands, 1997-2005." Tob Control 16(5): e5.

The objectives of this study were to determine whether nicotine yields in the smoke of cigarettes would show an overall increase over time or an increasing trend limited to any particular market category (e.g., full flavour vs light, medium (mild) or ultralight; mentholated vs non-mentholated), manufacturer, or brand family or brand style and if nicotine yields in smoke would be associated with measurable trends in cigarette design. Machine-based measures of nicotine yield in smoke and measures of cigarette design features related to nicotine delivery (ventilation, nicotine content in the tobacco rod and number of puffs), as well as market category descriptors, were obtained from annual reports filed with the Massachusetts Department of Public by tobacco manufacturers for 1997-2005. Trends in nicotine yield and its relationship with design features and market parameters were analysed with multilevel mixed-effects regression modelling procedures. A statistically significant trend was confirmed in increased nicotine yield, of 0.019 (1.1%) mg/cig/year over the period 1997-2005 and 0.029 (1.6%) mg/cig/year over the period 1998-2005. The increasing trend was observed in all major market categories (mentholated vs non-mentholated and full flavour vs light, medium (mild) or ultralight). Nicotine yield in smoke was positively associated with nicotine concentration in the tobacco and number of puffs per cigarette, both of which showed increasing trends during the study period. This study confirms increased machine-measured levels of nicotine, the addictive agent in cigarettes, in smoke, to be a result of increased nicotine in the tobacco rod and other design modifications.

Gu, F. N., Y. Cao, et al. (2008). Zeolite multifunctional materials as the menthol carrier and nitrosamines trapper. Stud Surf Sci Catal. 174: 565-568.

The attempt of utilizing zeolite as the multifunctional additive to carry given guest and to trap nitrosamines in smoke was reported for the first time. After the menthol was adsorbed by zeolite, the composite was added onto tobacco rod. The release of menthol took place when the hot coal of the burning cigarette approached the zeolite. At the same time, the zeolite reduced the nitrosamines level of cigarette smoke. The thermal release of menthol from zeolite was measured by a temperature programmed desorption (TPD) method. Most zeolites studied in this work showed a main desorption peak below 500 K with the exception of NaY, which displayed two desorption peaks around 545 and 650 K. In addition, the zeolite additives reduced about 30% of nitrosamines in the side stream smoke.

Gutcho, S. (1972). "Tobacco flavoring substances and methods." Noyes Data Corp, Park Ridge, N.J.

This book presents a detailed descriptive information on tobacco flavoring substances and methods based on US patents since 1962.

Kannan, A., M. Das, et al. (2001). "Analysis of menthol content in Pan Masala samples collected from the state of Uttar Pradesh." J Food Sci Tech Mys* 38(4): 339-342.

According to Prevention of Food Adulteration Act of India, 0.1% of menthol in Pan Masala (PM) samples is permitted. Pan Masala is a mixture of arecanut, catechu, lime, cardamom and unspecified flavouring agents with or without tobacco. It is being consumed as a substitute for betel quid. Among 622 samples collected from the State of Uttar Pradesh, Ind a, only 9.32 % samples showed the level of menthol below 0.1 %. Almost 89 % of sada and 94 % of zarda PM samples exceeded the permissible limits of menthol. In village and city markets, almost 89 and 93 % PM samples showed higher levels of menthol than the PFA limits, respectively. Only 3.3 and 15.4 % of packed and non-packed PM samples were within the permissible limits, respectively. Samples collected from one district of the State showed menthol within the permissible limit, while those collected from remaining 62 districts showed the average values above 0.1 %. The study showed that 6 brands of PM contained menthol within the permissible limit, while the remaining 44 brands exceeded the prescribed limits of menthol. It was suggested that Goods Manufacturing Practices should be adopted by those manufacturers whose products had the menthol concentration, exceeding the permissible limit. Menthol content was found to be more than 0.1 % in samples drawn from 5 zones of the State.

Pauly, J. L., H. J. Lee, et al. (1998). "Glass fiber contamination of cigarette filters: an additional health risk to the smoker?" Cancer Epidemiol Biomarkers Prev 7(11): 967-79.

We report here the results of studies documenting the contamination of a cigarette-appearing smoking article labeled Eclipse with glass fibers, fragments, and particles. Eclipse, a product of the R. J. Reynolds Tobacco Company (RJR), was commercialized in June of 1996. Eclipse is unlike conventional cigarettes in that, like its predecessor Premier, it is designed to heat and not burn tobacco. The purpose of Eclipse was to simplify the chemical composition and reduce the biological activity of the mainstream and sidestream smoke and to achieve a significant reduction of environmental tobacco smoke. In Eclipse, tobacco pyrolysis is reduced by a carbon fuel rod that serves as a heat source for generating an aerosol having nicotine and tobacco flavor. The carbon rod, at the tip of the cigarette, is insulated and bound with two wrapping mats of glass fibers. Recently, Eclipse has been modified to address consumer complaints of burdensome draw and off-taste. The redesigned Eclipse, which we have termed the NEW Eclipse, has an unconventional filter-appearing mouthpiece that consists of a cellulose acetate cylindrical bundle with a central hollow tunnel. In our analysis of Eclipse, glass fibers (length:width aspect ratio, > or = 3:1) were: (a) observed protruding from the tip; (b) identified on the white cigarette wrapping paper; (c) viewed on the surface of the cork-appearing tipping paper; (d) found in the pack residue; (e) discovered lying freely on the cut surface of the filter by both light and electron microscopy; (f) harvested from the filter with adhesive tape; and (g) displaced when Eclipse was smoked mechanically. In a study of Eclipse that had not been removed from carefully opened packs, we observed that > or = 95% of the filters were contaminated with glass fibers (Eclipse: Regular, n = 114/120, 95%; Milds, n = 118/120, 98%; Menthol, n = 120/120, 100%). Likewise, 99% of NEW Eclipse had glass fibers on the redesigned filter (Regular, n = 119/120). In contrast, glass fibers were never observed on the filters of

conventional United States filter cigarettes that had been used as controls (n = 0/120, 0%). In a study of Eclipse (n = 60), the number of glass fibers contaminating the filter surface ranged from 5 to 55. Glass fibers as well as fiber fracture items [aspect ratio, < 3:1 (e.g., particles, fragments, bits, chips, flakes, specks, and dust)] were discovered in the pack residue. The average number of glass fibers in the residue of a pack of Eclipse was 7,548 (SE +/- 3443; range, 1,164 to 26,725 glass fibers/pack; n = 7 packs). The thin and fragile glass fibers of the insulation mats had most likely been broken and fragmented in the high-speed multiple-step Eclipse manufacturing operation. Invariably, puffing on Eclipse discharged glass fibers and glass particles from the filter into the smoker's mouth. Subsequently, the bioresistant glass fibers and microscopic glass dust are inhaled and/or ingested. Contamination of Eclipse filters with glass fibers and glass dust poses a potential and unnecessary health hazard to uninformed consumers. Eclipse is a paradigm of the health danger that may be imposed by technically complex tobacco articles and nicotine delivery devices promoted by an unregulated industry to smokers worldwide, many of whom are addicted to nicotine and who seek a less hazardous cigarette.

Rustemeier, K., R. Stabbert, et al. (2002). "Evaluation of the potential effects of ingredients added to cigarettes. Part 2: Chemical composition of mainstream smoke." Food Chem Toxicol 40(1): 93-104.

Cigarette mainstream smoke from blended research cigarettes with and without the addition of ingredients was analyzed for its chemical composition. In total, 333 ingredients commonly used in cigarette manufacturing were assigned to three different groups. Each group of ingredients was introduced at a low and a high level to the test cigarettes. The list of the 51 smoke constituents determined is based on those analytes suggested for analysis in a US Consumer Product Safety Commission proposal for low ignition cigarettes and cigarette smoke constituents identified by the International Agency for Research on Cancer as worthy of concern and characterized as carcinogens. An increase in the yield of total particulate matter (TPM) in the range of 13 to 28% relative to the control cigarette without ingredients was observed for all test cigarettes. This was presumably caused by the higher transfer rates of the added ingredients to the smoke compared to the transfer from the tobacco part of the filler. When the yields of individual constituents were normalized to the TPM yields, a reduction in the majority of the constituents was observed when compared to the control. For one of the ingredient groups this reduction was especially high: for phenols a maximum of 70%, for polycyclic aromatic hydrocarbons 50%, and for N-nitrosamines 45%. An increase in the amount relative to TPM was observed for a few smoke constituents: hydrogen cyanide and cadmium (one ingredient group), formaldehyde (one ingredient group), and resorcinol and lead (two ingredient groups). These results are consistent with the lack of any increased activity in the in vitro and in vivo assays in this same series of studies (Food and Chemical Toxicology 2002, 40, 105-111; Food and Chemical Toxicology 2002, 40, 113-131). An overall assessment of our data suggests that these ingredients, when added to the tobacco, do not add to the toxicity of smoke, even at the elevated levels tested in this series of studies.

Schmeltz, I. and W. S. Schlotzhauer (1968). "Benzo(a)pyrene, phenols and other products from pyrolysis of the cigarette additive, (d,1)-menthol." Nature 219(5152): 370-1.

No abstract available.

Swauger, J. E., T. J. Steichen, et al. (2002). "An analysis of the mainstream smoke chemistry of samples of the U.S. cigarette market acquired between 1995 and 2000." Regul Toxicol Pharmacol 35(2 Pt 1): 142-56.

Surveys of the smoke composition of commercially marketed cigarettes were conducted in 1995, 1998, and 2000. For each of these surveys, the U.S. cigarette market was stratified into broad market sections based on "tar" category and menthol inclusion. Brand styles were selected from these market sections using techniques in which selection probability increased with increasing market share. Nineteen mainstream smoke constituents were evaluated. In addition, carbon dioxide values were obtained on all brand styles selected in 1998 and 2000. Collectively, the results of these surveys provide evidence that constituent yields are, in general, proportional to "tar" yield and that the relationships between constituent yields and "tar" have remained constant during this time span. Moreover, these data demonstrate that constituent yields of commercially marketed cigarettes available in the U.S. between 1995 and 2000 have been effectively constant.

Tucker and Ogg (1966). "Menthol in cigarette tobacco filler." J Assoc Off Ana Chem* 49(6): 1283.

No abstract available.

Tucker, C. L. (1967). "Determination of menthol in cigarette tobacco filler." J Assoc Off Ana Chem* 50(4): 770.

No abstract available.

Tucker, C. L. (1968). "Determination of menthol in cigarette tobacco filler." J Assoc Off Ana Chem* 51(3): 650.

No abstract available.

Van Amsterdam, J. G. C., T. M. Brunt, et al. (2006). "The relation between the quantity of ammonium compounds in tobacco and the nitrogen monoxide (NO) levels in the smoke of cigarettes marketed in the Netherlands." Beitr Tabakforsch/Contribu Tob Res 22(3): 196-203.

It has been suggested that ammonium compounds in tobacco generate nitrogen monoxide (NO) in cigarette smoke. This causes the smoke to retain the broncho-dilatory properties of the tobacco, which leads to an increased uptake of nicotine and thus to a potentially higher addiction to tobacco. The objective of this study was to ascertain putative correlations among the concentration of ammonium compounds in whole tobacco and the concentration

of NO in mainstream smoke. In 98 different cigarette brands marketed in the Netherlands, positive correlations were found between 'tar' and nicotine values (coefficient of variation, R2 = 0.95), and between 'tar' and NO concentration (R 2 = 0.47). The quantity of ammonium compounds in tobacco (expressed as the amount of NH4+ present) varied, however, from 0.1 to 3.3 mg per gram of tobacco and was not associated with any of the parameters investigated here. In addition, five cigarette types were compared with respect to the levels of ammonium-compounds in the tobacco, the concentration of NO in the smoke and 'tar'/nicotine ratio. The concentration of NO in the smoke from light menthol and light cigarettes ('tar' content < 9 mg/cig) was significantly lower than that from their regular equivalents ('tar' content > 9 mg/cig). As expected, the 'tar'/nicotine ratio of regular cigarettes was significantly higher than the ratio in light cigarettes. This study shows that the whole tobacco in the various cigarette brands differed in the amount of ammonium compounds it contained, but these amounts bore no relation to the level of NO and the level of nicotine and 'tar' in the smoke. Other factors that affect the burning process, such as nitrate content and product design may have made the association between ammonium compounds in tobacco and the level of NO in mainstream smoke less clear.

Wu, Y. Q., L. Yang, et al. (2007). "On-line investigation of the pyrolysis behavior of monomenthyl succinate by pyrolysis-gas chromatography-mass spectrometry." Chinese J Anal Chem* 35(7): 1035-1038.

The pyrolysis behavior of monomenthyl succinate was investigated by on-line pyrolysis-gas chromatography-mass spectrometry (PyGC-MS) in the presence of helium. GC-MS was used for the qualitative and semi-quantitative analysis of the pyrolysis products of the compound at 300, 400, 500, 600, 700, 800 and 900 degrees C. There are altogether 75 pyrolysis products were detected, including menthol, p-menth-3-ene and succinic acid. The results indicated that flavorous and refreshing substances, such as menthol, p-menth-3-ene and 3-methyl-6-isopropyl-cyclohexene, were released from parent compound under 700 degrees C. However, above this temperature, flavor was not found in the pyrolysis products. Moreover, with the raise of pyrolysis temperature, complicated pyrolysis products appeared, and the content of harmful substances, such as benzene, anthracene and fluoranthene, were also increased. This method possesses the merits of easy operation and good repeatability (RSD <= 2. 0%). According to the relative content and category of the pyrolysis products, the possible pyrolysis mechanism of monomenthyl succinate was also discussed.

Zhong, K. J., W. Z. Wei, et al. (2005). "Comparison of simultaneous distillation extraction and solid-phase micro-extraction for determination of volatile constituents in tobacco flavor." J Cent South Univ T* 12(5): 546-551.

The volatile and semi-volatile components in tobacco flavor additives were extracted by both simultaneous distillation extraction and solid-phase micro-extraction. Extraction conditions for solid-phase micro-extraction were optimized with information theory. Then, detection were accomplished by gas chromatography-mass spectrometry. Characteristic of each method was compared. Qualitative analysis and quantitative analysis of 6 0 tobacco flavor sample were accomplished through both simultaneous distillation extraction and solid-phase micro-extraction. The experimental results show that solid-phase micro-extraction method is the first choice for qualitative analysis and simultaneous distillation extraction is another good selection for quantitative analysis. By means of simultaneous distillation extraction, 20 components are identified, accounting for 92.77% of the total peak areas. Through solid-phase micro- extraction, there are 17 components identified accounting for 91.49% of the total peak areas. The main aromatic components in 6(#) tobacco flavor sample are propanoic acid, 2-hydroxy-, ethyl ester, menthol and menthyl acetate. The presented method has been successfully used for quality control of tobacco flavor.

Nicotine Metabolism and Addiction in Adults

[No author] (1999). "Women who smoke menthol cigarettes have greater nicotine exposure." Oncology (Williston Park) 13(7): 915.

No abstract available.

Ahijevych, K. (1999). "Nicotine metabolism variability and nicotine addiction." Nicotine Tob Res 1 Suppl 2: S59-62; discussion S69-70.

Individual variation in nicotine metabolism may play a role in a person's level of smoking, as well as in the transition from initiation to maintenance of a smoking behavior pattern. Since there is a paucity of research on nicotine metabolism in youth that smoke, a brief review of salient aspects of nicotine metabolism in adults provides a basis from which to extrapolate. We do know that factors influencing the rate of nicotine metabolism include differences in nicotine intake and absorption, inhalation patterns, genetic polymorphisms of pertinent enzymes, as well as daily activities such as meal consumption. Variability is illustrated with differences in cotinine levels identified in African-American and Caucasian women and in menthol and nonmenthol smokers. There are a number of areas where more information to improve understanding the initiation and maintenance of smoking behavior is needed. Characterization of nicotine metabolism and smoking topography in youth from multiple ethnic groups who are engaged in smoking initiation is currently lacking. Important measures of smoke constituent exposure such as carbon monoxide, nicotine and cotinine, as well as puff volume and duration and respiratory movements should be addressed. While there are numerous factors that impact initiation and maintenance of smoking behavior, nicotine metabolism may represent one important aspect.

Ahijevych, K. and B. E. Garrett (2004). "Menthol pharmacology and its potential impact on cigarette smoking behavior." Nicotine Tob Res 6 Suppl 1: S17-28.

Menthol is the only tobacco additive promoted and advertised by the tobacco industry. Although a considerable body of research has examined the effects of menthol when it is administered alone and unburned, the effects of menthol when burned in cigarette smoke are more complex because it is administered in a matrix of more than 4,000 substances. Therefore, it is difficult to isolate potential pharmacological and toxic effects of menthol when it is administered in a smoke mixture. Menthol properties include cooling and local anesthesia, as well as effects on drug absorption and metabolism, bronchodilation and

respiration changes, and electrophysiology. Subjective effects of smoothness and less harshness have been identified as reasons for menthol cigarette smoking, but findings have been inconclusive regarding the effect of menthol on carbon monoxide exposure and smoking topography parameters. Gaps in the research literature and future research areas include the following: (a) What is the role of menthol in tobacco reinforcement and addiction? (b) In the absence of nicotine, is menthol reinforcing? (c) Are the pharmacological and physiological effects of menthol mediated by a menthol-specific receptor or some other central nervous system-mediated action? (d) What are the influences of menthol and menthol metabolism on the metabolic activation and detoxification of carcinogens in tobacco smoke? and (e) Do differences exist in cigarette smoking topography in relation to the interaction of ethnicity, gender, and menthol cigarette preference? Answers to these questions will help to elucidate the function of menthol in cigarettes and its impact on smoking behavior.

Ahijevych, K. and M. E. Wewers (1993). "Factors associated with nicotine dependence among African American women cigarette smokers." Res Nurs Health 16(4): 283-92.

Cigarette smoking contributes to disproportionate morbidity and mortality among African Americans. Purposes of the study were to describe smoking behavior and test a model of nicotine dependence among African American women. Participants (n = 187) smoked a low rate of high nicotine mentholated cigarettes and had a mean salivary cotinine of 402 ng/mL. The proposed model predicted 48% of variance in nicotine dependence with smoking to cope, number of cigarettes/day, positive outcome expectancies about smoking, and interest in quitting, as significant contributors. Suggested interventions include developing alternative coping skills, cognitive restructuring, and techniques focused on the precontemplation stage of smoking cessation.

Ahijevych, K. L., R. F. Tyndale, et al. (2002). "Factors influencing cotinine half-life during smoking abstinence in African American and Caucasian women." Nicotine Tob Res 4(4): 423-31.

Cotinine, the proximate metabolite of nicotine, has been identified as an indicator of smoke constituent exposure. Higher cotinine levels in African American cigarette smokers have been identified. Because African Americans experience disproportionate smoking-related morbidity and mortality, it is important to examine potential factors influencing these higher levels of cotinine. The current study examined selected factors of ethnicity, menthol cigarette preference, body composition and alcohol-use history on cotinine half-life in 6 days of smoking abstinence in African American and Caucasian women. A 7-day inpatient protocol was conducted in the General Clinical Research Center, in which day 1 was ad lib smoking and days 2-7 were smoking abstinence (n = 32). Plasma cotinine was measured every 8 h throughout. Average cotinine half-life was 21.3 h, similar to previously reported 18-20 h. Three women exhibited >14 ng/ml cotinine after 136 h of smoking abstinence. Host factors explaining 52.0% of variance in cotinine half-life and associated with longer half-life were being an African American menthol smoker, fewer years of alcohol use and greater lean body mass. Among menthol smokers, baseline cotinine level and cotinine half-life were not significantly different in Caucasian and African American women.

Intra-individual cotinine half-life variation and CYP2A6 genotype were examined in sub-studies. To improve accuracy in correctly classifying non-smokers with cotinine levels, a period of at least 7 days of smoking abstinence may be warranted.

Benowitz, N. L. (2008). "Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction." Clin Pharmacol Ther 83(4): 531-41.

Understanding the basic and clinical pharmacology of nicotine provides a basis for improved prevention and treatment of tobacco addiction. Nicotine acts on nicotinic cholinergic receptors in the brain to release dopamine and other neurotransmitters that sustain addiction. Neuroadaptation and tolerance involve changes in both nicotinic receptors and neural plasticity. Nicotine addiction can occur in the context of physical dependence characterized by self-medication to modulate negative affect and/or to relieve withdrawal symptoms, as well as, in light or occasional smokers, primarily for positive reinforcement in specific situations. Nicotine is metabolized primarily by CYP2A6. Its clearance exhibits considerable individual variability that is determined by genetic, racial, and hormonal (sex) factors. Genetically slow metabolism of nicotine appears to be associated with a lower level of dependence. Nicotine dependence is highly heritable and appears to be influenced by genes coding for some nicotine receptor subtypes, some neurotransmitter genes, and genes involved in neural connectivity. Novel pharmacotherapies for nicotine dependence include partial agonists for nicotinic receptors and nicotine vaccines. Pharmacogenetic studies suggest various candidate genes and a nicotine metabolism phenotype that influence outcome. Human pharmacology studies of nicotine and smoking behavior also provide a basis for assessing the benefits and risks of long-term nicotine use for harm reduction and for a potential cigarette regulatory strategy that includes reducing nicotine content of cigarettes to nonaddictive levels.

Benowitz, N. L., B. Herrera, et al. (2004). "Mentholated cigarette smoking inhibits nicotine metabolism." J Pharmacol Exp Ther 310(3): 1208-15.

Smoking mentholated cigarettes has been suggested to convey a greater cancer risk compared with smoking nonmentholated cigarettes. Two of the possible mechanisms by which mentholated cigarette smoking could increase risk are by increasing systemic exposure to tobacco smoke toxins and by affecting the metabolism of nicotine or tobacco smoke carcinogens. To examine these possibilities, we performed a crossover study in 14 healthy smokers, one-half of whom were African-Americans and one-half whites. Subjects were randomly assigned to smoke mentholated or nonmentholated cigarettes for 1 week, then to cross over to the other type of cigarettes for another week. Subjects were confined to a Clinical Research Center for 3 days of each week, during which time blood levels of nicotine and carbon monoxide were measured throughout the day and an intravenous infusion of deuterium-labeled nicotine and cotinine was administered to determine the rate and pathways of nicotine metabolism. The systemic intake of nicotine and carbon monoxide was, on average, not affected by mentholation of cigarettes. Mentholated cigarette smoking did significantly inhibit the metabolism of nicotine (clearance: 1289 versus 1431 ml/min, two sided, $p = 0.02$). Inhibition of nicotine metabolism occurred both by slower oxidative

metabolism to cotinine and by slower glucuronide conjugation. Our data do not support the hypothesis that mentholated cigarette smoking results in a greater absorption of tobacco smoke toxins. Our finding of impaired metabolism of nicotine while mentholated cigarette smoking suggests that mentholated cigarette smoking enhances systemic nicotine exposure.

Benowitz, N. L., E. J. Perez-Stable, et al. (1999). "Ethnic differences in N-glucuronidation of nicotine and cotinine." J Pharmacol Exp Ther 291(3): 1196-203.

We previously reported that the metabolism of cotinine, the proximate metabolite of nicotine, is significantly slower in black than in white cigarette smokers. To understand why the metabolism of nicotine and cotinine might differ between blacks and whites, we studied the pattern of nicotine metabolism in blacks and whites. One hundred eight healthy smokers (51 blacks and 57 whites), of similar age, gender distribution, and smoking history, received an i.v. infusion of deuterium-labeled nicotine and cotinine. The clearance of cotinine, the fractional conversion of nicotine to cotinine, and the metabolic clearance of nicotine to cotinine were significantly lower in blacks than in whites. Blacks excreted significantly less nicotine as nicotine-N-glucuronide and less cotinine as cotinine-N-glucuronide than whites, but there was no difference in the excretion of 3'-hydroxycotinine-O-glucuronide. Nicotine and cotinine glucuronidation appeared to be polymorphic, with evidence of slow and fast N-glucuronide formers among blacks but was unimodal with fast conjugators only among whites. Other findings of note included the demonstration of a significant correlation between the distribution volumes of nicotine and cotinine with lean body mass: there was a smaller distribution volume and a shorter half-life for cotinine in women than in men and a smaller volume of distribution of cotinine in blacks than in whites. We conclude that the metabolism of cotinine is slower in blacks than in whites because of both slower oxidative metabolism of nicotine to cotinine (presumably via cytochrome P-450 2A6) and slower N-glucuronidation. Ethnic differences in the metabolism of other drugs undergoing N-glucuronidation should be studied.

Bover, M. T., J. Foulds, et al. (2008). "Waking at night to smoke as a marker for tobacco dependence: patient characteristics and relationship to treatment outcome." Int J Clin Pract 62(2): 182-90.

This study aimed to describe the characteristics of treatment-seeking patients who wake at night to smoke (night-smoking), identify factors that may be associated with night-smoking, and assess the association between night-smoking and treatment outcome. A total of 2312 eligible consecutive cigarette smokers who sought treatment at a specialist tobacco-dependence clinic declared a target quit date, provided baseline information at assessment, and were followed-up with 4 and 26 weeks after their target quit date. Of the total sample, 51.1% were identified as night-smokers and 25.1% reported smoking abstinence at the 26-week follow-up. Night-smoking was associated with a number of other patient characteristics, including African-American race or Hispanic ethnicity along with having smoking-related medical symptoms, having been treated for a behavioural health problem, smoking mentholated cigarettes, smoking within 30 min of waking in the morning, smoking an increasing number of cigarettes per day, and not having private health insurance.

In multivariate analyses, night-smoking at assessment remained a significant predictor of smoking at the 26-week follow-up when controlling for other factors associated with the treatment outcome (adjusted odds ratio: 0.77, 95% confidence interval: 0.62-0.96). Night-smokers also experienced a shorter average time-to-relapse (38.5 vs. 56 days, p<0.0001). It was concluded that several socioeconomic and tobacco use characteristics are shared among patients who wake at night to smoke. This behaviour can be assessed by a simple question and used as a marker for tobacco dependence and as an indicator that more intensive and sustained treatment may be required.

Caraballo, R. S., G. A. Giovino, et al. (1998). "Racial and ethnic differences in serum cotinine levels of cigarette smokers - Third National Health and Nutrition Examination Survey, 1988-1991." J Amer Med Assoc 280(2): 135-139.

Cotinine, a metabolite of nicotine, is a marker of exposure to tobacco smoke. Previous studies suggest that non-Hispanic blacks have higher levels of serum cotinine than non-Hispanic whites who report similar levels of cigarette smoking. The objective of this study was to investigate differences in levels of serum cotinine in black, white, and Mexican American cigarette smokers in the US adult population. The study is based on data from the Third National Health and Nutrition Examination Survey, 1988-1991. Participants included a nationally representative sample of persons aged 17 years or older who participated in the survey. Outcome measures included serum cotinine levels by reported number of cigarettes smoked per day and by race and ethnicity. A total of 7182 subjects were involved in the study; 2136 subjects reported smoking at least 1 cigarette in the last 5 days. Black smokers had cotinine concentrations substantially higher at all levels of cigarette smoking than did white or Mexican American smokers (P<.001). Serum cotinine levels for blacks were 125 nmol/L (22 ng/mL) (95% confidence interval [CI], 79-176 nmol/L. [14-31 ng/mL]) to 539 nmol/L (95 ng/mL) (95% CI, 289-630 nmol/L [51-111 ng/mL]) higher than for whites and 136 nmol/L (24 ng/mL) (95% CI, 85-182 nmol/L [15-32 ng/mL]) to 641 nmol/L (113 ng/mL) (95% CI, 386-897 nmol/L [68-158 ng/mL]I) higher than for Mexican Americans. These differences do not appear to be attributable to differences in environmental tobacco smoke exposure or in number of cigarettes smoked. To our knowledge, this study provides the first evidence from a national study that serum cotinine levels are higher among black smokers than among white or Mexican American smokers. If higher cotinine levels among blacks indicate higher nicotine intake or differential pharmacokinetics and possibly serve as a marker of higher exposure to cigarette carcinogenic components, they may help explain why blacks find it harder to quit and are more likely to experience higher rates of lung cancer than white smokers.

Clark, P. I., G. Caldito, et al. (1994). "Elevated serum cotinine in black-and-white menthol cigarette smokers." Circulation* 90(4): II-II.

No abstract available.

Clark, P. I., S. Gautam, et al. (1996). "Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers." Chest 110(5): 1194-8.

Black smokers have been reported to have higher serum cotinine levels than do white smoker, and have higher rates of most smoking-related diseases, despite smoking fewer cigarettes per day. Another striking racial difference is the preference for mentholated cigarettes among black smokers. The contribution of menthol to variability in biochemical markers of cigarette smoke exposure (end-expiratory carbon monoxide and serum cotinine) was evaluated in a biracial sample. A descriptive cross-sectional study was conducted in a university smoking research laboratory on 65 black and 96 white adult established smokers who were paid for their participation. Information was obtained through direct observation, self-report (interview and self-administered questionnaires), measurement of butts collected for a week, and laboratory analyses of the biochemical markers of exposure. Compared with the white smokers, the black smokers had significantly higher cotinine and carbon monoxide levels per cigarette smoked and per millimeter of smoked tobacco rod (both $p < 0.001$). After adjusting for race, cigarettes per day, and mean amount of each cigarette smoked, menthol was associated with higher cotinine levels ($p = 0.03$) and carbon monoxide concentrations ($p = 0.02$). It was concluded that the use of menthol may be associated with increased health risks of smoking. Menthol use should be considered when biochemical markers of smoke exposure are used as quantitative measures of smoking intensity or as indicators of compliance with smoking reduction programs. In addition, the effect of menthol on total "dose" should be considered in any efforts to regulate the amount of nicotine in cigarettes.

Dessirier, J. M., M. O'Mahony, et al. (2001). "Oral irritant properties of menthol: sensitizing and desensitizing effects of repeated application and cross-desensitization to nicotine." Physiol Behav 73(1-2): 25-36.

The irritant properties of menthol and its interactions with nicotine were investigated psychophysically in human subjects. In the first experiment, 0.3% L-menthol was applied successively to one side of the tongue 10 times at a 1-min interval (30-s interstimulus interval, ISI), and subjects rated the intensity of the perceived irritation. The intensity of irritation progressively decreased across trials, consistent with desensitization. To test for cross-desensitization of nicotine-evoked irritation by menthol, nicotine (0.6%) was applied to both sides of the tongue simultaneously, 5 min after the conclusion of menthol application. Using both a two-alternative forced choice (2-AFC) paradigm, and also by obtaining independent ratings of the irritant intensity on each side of the tongue, it was found that nicotine-evoked irritation was significantly weaker on the menthol-pretreated side. To control for a possible confounding effect of cooling, nicotine was applied bilaterally only after the cooling sensation of menthol had subsided. Nicotine-induced irritation was still significantly weaker on the menthol-pretreated side, consistent with cross-desensitization of nicotine-evoked irritation by menthol. In a final experiment, menthol was repeatedly applied to one side of the tongue at a shorter (20 s) interval (5-s ISI), and elicited a rapid increase in irritant sensation over the initial trials, consistent with sensitization, followed in subsequent trials by a progressive reduction in irritation (desensitization). After a 5-min rest period, self-desensitization was confirmed. Repeated application of menthol at the same short ISI

was then resumed, and resulted in a significant mean increase in irritant intensity consistent with stimulus-induced recovery (SIR).

Garten, S. and R. V. Falkner (2004). "Role of mentholated cigarettes in increased nicotine dependence and greater risk of tobacco-attributable disease." Prev Med 38(6): 793-8.

Cold air stimulates upper airway cold receptors causing a reflex depressive effect on respiratory activity. Menthol in low concentrations can also stimulate these same cold receptors, causing a depressive effect on respiratory activity. Menthol cigarettes, when smoked, deliver enough menthol to stimulate cold receptors, resulting in the smoker experiencing a "cool sensation." The "cool sensation" experienced by the menthol smoker can result in a reflex-depressive effect on respiratory activity. Literature searches of the NLM databases (e.g., MEDLINE from 1966, TOXLINE, OLDMEDLINE (1985-1965), CANCERLIT, plus tobacco industry documents and hardcopy indices were conducted and the evidence was evaluated with application to mentholated cigarette smoking. A logical progression is presented that develops the framework to prove that menthol found in mentholated cigarettes may cause respiratory depression, resulting in greater exposure to the toxic substances found in tobacco smoke. As a result of breath holding that results from the stimulation of cold receptors, there is a greater opportunity for exposure and transfer of the contents of the lungs to the pulmonary circulation. For the menthol smoker this results in a greater exposure to nicotine and the particulate matter (tar) of the smoked cigarette. This exposure can result in increased nicotine dependence and greater chance of tobacco-attributable disease.

Heck, J. D. (2009). "Smokers of menthol and nonmenthol cigarettes exhibit similar levels of biomarkers of smoke exposure." Cancer Epidemiol Biomarkers Prev 18(2): 622-9.

There has been speculation that the addition of menthol to cigarettes may affect the manner in which cigarettes are smoked, potentially influencing smokers' exposures to smoke constituents that have been associated with smoking-related diseases. One hundred twelve male and female smokers participated in a parallel-arm study to determine whether the ad libitum smoking of menthol cigarettes results in differences in smoke constituent exposure biomarkers in blood and urine relative to those smoking nonmenthol cigarettes having similar machine-measured (Federal Trade Commission) yields of approximately 9 to 10 mg "tar." The study subjects were provided cigarettes of their preferred menthol or nonmenthol types prior to two 24-hour study intervals spaced one week apart. Carboxyhemoglobin levels were measured in blood samples drawn at midafternoon following the two 24-hour urine collection periods. Six urinary nicotine metabolites (nicotine, cotinine, trans-3'-hydroxycotinine and respective glucuronides) were determined as measures of nicotine intake, and urinary 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide were determined to assess exposure to the tobacco-specific nitrosamine 4-(N-nitrosomethylamino)-1-(3-pyridinyl)-1-butanone. Subjects' median blood carboxyhemoglobin values did not differ significantly between the cigarette types. Neither total urinary NNAL nor urinary nicotine equivalents exhibited statistically significant differences between the menthol and nonmenthol cigarette smokers. The present findings indicate that moderately heavy smokers of menthol and nonmenthol cigarettes of similar

machine-generated smoke yield exhibit essentially identical levels of biomarkers of smoke constituent exposure. These results are consistent with the substantial majority of epidemiology studies to date that suggest the risks attending the smoking of menthol and nonmenthol cigarettes are similar.

Henningfield, J. E., N. L. Benowitz, et al. (2003). "Does menthol enhance the addictiveness of cigarettes? An agenda for research." Nicotine Tob Res 5(1): 9-11.

No abstract available.

Hyland, A., S. Garten, et al. (2002). "Mentholated cigarettes and smoking cessation: findings from COMMIT. Community Intervention Trial for Smoking Cessation." Tob Control 11(2): 135-9.

The majority of African American smokers smoke mentholated cigarettes. Some evidence suggests that African Americans may be more nicotine dependent than whites. One theory is that menthol in cigarettes is responsible for enhancing the dependence producing capacity of cigarettes; however, few studies have prospectively examined the association between menthol use and indicators of nicotine dependence. The objective of this study was to examine the association between the use of menthol cigarettes and smoking cessation, amount smoked, and time to first cigarette in the morning. Baseline smokers from the Community Intervention Trial for Smoking Cessation (COMMIT) completed a telephone tobacco use survey in 1988 and were re-interviewed in 1993. Use of mentholated cigarettes was assessed by self report at baseline. Indicators of dependence examined were six month cessation in 1993, amount smoked among continuing smokers in 1993, and time to first cigarette in the morning in 1988. Multivariate regression techniques were used to assess the association of baseline menthol use with these outcomes while controlling for other factors related to dependence. The results indicated that overall, 24% of the sample smoked a mentholated brand in 1988. No consistent associations were observed for menthol use and indicators of dependence in both overall and race specific analyses. Factors significantly associated with increased menthol use were female sex, age 25-34 years, African American and Asian race/ethnicity, greater education, greater than 60 minutes to the first cigarette in the morning, two or more past quit attempts, and use of premium brand cigarettes. Canadian respondents and those who smoked 15-24 cigarettes per day had lower rates of menthol use. Use of mentholated cigarettes was not associated with quitting, amount smoked, or time to first cigarette in the morning. It was concluded that future work is needed to clarify the physiological and sociocultural mechanisms involved in mentholated cigarette smoking.

Levin, E. D., F. Behm, et al. (1990). "The use of flavor in cigarette substitutes." Drug Alcohol Depend 26(2): 155-60.

Cigarette smokers identify flavor as an important factor in the pleasure derived from smoking and for their choice of cigarette brand. The issue of cigarette flavor has received a great deal of study by cigarette manufacturers but relatively little by academic investigators. The paucity of literature is particularly acute in terms of the importance of flavor in

cigarette substitutes, which are used to help people to reduce or quit smoking. In the current study, five different types of flavors added to a plastic cigarette substitute were assessed in experienced smokers. There were two menthol-like flavors and three tobacco-like flavors. Two groups of smokers were tested: menthol smokers and "regular" (non-menthol) smokers. Both types of smokers liked the two menthol flavors significantly more than placebo and rated the menthol flavors and the cigarette flavor as significantly more satisfying than placebo. Craving was differentially reduced in the two groups of smokers. Menthol smokers showed a small reduction in craving with the placebo, with a significant enhancement of this reduction seen with the addition of the "EZ Quit" menthol flavor.

Luke, E. (1962). "Addiction to Mentholated Cigarettes." Lancet* 1(7220): 110.

No abstract available.

Mangold, J. E., T. J. Payne, et al. (2008). "Bitter taste receptor gene polymorphisms are an important factor in the development of nicotine dependence in African Americans." J Med Genet* 45(9): 578-582.

Bitter sensitivity varies among individuals and ethnic groups partly due to polymorphisms in taste receptor genes (TAS2Rs). Although previous psychophysical studies suggest that taste status plays a role in nicotine dependence (ND), genetic evidence is lacking. The objectives of the study are to determine whether single nucleotide polymorphisms (SNPs) in TAS2R16 and TAS2R38 are associated with ND and if the effects differ by sex and ethnicity. During 1999-2004, 2037 individuals from 602 nuclear families of African American (AA) or European American (EA) origin were recruited from the US mid-south states. ND was assessed by three measures: indexed Smoking Quantity (SQ), Heaviness of Smoking Index (HSI), and the Fagerstrom Test for Nicotine Dependence (FTND). Peripheral blood samples were obtained for DNA extraction and genotyping. The results indicated that the TAS2R38 taster haplotype PAV was inversely associated (p= 0.0165), and the non-taster haplotype AVI was positively associated (p= 0.0120), with SQ in AA smokers. The non-taster haplotype was positively associated with all ND measures in AA female smokers (p= 0.01,0.003). No significant associations were observed in the EA sample. It was concluded that TAS2R38 polymorphisms are an important factor in determining ND in AAs. Heightened oral sensitivity confers protection against ND. Conversely, decreased sensitivity represents a risk factor for ND, especially in AA females. Together, our findings suggest that taster status plays a role in governing the development of ND and may represent a way to identify individuals at risk for developing ND, particularly in AA smokers.

McCarthy, W. J., N. H. Caskey, et al. (1992). "Ethnic differences in nicotine exposure." Am J Public Health 82(8): 1171-1173.

No abstract available.

Miller, G. E., M. E. Jarvik, et al. (1994). "Cigarette mentholation increases smokers' exhaled carbon monoxide levels." Exp Clin Psychopharm 2(2): 154-160.

Male smokers (N = 12) participated in 3 controlled-dose smoking sessions spaced 1 week apart. In each session, Ss inhaled 1, 200 cc of cigarette smoke. Menthol dosage varied across sessions, such that Ss smoked experimental cigarettes that had been injected with 0 mg, 4 mg, or 8 mg of menthol. Exhaled carbon monoxide levels increased concomitantly with menthol dosage. There were no differences in smoking topography across the 3 conditions. The ability of menthol to increase the toxicity of cigarette smoke by raising carbon monoxide levels is discussed. Results suggest that menthol cigarette preference may account for some of the racial differences in smoking behavior and smoking-related outcomes found in past literature.

Muscat, J. E., G. Chen, et al. (2009). "Effects of menthol on tobacco smoke exposure, nicotine dependence, and NNAL Glucuronidation." Cancer Epidemiol Biomarkers Prev 18(1): 35-41.

Menthol is a controversial cigarette additive because its physiologic or pharmacologic effects may possibly increase the risk for cancer and its targeted market is the Black community. In a community-based cross-sectional study on 525 Black and White volunteers, we compared levels of urinary and plasma cotinine, plasma thiocyanate, urinary 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL), and its detoxified form (NNAL-Gluc) between menthol and nonmenthol smokers. In regression models that adjusted for daily cigarette intake, no significant differences were observed in the concentration of these biomarkers by menthol status in both races. There was no significant association between high Fagerstrom nicotine dependence scores and the use of menthol cigarettes (odds ratio, 1.1; 95% confidence interval, 0.6-2.0), but an increased risk was observed with smoking a cigarette soon (</=30 minutes) after waking (odds ratio, 2.1; 95% confidence interval, 1.0-3.8). The ratio of NNAL-Gluc to NNAL, a possible indicator of lung cancer risk, was significantly lower in menthol versus nonmenthol smokers. The NNAL-Gluc/NNAL ratio was 34% lower in Whites ($P < 0.01$) and 22% lower in Blacks. In subsequent human liver microsome studies, menthol inhibited the rate of NNAL-O-glucuronidation and NNAL-N-glucuronidation. Collectively, these results show that menthol does not affect biological exposure to tobacco smoke constituents but indicates that menthol might inhibit the detoxification of the potent lung carcinogen NNAL. (Cancer Epidemiol Biomarkers Prev 2009;18(1):35-41).

Mustonen, T. K., S. M. Spencer, et al. (2005). "The influence of gender, race, and menthol content on tobacco exposure measures." Nicotine Tob Res 7(4): 581-90.

Research has suggested that race, gender, and menthol cigarette use influence tobacco-smoke exposure measures and smoking-related disease risk. For example, a high proportion of Black smokers prefer menthol cigarettes and, despite smoking fewer cigarettes per day (CPD) than do Whites, tend to have higher cotinine levels. Additionally, Black males are more at risk for smoking-related lung cancer. High cotinine levels and smoking menthol cigarettes may lead to higher toxin intake, which contributes to increased disease risk.

We explored the relationship between tobacco exposure variables (i.e., cotinine, CPD, carbon monoxide [CO], nicotine content, and nicotine dependence) with respect to race, gender, and menthol content in a sample of 307 smokers recruited from the greater Boston area to participate in a smoking cessation treatment trial. The pattern of correlations between tobacco exposure measures and cotinine showed a consistently positive correlation between cotinine and CO in all smokers and a correlation between cotinine and CPD in those who smoked nonmenthol cigarettes. Cotinine and CPD correlations varied by gender and race among menthol cigarette smokers. Consistently, we found a significant gender x race x menthol interaction on salivary cotinine level as well as cotinine/CPD ratio. These findings suggest that the relationship between number of cigarettes consumed and salivary cotinine is more complex than previously believed. It is not sufficient to look at race alone; researchers and clinicians need to look at race and gender concurrently, as well as type of cigarette consumed.

Okuyemi, K. S., J. N. Powell, et al. (2006). "Enhanced cue-elicited brain activation in African American compared with Caucasian smokers: an fMRI study." Addict Biol 11(1): 97-106.

Current evidence indicates that, although African Americans (AA) are more likely to attempt to quit smoking than Caucasians (CC) in any given year, success rates are lower for AA. However, factors contributing to these differences are not well known. In order to explore potential factors, this study assessed differences in attention to smoking cues between ethnic groups. Participants underwent morning functional magnetic resonance imaging scanning while viewing images of AA models and CC models who were either smoking (smoking cues) or engaging in everyday activities (neutral cues), interspersed with a fixation baseline period. The study was conducted at the Hoglund Brain Imaging Center of the University of Kansas Medical Center in Kansas City, KS. We studied 17 smokers (eight AA, nine CC) after 12-hour abstinence and 17 non-smokers (eight AA, nine CC) matched by age, gender, years of education, and handedness. The AA and CC smoking groups were also matched for number of cigarettes smoked per day. All results are $P < 0.01$, corrected for whole brain. There was a strong ethnicity by condition interaction among smokers in several a priori regions of interest. AA smokers showed a greater increase in response to smoking (versus neutral cues) than CC smokers in the medial prefrontal cortex, right lateral orbitofrontal cortex, and bilateral ventrolateral prefrontal cortex. In smoking versus baseline contrasts, additional areas of greater activation were found in AA, including the right amygdala and left caudate nucleus. No significant differences in cue-elicited brain activation were found between AA and CC non-smokers. These preliminary findings demonstrate variation in brain activation in response to smoking cues between AA and CC smokers in structures known to be associated with nicotine addiction. Differences in neural response may reflect fundamental differences in attention to smoking cues, which may in turn contribute to differences in effectiveness of nicotine dependence treatments among ethnic populations.

Perez-Stable, E. J., B. Herrera, et al. (1998). "Nicotine metabolism and intake in black and white smokers." J Am Med Assoc 280(2): 152-6.

Racial differences in tobacco-related diseases are not fully explained by cigarette-smoking behavior. Despite smoking fewer cigarettes per day, blacks have higher levels of serum cotinine, the proximate metabolite of nicotine. To compare the rates of metabolism and the daily intake of nicotine in black smokers and white smokers, participants received simultaneous infusions of deuterium-labeled nicotine and cotinine. Urine was collected for determination of total clearance of nicotine and cotinine, fractional conversion of nicotine to cotinine, and cotinine elimination rate. Using cotinine levels during ad libitum smoking and clearance data, the daily intake of nicotine from smoking was estimated. A total of 40 black and 39 white smokers, average consumption of 14 and 14.7 cigarettes per day, respectively, of similar age (mean, 32.5 and 32.3 years, respectively) and body weight (mean, 73.3 and 68.8 kg, respectively) participated in the study, which took place in a metabolic ward of a university-affiliated public hospital. Clearance (renal and nonrenal), half-life, and volume of distribution of nicotine and cotinine and the calculated daily intake of nicotine were measured. The total and nonrenal clearances of nicotine were not significantly different, respectively, in blacks (17.7 and 17.2 mL x min(-1) x kg(-1)) compared with whites (19.6 and 18.9 mL x min(-1) x kg(-1)) (P=.11 and .20). However, the total and nonrenal clearances of cotinine were significantly lower, respectively, in blacks (0.56 and 0.47 mL x min(-1) x kg(-1)) than in whites (0.68 vs 0.61 mL x min(-1) x kg(-1); P=.009 for each comparison). The nicotine intake per cigarette was 30% greater in blacks compared with whites (1.41 vs 1.09 mg per cigarette, respectively; P=.02). Volume of distribution did not differ for the 2 groups, but cotinine half-life was higher in blacks than in whites (1064 vs 950 minutes, respectively; P = .07). Higher levels of cotinine per cigarette smoked by blacks compared with whites can be explained by both slower clearance of cotinine and higher intake of nicotine per cigarette in blacks. Greater nicotine and, therefore, greater tobacco smoke intake per cigarette could, in part, explain some of the ethnic differences in smoking-related disease risks.

Pickworth, W. B., E. T. Moolchan, et al. (2002). "Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery." Pharmacol Biochem Behav 71(1-2): 55-61.

Many smokers choose menthol-flavored cigarettes, however, the influence of menthol on the effects of smoke-delivered nicotine is unknown. Research and commercial cigarettes, menthol and non-menthol, that delivered a wide range of nicotine were evaluated. Menthol (n=18) and non-menthol (n=18) cigarette smokers participated in a single session during which three cigarettes were smoked 45 min apart, in random order. Federal Trade Commission (FTC) nicotine yields of the three cigarettes were: research, low yield, 0.2 mg, commercial cigarettes (average), 1.2 mg; research, high yield, 2.5 mg. Commercial and high-yield cigarettes increased heart rate (HR) and blood pressure more than low-yield cigarettes; although, no differences in exhaled carbon monoxide (CO) occurred. Participants smoked commercial cigarettes faster and with fewer puffs than either of the research cigarette indicating production differences can affect topography. There was a significant group by cigarette interaction on satisfaction, and relief from cigarette craving. High-yield

non-menthol cigarettes reduced craving and were rated as more satisfying than high-yield menthol cigarettes. No differences between menthol and non-menthol cigarettes on other subjective measures (strength, psychological reward, negative effects) were observed. Our findings indicate that nicotine delivery, but not mentholation, influences cardiovascular and most subjective measures. These results illustrate the importance of threshold levels of nicotine on subjective responses to cigarette smoking.

Rabinoff, M., N. Caskey, et al. (2007). "Pharmacological and chemical effects of cigarette additives." Am J Public Health 97(11): 1981-1991.

We investigated tobacco industry documents and other sources for evidence of possible pharmacological and chemical effects of tobacco additives. Our findings indicated that more than 100 of 599 documented cigarette additives have pharmacological actions that camouflage the odor of environmental tobacco smoke emitted from cigarettes, enhance or maintain nicotine delivery, could increase the addictiveness of cigarettes, and mask symptoms and illnesses associated with smoking behaviors. Whether such uses were specifically intended for these agents is unknown. Our results provide a clear rationale for regulatory control of tobacco additives.

Rose, J. E. and F. M. Behm (1994). "Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms." Drug Alcohol Depend 34(3): 225-9.

Previous studies have suggested that sensory cues associated with cigarette smoking can suppress certain smoking withdrawal symptoms, including craving for cigarettes. In this study we investigated the subjective effects of a cigarette substitute delivering a vapor of black pepper essential oil. Forty-eight cigarette smokers participated in a 3-h session conducted after overnight deprivation from smoking. Subjects were randomly assigned to one of three conditions: one group of smokers puffed on a device that delivered a vapor from essential oil of black pepper; a second group puffed on the device with a mint/menthol cartridge, and a third group used a device containing an empty cartridge. Subjects puffed and inhaled ad libitum from the device throughout the session during which no smoking was allowed. Reported craving for cigarettes was significantly reduced in the pepper condition relative to each of the two control conditions. In addition, negative affect and somatic symptoms of anxiety were alleviated in the pepper condition relative to the unflavored placebo. The intensity of sensations in the chest was also significantly higher for the pepper condition. These results support the view that respiratory tract sensations are important in alleviating smoking withdrawal symptoms. Cigarette substitutes delivering pepper constituents may prove useful in smoking cessation treatment.

Sellers, E. M. (1998). "Pharmacogenetics and ethnoracial differences in smoking." J Am Med Assoc 280(2): 179-180.

No abstract available.

Wagenknecht, L. E., G. R. Cutter, et al. (1990). "Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults study." Am J Public Health 80(9): 1053-6.

Cotinine was measured in the serum of nearly all 5,115 18-30 year old, Black and White, men and women participating in the Coronary Artery Risk Development in (Young) Adults Study, 30 percent of whom reported current cigarette smoking. Ninety-five percent of the reported smokers had serum cotinine levels indicative of smoking (greater than 13 ng/ml). The median cotinine level was higher in Black than White smokers (221 ng/ml versus 170 ng/ml; 95 percent CI for difference: 34, 65) in spite of the fact that estimated daily nicotine exposure and serum thiocyanate were higher in Whites. The difference persisted after controlling for number of cigarettes, nicotine content, frequency of inhalation, weekly sidestream smoke exposure, age, gender, and education. A reporting bias and nicotine intake were ruled out as explanations for the racial difference suggesting that the metabolism of nicotine or the excretion of cotinine may differ by race. Racial differences in cotinine levels may provide clues to the reasons for the observed lower cessation rates and higher rates of some smoking-related cancers in Blacks.

World Health Organization (2007). Contents and design features of tobacco products: Their relationship to dependence potential and consumer appeal. WHO - Tech Rep Series 945: 7-23.

No abstract available.

Nicotine Metabolism and Addiction in Youth

Collins, C. C. and E. T. Moolchan (2006). "Shorter time to first cigarette of the day in menthol adolescent cigarette smokers." Addict Behav 31(8): 1460-4.

Menthol smoking is thought to contribute to the addictiveness of smoking. Given the high prevalence of menthol smoking among youth, the aim of the current analysis was to examine differences in consumption and tobacco dependence, including smoking urgency among menthol and non-menthol adolescent smokers. Data for the current analysis were collected from telephone interviews with adolescent smokers applying to a cessation treatment study. Of 572 adolescent smokers (mean age=15.6+/-1.6 years; 55.1% female; 46.9% African American, 48.2% European American), 531 smoked menthol cigarettes and 41 smoked non-menthol as their usual brand. Analysis using Fisher's Exact (one-tailed) Test revealed that menthol smokers had a significantly shorter time to first (TTF) cigarette of the day compared to non-menthol smokers (smoking within the first 5 min of the day, 45% vs. 29%, respectively; p<0.04). Independent t tests revealed no significant difference in number of cigarettes per day (CPD) (mean=12.2+/-8.5 vs. 11.4+/-8.8; p<0.28) or Fagerstrom Test for Nicotine Dependence (FTND) scores (3.4+/-1.4 vs. 3.2+/-1.3; p<0.23). While preliminary, our findings suggest greater smoking urgency among menthol compared to non-menthol adolescent cessation-treatment seekers. Further study in a broader sample of adolescent smokers is warranted to elucidate the mechanisms underlying the effects of menthol smoking for youths.

DiFranza, J. R., J. A. Savageau, et al. (2004). "Recollections and repercussions of the first inhaled cigarette." Addict Behav 29(2): 261-72.

It has not been determined if a youth's reaction to the first smoking experience is predictive of future nicotine dependence, or whether the impact of the first cigarette can be altered by manipulating levels of tar, nicotine and menthol. The objective of this study was to determine if the recalled response to the first cigarette is predictive of the development of symptoms of nicotine dependence and whether it is influenced by the type of cigarette smoked. A retrospective/prospective longitudinal study of the natural history of nicotine dependence employing individual interviews was conducted three times annually in two urban school systems over 3 years. A cohort of 237 subjects who had inhaled on a cigarette were asked to recall their first smoking experience. Main outcome measures included the symptoms associated with smoking; the Hooked on Nicotine Checklist of 10 symptoms of dependence. The results indicated that reactions to the initial smoking experience were

unrelated to gender or cigarette brand, strength or mentholation. Relaxation in response to the first inhalation was the strongest predictor of symptoms of nicotine dependence. Dizziness and nausea were also independent predictors of dependence symptoms. The data suggest that increased sensitivity to nicotine as manifested by relaxation, dizziness, or nausea in response to the first exposure to nicotine represents a risk factor for the development of nicotine dependence.

Hersey, J. C., S. W. Ng, et al. (2006). "Are menthol cigarettes a starter product for youth?" Nicotine Tob Res 8(3): 403-13.

This study assessed the relationship between menthol use and nicotine dependence. Data from the National Youth Tobacco Survey indicated that menthol cigarette use was significantly more common among newer, younger smokers. Additionally, youth who smoked menthol cigarettes had significantly higher scores on a scale of nicotine dependence compared with nonmenthol smokers, controlling for demographic background and the length, frequency, and level of smoking. The study suggests that menthol cigarettes are a starter product that may be associated with smoking uptake by youth.

Moolchan, E. T., F. H. Franken, et al. (2006). "Adolescent nicotine metabolism: ethnoracial differences among dependent smokers." Ethn Dis 16(1): 239-43.

Variations in nicotine metabolism are thought to contribute to differences in cigarette consumption between African Americans and Caucasian adult smokers. To investigate the potential mechanism of previously documented lower smoking rates among African-American adolescent smokers seeking cessation treatment, we measured nicotine metabolite ratios as markers of the metabolic disposition of nicotine, which is generally considered to be under the influence of cytochrome P450 (CYP) 2A6. Plasma ratios of trans-3'-hydroxycotinine (3HC) to cotinine (COT) were examined in 92 cessation treatment-seeking adolescents (mean age 15.2 years, standard deviation [SD] 1.3, 69% female, 31% African American, mean Fagerstrom Test for Nicotine Dependence [FTND] 6.5, SD 1.6, mean years smoked 2.6, SD 1.6). Groups were similar in age, gender distribution, and mean FTND score. Analysis with independent t tests revealed significantly lower number of cigarettes per day (CPD) (15.1, SD 7.6 vs 19.6, SD 8.0, P=.013) and nicotine metabolite ratios (0.27, SD 0.15 vs 0.35, SD 0.16, P=.026) in African-American compared to Caucasian adolescent smokers. Consistent with metabolic variation, mean COT/CPD ratio was significantly higher in African-American compared to Caucasian adolescents. Results remained statistically significant when comparing menthol smokers by ethnicity. These findings are consistent with those found among adult smokers and provide a putative mechanism for reported ethnoracial differences in adolescent cigarette consumption. Our results underscore the need for measures independent of consumption for determining degree of nicotine dependence and treatment selection across ethnicities, even among youths.

Wackowski, O. and C. D. Delnevo (2007). "Menthol cigarettes and indicators of tobacco dependence among adolescents." Addict Behav 32(9): 1964-9.

This study examines measures of nicotine dependence among adolescent menthol and non-menthol cigarette smokers in a nationally representative sample. We examined rates of menthol smoking and measures of nicotine dependence among 1345 current established smokers in grades 9-12 who participated in the 2004 National Youth Tobacco Survey. Logistic regression was used to generate an adjusted odds ratio (OR) for menthol smoking for four measures of nicotine dependence, controlling for demographic characteristics and smoking patterns. The results indicated that approximately 46% of all current established cigarette smokers were menthol smokers. Menthol smokers had 2.6 and 1.6 greater odds than non-menthol smokers for reporting that they could go for less than 1 h before feeling like they need a cigarette and that they experience cravings after not smoking for a while, respectively. It was concluded that menthol cigarette smoking was associated with two dependence measures and may be more addictive than regular cigarettes in young smokers. Future research should continue to explore relationships between dependency and menthol use as well as the high prevalence of menthol use among adolescents.

Smoking Topography

Ahijevych, K., J. Gillespie, et al. (1996). "Menthol and nonmenthol cigarettes and smoke exposure in black and white women." Pharmacol Biochem Behav 53(2): 355-60.

Purposes of this investigation were to compare smoke constituent exposure (CO and nicotine boosts) and smoking topography parameters between black and white women, and between women regularly using menthol or nonmenthol cigarettes. A two-factor factorial design with a sample of 37 women stratified by race and menthol or nonmenthol cigarette use was implemented. There were significant main and interaction effects of race and menthol/nonmenthol use on CO boost. Black women had a mean CO boost of 10.1 ppm vs. 7.2 ppm for white women, while women using nonmenthol cigarettes had a higher CO boost (mean = 10.6 ppm) compared to those regularly using menthol cigarettes mean = 6.5 ppm). White menthol smokers had the lowest CO boost of all subgroups. There was a trend for black women to have higher nicotine boost than white women (21.4 ng/ml vs. 15.9 ng/ml). Black women had nonsignificantly higher puff volumes compared to white women (mean = 48.4 vs. 43.5 ml), while nonmenthol smokers had nonsignificantly higher puff volumes than menthol smokers (mean = 48.5 vs. 42.7 ml). Lower CO boost with mentholated cigarettes suggests factors beyond mentholation may affect elevated smoke constituent exposure among black women.

Ahijevych, K. and L. A. Parsley (1999). "Smoke constituent exposure and stage of change in black and white women cigarette smokers." Addict Behav 24(1): 115-20.

Differences in smoke constituent exposure by ethnicity and menthol preference and differences in decisional balance and habit strength by stage of change, ethnicity, and menthol preference were examined in this 2-factor study design. Ninety-five women, half of whom were Black and half of who smoked menthol cigarettes, participated in a cigarette smoking bout in the Clinical Research Center. Measures of smoking topography, plasma cotinine and nicotine, and expired carbon monoxide were obtained in addition to self-report of the pros and cons of smoking, time to first cigarette, and smoking history. Black women smoked significantly fewer cigarettes per day, but had higher cotinine levels compared to White women. Menthol smokers (n = 49) had significantly larger puff volumes, higher cotinine levels, and shorter time to first cigarette compared to nonmenthol smokers (n = 46). Precontemplators (n = 44) were significantly lower on beliefs about the negative aspects of smoking compared to contemplators and those in preparation stage. Black women, all stages combined, had higher negative beliefs about smoking than did White women. Implications for assessment of smoking patterns and intervention are discussed.

Caskey, N. H., M. E. Jarvik, et al. (1993). "Rapid smoking of menthol and nonmenthol cigarettes by black and white smokers." Pharmacol Biochem Behav 46(2): 259-63.

White subjects took significantly more puffs of cigarette smoke before stopping than did black subjects in a modified, controlled-dose rapid smoking procedure. Paradoxically, however, no racial differences were detected for changes in carbon monoxide levels, or changes in cardiovascular variables (systolic and diastolic blood pressure, and heart rate). Due to the cooling and topical anesthetic properties of menthol, it was hypothesized that menthol and regular cigarette smokers would take more puffs from menthol cigarettes than from regular cigarettes before stopping in the controlled-dose rapid smoking procedure. However, no difference was observed for the number of puffs taken from regular as opposed to menthol cigarettes (cigarette type condition) and no differences were found for Cigarette Preference (regular smokers vs. menthol smokers).

Jarvik, M. E., D. P. Tashkin, et al. (1994). "Mentholated cigarettes decrease puff volume of smoke and increase carbon monoxide absorption." Physiol Behav 56(3): 563-70.

The influence of mentholated vs. regular cigarettes on selected chemical and topographic parameters was measured in 20 smokers in a pulmonary function laboratory. Half the subjects were black and half were white; half were menthol and half regular smokers. All subjects smoked both types of cigarettes, one on each of 2 days. Compared to regular cigarettes, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhemoglobin and end-expired carbon monoxide, despite the fact that mentholated cigarettes decreased average and total cumulative puff volumes and increased mean puff flow rates of inhaled smoke. These chemical and topographic differences were independent of race. No significant differences in depth of inhalation of the smoke or in the amount of insoluble smoke particulates delivered to or retained in the respiratory tract were noted between the two types of cigarettes. Mentholation of cigarettes may decrease volume of smoke inhaled but appears to increase exposure of smokers to toxic effects of carbon monoxide.

McCarthy, W. J., N. H. Caskey, et al. (1995). "Menthol vs nonmenthol cigarettes: effects on smoking behavior." Am J Public Health 85(1): 67-72.

The purpose of this study was to examine intraindividual differences in smoking behavior between smoking regular and mentholated cigarettes. Healthy male smokers (n = 29) smoked either a regular or a mentholated cigarette in two separate sessions 1 week apart. Commercial brands with comparable tar, nicotine, and CO content were used. Smoking behavior was constrained by fixed 15-second interpuff intervals, but puff volume and number of puffs were unconstrained. When smoking the non-mentholated brand of cigarettes, participants smoked 22% more puffs and had 13% higher mean volumes per puff than they did when smoking the mentholated brand of cigarettes. The aggregate 39% excess exposure to cigarette smoke in the regular-cigarette condition was not accompanied by commensurate excesses in expired carbon monoxide or in physiological measures normally correlated with nicotine exposure. These findings parallel differences in physiological correlates of

exposure to nicotine found in cross-sectional comparisons of African-American and White smokers and are consistent with the results of emerging laboratory investigations.

Melikian, A. A., M. V. Djordjevic, et al. (2007). "Effect of delivered dosage of cigarette smoke toxins on the levels of urinary biomarkers of exposure." Cancer Epidemiol Biomarkers Prev 16(7): 1408-15.

Urinary metabolites of tobacco smoke toxins are often used as biomarkers for the evaluation of active and passive exposure to cigarette smoke toxins. In a study of healthy smokers, we investigated concentrations of urinary biomarkers in relation to concentrations of selected toxins in mainstream cigarette smoke as determined by machine smoking of cigarettes in a manner that mimics an individual's smoking behavior (topography). Concentrations of nicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and benzo(a)pyrene, in mainstream smoke determined under human smoking conditions, and their urinary metabolites cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and 1-hydroxypyrene were established for 257 individuals who smoked low-yield (0.1-0.8 mg Federal Trade Commission nicotine/cigarette; mean, 0.66; n = 87), medium-yield (0.9-1.2 mg nicotine/cigarette; mean, 1.1; n = 109), and high-yield cigarettes (nicotine, >1.3 mg nicotine/cigarette; mean, 1.41; n = 61). Levels of urinary metabolites expressed per unit of delivered parent compounds decreased with increased smoke emissions. In smokers of low-, medium-, and high-yield cigarettes, the respective cotinine (ng/mg creatinine)-to-nicotine (mg/d) ratios were 89.4, 77.8, and 57.1 (low versus high; P = 0.06); the 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pmol/mg creatinine)-to-4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (ng/d) ratios were 0.81, 0.55, and 0.57 (low versus high; P = 0.05); and the 1-hydroxypyrene (pg/mg creatinine)-to-benzo(a)pyrene (ng/d) ratios were 1.55, 1.13, and 0.97 (low versus high; P = 0.008). Similarly, means of cotinine per unit of delivered nicotine in smokers who consumed <20 cigarettes per day was 3.5-fold higher than in those who smoked >20 cigarettes per day. Likewise, a negative correlation was observed between cotinine-to-nicotine ratios and delivered doses of nicotine in subgroups of smokers who used the identical brand of cigarette, namely a filter tip-vented Marlboro (r = -0.59), which is a popular brand among Euro-Americans, and Newport (r = -0.37), a menthol-flavored cigarette without filter tip vents that is preferred by African-Americans. Thus, the intensity of the exposures significantly affects the levels of urinary biomarkers of exposure and should be taken into account in the evaluation of human exposure to cigarette smoke toxins.

Moolchan, E. T., D. L. Hudson, et al. (2004). "Heart rate and blood pressure responses to tobacco smoking among African-American adolescents." J Natl Med Assoc 96(6): 767-71.

Ethnic differences in both physiological response to and health consequences of tobacco smoking-some of which have been attributed to ethnic preferences for menthol cigarettes-have been described in the literature. We compared acute physiological responses to smoking in African-American and European-American adolescent menthol cigarette smokers seeking smoking cessation treatment. One-hundred- twenty-eight adolescents (32% African-American, 71% female; mean age 15.16 +/- 1.32 years, mean Fagerstrom Test of

Nicotine Dependence (FTND) score 6.73 +/- 1.53, cigarettes per day (CPD) 16.9 +/- 2.64) participated in an experimental session during which they smoked one menthol cigarette of their usual brand. Blood pressure, heart rate, and exhaled carbon monoxide (CO) concentrations were measured before and after smoking; mean puff volume (mL), puff duration (sec) and maximal puff velocity (mL/sec) during smoking were also determined. Two sample t-tests were performed to assess ethnic differences in smoking topography; analysis of covariance was used to determine whether heart rate and blood pressure after smoking one menthol cigarette varied by ethnicity, after controlling for baseline physiological measures. No significant ethnic differences were observed in either smoking topography or acute cardiovascular response to smoking. These preliminary findings warrant extension to a broader group of nontreatment-seeking adolescent smokers of both ethnicities.

Nil, R. and K. Battig (1989). "Separate effects of cigarette smoke yield and smoke taste on smoking behavior." Psychopharmacology (Berl) 99(1): 54-9.

The purpose of this experiment was to compare independently the influence of different cigarette smoke taste categories and different machine standard smoke yield values on cigarette smoking behavior and related subjective measures. In six separate sessions 15 regular smokers were presented with a medium and a low smoke yield cigarette of each of the three taste categories, mentholated, dark (Gauloises) and blond (Muratti) tobacco. Each session included a "natural" and a "forced" smoking procedure of one cigarette type only. Forced smoking consisted of smoking 30 puffs whereby a new half-length cigarette was presented after every third puff. During the seventh session, habitual brand cigarettes were smoked as a reference. The sessions followed in weekly intervals, and the subjects became familiar with the test cigarettes during the last 5 days preceding each test session. Although general acceptability of the cigarettes, smoking satisfaction and pleasantness of taste were clearly lower for all test cigarettes as opposed to the habitual brand reference cigarettes, these measures remained unaffected by taste or smoke yield of the test cigarettes. Harshness of smoke was higher in the dark tobacco category and generally decreased with the lower smoke yield cigarettes. Independent effects of taste and smoke yield were obtained for total puff volume, inhalation time and CO absorption, suggesting a compensatory intensification of smoking behavior for low yield cigarettes and an independent increase of smoking intensity from mentholated to dark tobacco to blond tobacco. The results suggest therefore that factors which affect cigarette smoke taste have effects on smoking behavior which are separate from those obtained by comparing smoke yields.

Biomarkers, Physiological, and Biological Responses

Ahijevych, K. and B. E. Garrett (2004). "Menthol pharmacology and its potential impact on cigarette smoking behavior." Nicotine Tob Res 6 Suppl 1: S17-28.

Menthol is the only tobacco additive promoted and advertised by the tobacco industry. Although a considerable body of research has examined the effects of menthol when it is administered alone and unburned, the effects of menthol when burned in cigarette smoke are more complex because it is administered in a matrix of more than 4,000 substances. Therefore, it is difficult to isolate potential pharmacological and toxic effects of menthol when it is administered in a smoke mixture. Menthol properties include cooling and local anesthesia, as well as effects on drug absorption and metabolism, bronchodilation and respiration changes, and electrophysiology. Subjective effects of smoothness and less harshness have been identified as reasons for menthol cigarette smoking, but findings have been inconclusive regarding the effect of menthol on carbon monoxide exposure and smoking topography parameters. Gaps in the research literature and future research areas include the following: (a) What is the role of menthol in tobacco reinforcement and addiction? (b) In the absence of nicotine, is menthol reinforcing? (c) Are the pharmacological and physiological effects of menthol mediated by a menthol-specific receptor or some other central nervous system-mediated action? (d) What are the influences of menthol and menthol metabolism on the metabolic activation and detoxification of carcinogens in tobacco smoke? and (e) Do differences exist in cigarette smoking topography in relation to the interaction of ethnicity, gender, and menthol cigarette preference? Answers to these questions will help to elucidate the function of menthol in cigarettes and its impact on smoking behavior.

Ahijevych, K., J. Gillespie, et al. (1996). "Menthol and nonmenthol cigarettes and smoke exposure in black and white women." Pharmacol Biochem Behav 53(2): 355-60.

Purposes of this investigation were to compare smoke constituent exposure (CO and nicotine boosts) and smoking topography parameters between black and white women, and between women regularly using menthol or nonmenthol cigarettes. A two-factor factorial design with a sample of 37 women stratified by race and menthol or nonmenthol cigarette use was implemented. There were significant main and interaction effects of race and menthol/nonmenthol use on CO boost. Black women had a mean CO boost of 10.1 ppm vs. 7.2 ppm for white women, while women using nonmenthol cigarettes had a higher CO boost (mean = 10.6 ppm) compared to those regularly using menthol cigarettes mean = 6.5 ppm). White menthol smokers had the lowest CO boost of all subgroups. There was a trend for

black women to have higher nicotine boost than white women (21.4 ng/ml vs. 15.9 ng/ml). Black women had nonsignificantly higher puff volumes compared to white women (mean = 48.4 vs. 43.5 ml), while nonmenthol smokers had nonsignificantly higher puff volumes than menthol smokers (mean = 48.5 vs. 42.7 ml). Lower CO boost with mentholated cigarettes suggests factors beyond mentholation may affect elevated smoke constituent exposure among black women.

Ahijevych, K. and L. A. Parsley (1999). "Smoke constituent exposure and stage of change in black and white women cigarette smokers." Addict Behav 24(1): 115-20.

Differences in smoke constituent exposure by ethnicity and menthol preference and differences in decisional balance and habit strength by stage of change, ethnicity, and menthol preference were examined in this 2-factor study design. Ninety-five women, half of whom were Black and half of who smoked menthol cigarettes, participated in a cigarette smoking bout in the Clinical Research Center. Measures of smoking topography, plasma cotinine and nicotine, and expired carbon monoxide were obtained in addition to self-report of the pros and cons of smoking, time to first cigarette, and smoking history. Black women smoked significantly fewer cigarettes per day, but had higher cotinine levels compared to White women. Menthol smokers (n = 49) had significantly larger puff volumes, higher cotinine levels, and shorter time to first cigarette compared to nonmenthol smokers (n = 46). Precontemplators (n = 44) were significantly lower on beliefs about the negative aspects of smoking compared to contemplators and those in preparation stage. Black women, all stages combined, had higher negative beliefs about smoking than did White women. Implications for assessment of smoking patterns and intervention are discussed.

Ahijevych, K. L., R. F. Tyndale, et al. (2002). "Factors influencing cotinine half-life during smoking abstinence in African American and Caucasian women." Nicotine Tob Res 4(4): 423-31.

Cotinine, the proximate metabolite of nicotine, has been identified as an indicator of smoke constituent exposure. Higher cotinine levels in African American cigarette smokers have been identified. Because African Americans experience disproportionate smoking-related morbidity and mortality, it is important to examine potential factors influencing these higher levels of cotinine. The current study examined selected factors of ethnicity, menthol cigarette preference, body composition and alcohol-use history on cotinine half-life in 6 days of smoking abstinence in African American and Caucasian women. A 7-day inpatient protocol was conducted in the General Clinical Research Center, in which day 1 was ad lib smoking and days 2-7 were smoking abstinence (n = 32). Plasma cotinine was measured every 8 h throughout. Average cotinine half-life was 21.3 h, similar to previously reported 18-20 h. Three women exhibited >14 ng/ml cotinine after 136 h of smoking abstinence. Host factors explaining 52.0% of variance in cotinine half-life and associated with longer half-life were being an African American menthol smoker, fewer years of alcohol use and greater lean body mass. Among menthol smokers, baseline cotinine level and cotinine half-life were not significantly different in Caucasian and African American women. Intraindividual cotinine half-life variation and CYP2A6 genotype were examined in substudies.

To improve accuracy in correctly classifying non-smokers with cotinine levels, a period of at least 7 days of smoking abstinence may be warranted.

Caskey, N. H., M. E. Jarvik, et al. (1993). "Rapid smoking of menthol and nonmenthol cigarettes by black and white smokers." Pharmacol Biochem Behav 46(2): 259-63.

White subjects took significantly more puffs of cigarette smoke before stopping than did black subjects in a modified, controlled-dose rapid smoking procedure. Paradoxically, however, no racial differences were detected for changes in carbon monoxide levels, or changes in cardiovascular variables (systolic and diastolic blood pressure, and heart rate). Due to the cooling and topical anesthetic properties of menthol, it was hypothesized that menthol and regular cigarette smokers would take more puffs from menthol cigarettes than from regular cigarettes before stopping in the controlled-dose rapid smoking procedure. However, no difference was observed for the number of puffs taken from regular as opposed to menthol cigarettes (cigarette type condition) and no differences were found for Cigarette Preference (regular smokers vs. menthol smokers).

Castro, F. G. (2004). "Physiological, psychological, social, and cultural influences on the use of menthol cigarettes among Blacks and Hispanics." Nicotine Tob Res 6 Suppl 1: S29-41.

Patterns of menthol cigarette consumption among Blacks and Hispanics are likely a product of the interactive effects of several factors: the physiological and pharmacological sensory effects of menthol, the "cool" psychological identity of being menthol smokers, the promotional marketing of menthol cigarettes, and the cultural effects of health-related beliefs and subjective culture norms. This article presents two conceptual frameworks—a moderation logic model and a mediation logic model--for organizing the disparate literature on factors affecting the consumption of menthol cigarettes among Blacks and Hispanics. Three factor domains are examined as direct effect predictors of menthol cigarette smoking: (a) physiological and pharmacological, (b) psychological, and (c) social and environmental. In addition, a fourth domain of cultural variables is presented as a class of moderator or mediator variables that can interact with these physiological, psychological, and social factors as determinants of menthol cigarette use. These cultural variables are examined as mediating or moderating factors that influence the use of menthol cigarettes by Black and Hispanic consumers. Recommendations are offered for future research to further understand the influence of cultural and other factors as determinants of menthol cigarette smoking among Blacks and Hispanics.

Clark, P. I., G. Caldito, et al. (1994). "Elevated serum cotinine in Black-and-White menthol cigarette smokers." Circulation* 90(4): II-II.

No abstract available.

Clark, P. I., S. Gautam, et al. (1996). "Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers." Chest 110(5): 1194-8.

Black smokers have been reported to have higher serum cotinine levels than do white smokers, and have higher rates of most smoking-related diseases, despite smoking fewer cigarettes per day. Another striking racial difference is the preference for mentholated cigarettes among black smokers. The contribution of menthol to variability in biochemical markers of cigarette smoke exposure (end-expiratory carbon monoxide and serum cotinine) was evaluated in a biracial sample. A descriptive cross-sectional study in a university smoking research laboratory was conducted on 65 black and 96 white adult established smokers who were paid for their participation. Information was obtained through direct observation, self-report (interview and self-administered questionnaires), measurement of butts collected for a week, and laboratory analyses of the biochemical markers of exposure. Compared with the white smokers, the black smokers had significantly higher cotinine and carbon monoxide levels per cigarette smoked and per millimeter of smoked tobacco rod (both $p < 0.001$). After adjusting for race, cigarettes per day, and mean amount of each cigarette smoked, menthol was associated with higher cotinine levels ($p = 0.03$) and carbon monoxide concentrations ($p = 0.02$).It was concluded that the use of menthol may be associated with increased health risks of smoking. Menthol use should be considered when biochemical markers of smoke exposure are used as quantitative measures of smoking intensity or as indicators of compliance with smoking reduction programs. In addition, the effect of menthol on total "dose" should be considered in any efforts to regulate the amount of nicotine in cigarettes.

Dessirier, J. M., M. O'Mahony, et al. (2001). "Oral irritant properties of menthol: sensitizing and desensitizing effects of repeated application and cross-desensitization to nicotine." Physiol Behav 73(1-2): 25-36.

The irritant properties of menthol and its interactions with nicotine were investigated psychophysically in human subjects. In the first experiment, 0.3% L-menthol was applied successively to one side of the tongue 10 times at a 1-min interval (30-s interstimulus interval, ISI), and subjects rated the intensity of the perceived irritation. The intensity of irritation progressively decreased across trials, consistent with desensitization. To test for cross-desensitization of nicotine-evoked irritation by menthol, nicotine (0.6%) was applied to both sides of the tongue simultaneously, 5 min after the conclusion of menthol application. Using both a two-alternative forced choice (2-AFC) paradigm, and also by obtaining independent ratings of the irritant intensity on each side of the tongue, it was found that nicotine-evoked irritation was significantly weaker on the menthol-pretreated side. To control for a possible confounding effect of cooling, nicotine was applied bilaterally only after the cooling sensation of menthol had subsided. Nicotine-induced irritation was still significantly weaker on the menthol-pretreated side, consistent with cross-desensitization of nicotine-evoked irritation by menthol. In a final experiment, menthol was repeatedly applied to one side of the tongue at a shorter (20 s) interval (5-s ISI), and elicited a rapid increase in irritant sensation over the initial trials, consistent with sensitization, followed in subsequent trials by a progressive reduction in irritation (desensitization). After a 5-min rest period, self-desensitization was confirmed. Repeated application of menthol at the same

short ISI was then resumed, and resulted in a significant mean increase in irritant intensity consistent with stimulus-induced recovery (SIR).

Duner-Engstrom, M., O. Larsson, et al. (1986). "Effect of nicotine chewing gum on salivary secretion." Swed Dent J 10(3): 93-6.

The effect of nicotine, placebo for nicotine or menthol-tasting chewing gums on salivation was studied in 25 healthy volunteers. The chewing of a commercial nicotine containing (2 mg) chewing gum (Nicorette) did not give a larger rate of salivation than did the chewing of a placebo chewing gum. For both types of chewing gums the rate of salivation was highest during the initial 5 min and it decreased thereafter. Menthol-tasting chewing gum gave a significantly higher amount of stimulated saliva. It is concluded that the addition of nicotine to a chewing gum does not provide an additional stimulus for salivation.

Ferris Wayne, G. and G. N. Connolly (2004). "Application, function, and effects of menthol in cigarettes: a survey of tobacco industry documents." Nicotine Tob Res 6 Suppl 1: S43-54.

Menthol cigarettes are the only cigarette market category identified by use of a flavor additive and constitute more than a quarter of the overall market. Menthol also is used at reduced levels in many nonmenthol brands. Public health research has suggested patterns of use of mentholated brands as a potential explanation for the health disparities between Black (largely menthol) and White (largely nonmenthol) smokers and has explored the effects of menthol on smoker behavior, consumption patterns, and consequent delivery of smoke constituents. However, relatively few published studies have directly examined the physiological impact and function of menthol delivery in cigarettes. In this study, we review internal tobacco industry documents to assess industry research on function and effects of menthol in cigarettes. Industry documents describe a range of physiological effects of menthol, with important implications for use and consumption patterns. These effects include altered perception of tobacco smoke and its constituents via cooling, smoothing, and anesthetic effects; increased impact through stimulation of trigeminal receptors; interaction with nicotine controlling its perception, delivery, and uptake; and increased respiratory irritation and toxic effects. Further studies are needed to evaluate these findings. We conclude that the unique differences between menthol cigarettes and nonmenthol cigarettes must be considered in research, cessation treatment, and enactment of tobacco product regulations.

Gan, W. Q., S. B. Cohen, et al. (2008). "Sex-related differences in serum cotinine concentrations in daily cigarette smokers." Nicotine Tob Res 10(8): 1293-300.

Self-reported use of cigarettes generally underestimates the true cigarette exposure of smokers. Serum cotinine is considered the best biomarker to evaluate tobacco exposure. This study determined whether or not there were any significant differences in serum cotinine concentrations between men and women when they reported smoking the same number of cigarettes per day. We analyzed cotinine and tobacco consumption data on 680 women and 840 men, aged 20 years or older, who smoked at least 100 cigarettes during their lifetime and were still actively smoking at the time of the National Health and

Nutrition Examination Surveys (1999-2002). Overall, compared with men, women reported smoking fewer cigarettes per day (16.1 vs. 18.7, p<.001) and had lower serum cotinine concentrations (1163.3 nmol/L vs. 1343.9 nmol/L, p<.001). Women were more likely than men to smoke filtered (p = .018) and mentholated (p<.001) cigarettes. After adjustment for the number of cigarettes smoked per day, age, race, body mass index, poverty status, the use of either menthol or regular cigarettes, and the nicotine content in cigarettes, female compared with male smokers had lower serum cotinine concentrations (difference of 117.6 nmol/L; 95% CI = 42.6-192.6, p = .003). The difference was particularly notable in moderate to heavy smokers (i.e., those who smoked more than 15 cigarettes/day). These findings indicate that significant sex-related differences exist in serum cotinine levels among smokers, which suggests that self-reports may overestimate cigarette exposure in women compared with men.

Gardner, M. J., T. L. McCarthy, et al. (1984). "Relationship of serum thiocyanate concentrations to smoking characteristics." J Toxicol Environ Health 14(2-3): 393-406.

Thiocyanate (SCN) concentrations were determined in serum samples from 130 young healthy persons (60 smokers) and related to their smoking and physiologic characteristics. Serum thiocyanate correlated strongly and approximately equally with the number of cigarettes/d X kg of ideal body weight (IBW) (r = 0.748), total nicotine intake in mg/d X kg IBW (r = 0.735), and total tar intake in mg/d X kg IBW (r = 0.731). Multiple linear regression analysis that included these factors as well as sex, marijuana use, menthol, and degree of inhalation only increased the multiple r to 0.803. A more sensitive statistical method (NYBAID) was also used to determine the most significant influences of these variables on serum SCN. The association with depth of inhalation (i.e., smoking versus nonsmoking) was dominant among the relationships considered. The highest SCN levels were exhibited in heavy nicotine users (8.58 +/- 3.00 mg/l), while average users had slightly lower concentrations (6.49 +/- 2.37 mg/l) (p less than 0.03). In nontobacco smokers, those who smoked marijuana several times weekly had higher SCN levels (4.66 +/- 2.16 mg/l) than noncannabis users (2.38 +/- 1.38 mg/l) (p less than 0.03). These studies confirm the utility of serum SCN as an index of smoking rate and demonstrate the role of secondary variables in accounting for the chemical in serum.

Garten, S. and R. V. Falkner (2004). "Role of mentholated cigarettes in increased nicotine dependence and greater risk of tobacco-attributable disease." Prev Med 38(6): 793-8.

Cold air stimulates upper airway cold receptors causing a reflex depressive effect on respiratory activity. Menthol in low concentrations can also stimulate these same cold receptors causing a depressive effect on respiratory activity. Menthol cigarettes when smoked, deliver enough menthol to stimulate cold receptors resulting in the smoker experiencing a "cool sensation." The "cool sensation" experienced by the menthol smoker can result in a reflex-depressive effect on respiratory activity. Literature searches of the NLM databases (e.g., MEDLINE from 1966, TOXLINE, OLDMEDLINE (1985-1965), CANCERLIT, plus tobacco industry documents and hardcopy indices were conducted and the evidence was evaluated with application to mentholated cigarette smoking. A logical progression develops the framework to prove that menthol found in mentholated cigarettes may cause

respiratory depression resulting in greater exposure to the toxic substances found in tobacco smoke. As a result of breath holding that results from the stimulation of cold receptors there is a greater opportunity for exposure and transfer of the contents of the lungs to the pulmonary circulation. For the menthol smoker this results in a greater exposure to nicotine and the particulate matter (tar) of the smoked cigarette. This exposure can result in increased nicotine dependence and greater chance of tobacco-attributable disease.

Heck, J. D. (2009). "Smokers of menthol and nonmenthol cigarettes exhibit similar levels of biomarkers of smoke exposure." Cancer Epidemiol Biomarkers Prev 18(2): 622-9.

There has been speculation that the addition of menthol to cigarettes may affect the manner in which cigarettes are smoked, potentially influencing smokers' exposures to smoke constituents that have been associated with smoking-related diseases. One hundred twelve male and female smokers participated in a parallel-arm study to determine whether the ad libitum smoking of menthol cigarettes results in differences in smoke constituent exposure biomarkers in blood and urine relative to those smoking nonmenthol cigarettes having similar machine-measured (Federal Trade Commission) yields of approximately 9 to 10 mg "tar." The study subjects were provided cigarettes of their preferred menthol or nonmenthol types prior to two 24-hour study intervals spaced one week apart. Carboxyhemoglobin levels were measured in blood samples drawn at midafternoon following the two 24-hour urine collection periods. Six urinary nicotine metabolites (nicotine, cotinine, trans-3'-hydroxycotinine and respective glucuronides) were determined as measures of nicotine intake, and urinary 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide were determined to assess exposure to the tobacco-specific nitrosamine 4-(N-nitrosomethylamino)-1-(3-pyridinyl)-1-butanone. Subjects' median blood carboxyhemoglobin values did not differ significantly between the cigarette types. Neither total urinary NNAL nor urinary nicotine equivalents exhibited statistically significant differences between the menthol and nonmenthol cigarette smokers. The present findings indicate that moderately heavy smokers of menthol and nonmenthol cigarettes of similar machine-generated smoke yield exhibit essentially identical levels of biomarkers of smoke constituent exposure. These results are consistent with the substantial majority of epidemiology studies to date that suggest the risks attending the smoking of menthol and nonmenthol cigarettes are similar.

Jarvik, M. E., D. P. Tashkin, et al. (1994). "Mentholated cigarettes decrease puff volume of smoke and increase carbon monoxide absorption." Physiol Behav 56(3): 563-70.

The influence of mentholated vs. regular cigarettes on selected chemical and topographic parameters was measured in 20 smokers in a pulmonary function laboratory. Half the subjects were black and half were white; half were menthol and half regular smokers. All subjects smoked both types of cigarettes, one on each of 2 days. Compared to regular cigarettes, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhemoglobin and end-expired carbon monoxide, despite the fact that mentholated cigarettes decreased average and total cumulative puff volumes and increased mean puff flow rates of inhaled smoke. These chemical and topographic differences were independent of race. No significant differences in depth of inhalation of

the smoke or in the amount of insoluble smoke particulates delivered to or retained in the respiratory tract were noted between the two types of cigarettes. Mentholation of cigarettes may decrease volume of smoke inhaled but appears to increase exposure of smokers to toxic effects of carbon monoxide.

McCarthy, W. J., N. H. Caskey, et al. (1995). "Menthol vs nonmenthol cigarettes: effects on smoking behavior." Am J Public Health 85(1): 67-72.

The purpose of this study was to examine intraindividual differences in smoking behavior between smoking regular and mentholated cigarettes. Healthy male smokers (n = 29) smoked either a regular or a mentholated cigarette in two separate sessions 1 week apart. Commercial brands with comparable tar, nicotine, and CO content were used. Smoking behavior was constrained by fixed 15-second interpuff intervals, but puff volume and number of puffs were unconstrained. When smoking the non-mentholated brand of cigarettes, participants smoked 22% more puffs and had 13% higher mean volumes per puff than they did when smoking the mentholated brand of cigarettes. The aggregate 39% excess exposure to cigarette smoke in the regular-cigarette condition was not accompanied by commensurate excesses in expired carbon monoxide or in physiological measures normally correlated with nicotine exposure. These findings parallel differences in physiological correlates of exposure to nicotine found in cross-sectional comparisons of African-American and White smokers and are consistent with the results of emerging laboratory investigations.

McClernon, F. J., E. C. Westman, et al. (2007). "The effects of foods, beverages, and other factors on cigarette palatability." Nicotine Tob Res 9(4): 505-10.

While smokers commonly report that various foods and beverages worsen or enhance the taste of cigarettes, the prevalence and diversity of these phenomena have not been studied. We administered an open-ended questionnaire to 209 smokers asking for reports of foods or beverages that worsen or enhance the taste of cigarettes. Commonly reported categories that worsen the taste of cigarettes were fruits/vegetables, noncaffeinated beverages, and dairy products. Commonly reported categories that enhance the taste of cigarettes were caffeinated and alcoholic beverages, and meat products. Regression analyses indicated that increased sensitivity to both taste worsening and enhancing were associated with smoking nonmenthol cigarettes. These findings suggest smoking menthol cigarettes reduces both negative and positive effects of food and beverage consumption on smoking satisfaction - thus "evening out" the smoking experience. Clinical implications and directions for future research are discussed.

Melikian, A. A., M. V. Djordjevic, et al. (2007). "Effect of delivered dosage of cigarette smoke toxins on the levels of urinary biomarkers of exposure." Cancer Epidemiol Biomarkers Prev 16(7): 1408-15.

Urinary metabolites of tobacco smoke toxins are often used as biomarkers for the evaluation of active and passive exposure to cigarette smoke toxins. In a study of healthy smokers, we investigated concentrations of urinary biomarkers in relation to concentrations of selected toxins in mainstream cigarette smoke as determined by machine smoking of cigarettes

in a manner that mimics an individual's smoking behavior (topography). Concentrations of nicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and benzo(a)pyrene, in mainstream smoke determined under human smoking conditions, and their urinary metabolites cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and 1-hydroxypyrene were established for 257 individuals who smoked low-yield (0.1-0.8 mg Federal Trade Commission nicotine/cigarette; mean, 0.66; n = 87), medium-yield (0.9-1.2 mg nicotine/cigarette; mean, 1.1; n = 109), and high-yield cigarettes (nicotine, >1.3 mg nicotine/cigarette; mean, 1.41; n = 61). Levels of urinary metabolites expressed per unit of delivered parent compounds decreased with increased smoke emissions. In smokers of low-, medium-, and high-yield cigarettes, the respective cotinine (ng/mg creatinine)-to-nicotine (mg/d) ratios were 89.4, 77.8, and 57.1 (low versus high; P = 0.06); the 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pmol/mg creatinine)-to-4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (ng/d) ratios were 0.81, 0.55, and 0.57 (low versus high; P = 0.05); and the 1-hydroxypyrene (pg/mg creatinine)-to-benzo(a)pyrene (ng/d) ratios were 1.55, 1.13, and 0.97 (low versus high; P = 0.008). Similarly, means of cotinine per unit of delivered nicotine in smokers who consumed <20 cigarettes per day was 3.5-fold higher than in those who smoked >20 cigarettes per day. Likewise, a negative correlation was observed between cotinine-to-nicotine ratios and delivered doses of nicotine in subgroups of smokers who used the identical brand of cigarette, namely a filter tip-vented Marlboro (r = -0.59), which is a popular brand among Euro-Americans, and Newport (r = -0.37), a menthol-flavored cigarette without filter tip vents that is preferred by African-Americans. Thus, the intensity of the exposures significantly affects the levels of urinary biomarkers of exposure and should be taken into account in the evaluation of human exposure to cigarette smoke toxins.

Miller, G. E., M. E. Jarvik, et al. (1994). "Cigarette mentholation increases smokers' exhaled carbon monoxide levels." Exp Clin Psychopharm 2(2): 154-160.

Male smokers (N = 12) participated in 3 controlled-dose smoking sessions spaced 1 week apart. In each session, Ss inhaled 1, 200 cc of cigarette smoke. Menthol dosage varied across sessions, such that Ss smoked experimental cigarettes that had been injected with 0 mg, 4 mg, or 8 mg of menthol. Exhaled carbon monoxide levels increased concomitantly with menthol dosage. There were no differences in smoking topography across the 3 conditions. The ability of menthol to increase the toxicity of cigarette smoke by raising carbon monoxide levels is discussed. Results suggest that menthol cigarette preference may account for some of the racial differences in smoking behavior and smoking-related outcomes found in past literature.

Moolchan, E. T., D. L. Hudson, et al. (2004). "Heart rate and blood pressure responses to tobacco smoking among African-American adolescents." J Natl Med Assoc 96(6): 767-71.

Ethnic differences in both physiological response to and health consequences of tobacco smoking-some of which have been attributed to ethnic preferences for menthol cigarettes-have been described in the literature. We compared acute physiological responses to smoking in African-American and European-American adolescent menthol cigarette smokers seeking smoking cessation treatment. One-hundred- twenty-eight adolescents

(32% African-American, 71% female; mean age 15.16 +/- 1.32 years, mean Fagerstrom Test of Nicotine Dependence (FTND) score 6.73 +/- 1.53, cigarettes per day (CPD) 16.9 +/- 2.64) participated in an experimental session during which they smoked one menthol cigarette of their usual brand. Blood pressure, heart rate, and exhaled carbon monoxide (CO) concentrations were measured before and after smoking; mean puff volume (mL), puff duration (sec) and maximal puff velocity (mL/sec) during smoking were also determined. Two sample t-tests were performed to assess ethnic differences in smoking topography; analysis of covariance was used to determine whether heart rate and blood pressure after smoking one menthol cigarette varied by ethnicity, after controlling for baseline physiological measures. No significant ethnic differences were observed in either smoking topography or acute cardiovascular response to smoking. These preliminary findings warrant extension to a broader group of nontreatment-seeking adolescent smokers of both ethnicities.

Muscat, J. E., G. Chen, et al. (2009). "Effects of menthol on tobacco smoke exposure, nicotine dependence, and NNAL Glucuronidation." Cancer Epidemiol Biomarkers Prev 18(1): 35-41.

Menthol is a controversial cigarette additive because its physiologic or pharmacologic effects may possibly increase the risk for cancer and its targeted market is the Black community. In a community-based cross-sectional study on 525 Black and White volunteers, we compared levels of urinary and plasma cotinine, plasma thiocyanate, urinary 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL), and its detoxified form (NNAL-Gluc) between menthol and nonmenthol smokers. In regression models that adjusted for daily cigarette intake, no significant differences were observed in the concentration of these biomarkers by menthol status in both races. There was no significant association between high Fagerstrom nicotine dependence scores and the use of menthol cigarettes (odds ratio, 1.1; 95% confidence interval, 0.6-2.0), but an increased risk was observed with smoking a cigarette soon (</=30 minutes) after waking (odds ratio, 2.1; 95% confidence interval, 1.0-3.8). The ratio of NNAL-Gluc to NNAL, a possible indicator of lung cancer risk, was significantly lower in menthol versus nonmenthol smokers. The NNAL-Gluc/NNAL ratio was 34% lower in Whites ($P < 0.01$) and 22% lower in Blacks. In subsequent human liver microsome studies, menthol inhibited the rate of NNAL-O-glucuronidation and NNAL-N-glucuronidation. Collectively, these results show that menthol does not affect biological exposure to tobacco smoke constituents but indicates that menthol might inhibit the detoxification of the potent lung carcinogen NNAL.

Mustonen, T. K., S. M. Spencer, et al. (2005). "The influence of gender, race, and menthol content on tobacco exposure measures." Nicotine Tob Res 7(4): 581-90.

Research has suggested that race, gender, and menthol cigarette use influence tobacco-smoke exposure measures and smoking-related disease risk. For example, a high proportion of Black smokers prefer menthol cigarettes and, despite smoking fewer cigarettes per day (CPD) than do Whites, tend to have higher cotinine levels. Additionally, Black males are more at risk for smoking-related lung cancer. High cotinine levels and smoking menthol cigarettes may lead to higher toxin intake, which contributes to increased disease risk. We explored the relationship between tobacco exposure variables (i.e., cotinine, CPD, carbon

monoxide [CO], nicotine content, and nicotine dependence) with respect to race, gender, and menthol content in a sample of 307 smokers recruited from the greater Boston area to participate in a smoking cessation treatment trial. The pattern of correlations between tobacco exposure measures and cotinine showed a consistently positive correlation between cotinine and CO in all smokers and a correlation between cotinine and CPD in those who smoked nonmenthol cigarettes. Cotinine and CPD correlations varied by gender and race among menthol cigarette smokers. Consistently, we found a significant gender x race x menthol interaction on salivary cotinine level as well as cotinine/CPD ratio. These findings suggest that the relationship between number of cigarettes consumed and salivary cotinine is more complex than previously believed. It is not sufficient to look at race alone; researchers and clinicians need to look at race and gender concurrently, as well as type of cigarette consumed.

Nil, R. and K. Battig (1989). "Separate effects of cigarette smoke yield and smoke taste on smoking behavior." Psychopharmacology (Berl) 99(1): 54-9.

The purpose of this experiment was to compare independently the influence of different cigarette smoke taste categories and different machine standard smoke yield values on cigarette smoking behavior and related subjective measures. In six separate sessions 15 regular smokers were presented with a medium and a low smoke yield cigarette of each of the three taste categories, mentholated, dark (Gauloises) and blond (Muratti) tobacco. Each session included a "natural" and a "forced" smoking procedure of one cigarette type only. Forced smoking consisted of smoking 30 puffs whereby a new half-length cigarette was presented after every third puff. During the seventh session, habitual brand cigarettes were smoked as a reference. The sessions followed in weekly intervals, and the subjects became familiar with the test cigarettes during the last 5 days preceding each test session. Although general acceptability of the cigarettes, smoking satisfaction and pleasantness of taste were clearly lower for all test cigarettes as opposed to the habitual brand reference cigarettes, these measures remained unaffected by taste or smoke yield of the test cigarettes. Harshness of smoke was higher in the dark tobacco category and generally decreased with the lower smoke yield cigarettes. Independent effects of taste and smoke yield were obtained for total puff volume, inhalation time and CO absorption, suggesting a compensatory intensification of smoking behavior for low yield cigarettes and an independent increase of smoking intensity from mentholated to dark tobacco to blond tobacco. The results suggest therefore that factors which affect cigarette smoke taste have effects on smoking behavior which are separate from those obtained by comparing smoke yields.

Perez-Stable, E. J., B. Herrera, et al. (1998). "Nicotine metabolism and intake in black and white smokers." J Am Med Assoc 280(2): 152-6.

Racial differences in tobacco-related diseases are not fully explained by cigarette-smoking behavior. Despite smoking fewer cigarettes per day, blacks have higher levels of serum cotinine, the proximate metabolite of nicotine. To compare the rates of metabolism and the daily intake of nicotine in black smokers and white smokers, participants received simultaneous infusions of deuterium-labeled nicotine and cotinine. Urine was collected for determination of total clearance of nicotine and cotinine, fractional conversion of nicotine to

cotinine, and cotinine elimination rate. Using cotinine levels during ad libitum smoking and clearance data, the daily intake of nicotine from smoking was estimated. A total of 40 black and 39 white smokers, average consumption of 14 and 14.7 cigarettes per day, respectively, of similar age (mean, 32.5 and 32.3 years, respectively) and body weight (mean, 73.3 and 68.8 kg, respectively) participated in the study, which took place in a metabolic ward of a university-affiliated public hospital. Clearance (renal and nonrenal), half-life, and volume of distribution of nicotine and cotinine and the calculated daily intake of nicotine were measured. The total and nonrenal clearances of nicotine were not significantly different, respectively, in blacks (17.7 and 17.2 mL x min(-1) x kg(-1)) compared with whites (19.6 and 18.9 mL x min(-1) x kg(-1)) (P=.11 and .20). However, the total and nonrenal clearances of cotinine were significantly lower, respectively, in blacks (0.56 and 0.47 mL x min(-1) x kg(-1)) than in whites (0.68 vs 0.61 mL x min(-1) x kg(-1); P=.009 for each comparison). The nicotine intake per cigarette was 30% greater in blacks compared with whites (1.41 vs 1.09 mg per cigarette, respectively; P=.02). Volume of distribution did not differ for the 2 groups, but cotinine half-life was higher in blacks than in whites (1064 vs 950 minutes, respectively; P = .07). Higher levels of cotinine per cigarette smoked by blacks compared with whites can be explained by both slower clearance of cotinine and higher intake of nicotine per cigarette in blacks. Greater nicotine, and therefore, greater tobacco smoke intake per cigarette could, in part, explain some of the ethnic differences in smoking-related disease risks.

Pickworth, W. B., E. T. Moolchan, et al. (2002). "Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery." Pharmacol Biochem Behav 71(1-2): 55-61.

Many smokers choose menthol-flavored cigarettes, however, the influence of menthol on the effects of smoke-delivered nicotine is unknown. Research and commercial cigarettes, menthol and non-menthol, that delivered a wide range of nicotine were evaluated. Menthol (n=18) and non-menthol (n=18) cigarette smokers participated in a single session during which three cigarettes were smoked 45 min apart, in random order. Federal Trade Commission (FTC) nicotine yields of the three cigarettes were: research, low yield, 0.2 mg, commercial cigarettes (average), 1.2 mg; research, high yield, 2.5 mg. Commercial and high-yield cigarettes increased heart rate (HR) and blood pressure more than low-yield cigarettes; although, no differences in exhaled carbon monoxide (CO) occurred. Participants smoked commercial cigarettes faster and with fewer puffs than either of the research cigarette indicating production differences can affect topography. There was a significant group by cigarette interaction on satisfaction, and relief from cigarette craving. High-yield non-menthol cigarettes reduced craving and were rated as more satisfying than high-yield menthol cigarettes. No differences between menthol and non-menthol cigarettes on other subjective measures (strength, psychological reward, negative effects) were observed. Our findings indicate that nicotine delivery, but not mentholation, influences cardiovascular and most subjective measures. These results illustrate the importance of threshold levels of nicotine on subjective responses to cigarette smoking.

Pritchard, W. S., M. E. Houlihan, et al. (1999). "Little evidence that "denicotinized" menthol cigarettes have pharmacological effects: an EEG/heart-rate/sujective-response study." Psychopharmacology (Berl) 143(3): 273-9.

A substantial portion of cigarette smokers prefer menthol-flavored cigarettes. To date, however, no studies have examined whether menthol in cigarettes has central pharmacological effects. We investigated psychophysiological and subjective effects of smoking menthol versus non-menthol cigarettes in both menthol and non-menthol smokers. To assess these effects independently of the immediate effects of nicotine, all cigarettes employed were "denicotinized" (FTC nicotine yield = 0.06 mg). The psychophysiological measures were EEG and heart rate (HR). The subjective measures assessed mental alertness, muscular relaxation, anxiety/nervousness, and how much a participant wanted to smoke one of his usual brand of cigarettes. Menthol and non-menthol smokers participated in a single session in which each participant smoked both a menthol and a non-menthol denicotinized cigarette (order balanced across participants). The psychophysiological and subjective measures were recorded before and after smoking each cigarette. Out of 48 F-ratios spanning 22 analyses of variance involving the critical interaction between pre-/post-smoking and menthol/non-menthol cigarette, only one unambiguously fit a "pharmacological" pattern, a result indistinguishable from a type-I statistical error. We report evidence that menthol smokers may be chronically less aroused and more sensitive to the effects of nicotine than non-menthol smokers. We found little evidence that menthol in cigarettes has central pharmacological effects.

Rabinoff, M., N. Caskey, et al. (2007). "Pharmacological and chemical effects of cigarette additives." Am J Public Health 97(11): 1981-1991.

We investigated tobacco industry documents and other sources for evidence of possible pharmacological and chemical effects of tobacco additives. Our findings indicated that more than 100 of 599 documented cigarette additives have pharmacological actions that camouflage the odor of environmental tobacco smoke emitted from cigarettes, enhance or maintain nicotine delivery, could increase the addictiveness of cigarettes, and mask symptoms and illnesses associated with smoking behaviors. Whether such uses were specifically intended for these agents is unknown. Our results provide a clear rationale for regulatory control of tobacco additives.

Richie, J. P., Jr., S. G. Carmella, et al. (1997). "Differences in the urinary metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in black and white smokers." Cancer Epidemiol Biomarkers Prev 6(10): 783-90.

Incidence and mortality rates for lung cancer in the United States are significantly greater in blacks than in whites. This disparity cannot be explained by differences in smoking behavior. We hypothesize that the observed racial differences in risk may be due to differences in the metabolic activation or detoxification of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). To test this, different biomarkers of NNK exposure and metabolism, including the urinary metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and the presumed detoxification

product [4-(methylnitrosamino)-1-(3-pyridyl)but-1-yl]-beta-O-D-glucosiduronic acid (NNAL-Gluc), were examined along with questionnaire data on lifestyle habits and diet in a metabolic epidemiological study of 34 black and 27 white healthy smokers. Results demonstrated that urinary NNAL-Gluc:NNAL ratios, a likely indicator of NNAL glucuronidation and detoxification, were significantly greater in whites than in blacks ($P < 0.02$). In addition, two phenotypes were apparent by probit analysis representing poor (ratio < 6) and extensive (ratio > or = 6) glucuronidation groups. The proportion of blacks falling into the former, potentially high-risk group was significantly greater than that of whites ($P < 0.05$). The absolute levels of urinary NNAL, NNAL-Gluc, and cotinine were also greater in blacks than in whites when adjusted for the number of cigarettes smoked. None of the observed racial differences could be explained by dissimilarities in exposure or other sociodemographic or dietary factors. Also, it is unlikely that the dissimilarities are due to racial differences in preference for mentholated cigarettes, because chronic administration of menthol to NNK-treated rats did not result in either increases in urinary total NNAL or decreases in NNAL-Gluc:NNAL ratios. Altogether, these results suggest that racial differences in NNAL glucuronidation, a putative detoxification pathway for NNK, may explain in part the observed differences in cancer risk.

Rosenblatt, M. R., R. E. Olmstead, et al. (1998). "Olfactory thresholds for nicotine and menthol in smokers (abstinent and nonabstinent) and nonsmokers." Physiol Behav 65(3): 575-9.

Nonsmokers and smokers were compared for olfactory sensitivity to two odors associated with cigarettes: nicotine and menthol. Smokers were tested twice—while nonabstinent, and after 16-20 h of smoking abstinence. Smokers showed a higher olfactory threshold for nicotine than did nonsmokers, but the same threshold for menthol. Furthermore, when the smokers were abstinent, they showed a lower olfactory threshold for nicotine than when they were nonabstinent, but again, the same threshold for menthol. These results suggest a nicotine specific olfactory deficit in smokers that is reduced during abstinence.

Sellers, E. M. (1998). "Pharmacogenetics and ethnoracial differences in smoking." J Am Med Assoc 280(2): 179-180.

No abstract available.

Simons, C. T., M. I. Carstens, et al. (2003). "Oral irritation by mustard oil: self-desensitization and cross-desensitization with capsaicin." Chem Senses 28(6): 459-65.

We investigated the temporal pattern of oral irritation elicited by sequential application of mustard oil (allyl-isothiocyanate), and whether it exhibits self-desensitization and cross-desensitization with capsaicin. Mustard oil (0.125%, 40 micro l) was sequentially applied to one side of the tongue at 1 min intervals, and subjects rated the intensity of the irritant sensation elicited by each stimulus. Ratings successively declined across trials, indicating desensitization. In contrast, sequential application of capsaicin (10 ppm) elicited irritation that increased in intensity across trials (sensitization). To test for self-desensitization by mustard oil, a 10 min hiatus was imposed following the series of unilateral mustard oil

stimuli, after which mustard oil was applied to both sides of the tongue. In a two-alternative forced-choice paradigm, subjects chose which side had stronger irritation and also independently rated the irritant intensity on each side. A significant majority of subjects chose the side not previously receiving mustard oil as more intense, and assigned significantly higher intensity ratings to that side, indicating self-desensitization. In two additional sessions, the same paradigm was used to show mustard oil cross-desensitization of irritation elicited by capsaicin, and capsaicin cross-desensitization of irritation from mustard oil. In a final session, sequential application of mustard oil at faster (20 s) intervals initially evoked a sensitizing pattern followed by desensitization. The temporal patterns of oral irritation exhibited by mustard oil, and its reciprocal cross-desensitization with capsaicin, are similar to those of menthol and nicotine.

Wagenknecht, L. E., G. R. Cutter, et al. (1990). "Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults study." Am J Public Health 80(9): 1053-6.

Cotinine was measured in the serum of nearly all 5,115 18-30 year old, Black and White, men and women participating in the Coronary Artery Risk Development in (Young) Adults Study, 30 percent of whom reported current cigarette smoking. Ninety-five percent of the reported smokers had serum cotinine levels indicative of smoking (greater than 13 ng/ml). The median cotinine level was higher in Black than White smokers (221 ng/ml versus 170 ng/ml; 95 percent CI for difference: 34, 65) in spite of the fact that estimated daily nicotine exposure and serum thiocyanate were higher in Whites. The difference persisted after controlling for number of cigarettes, nicotine content, frequency of inhalation, weekly sidestream smoke exposure, age, gender, and education. A reporting bias and nicotine intake were ruled out as explanations for the racial difference suggesting that the metabolism of nicotine or the excretion of cotinine may differ by race. Racial differences in cotinine levels may provide clues to the reasons for the observed lower cessation rates and higher rates of some smoking-related cancers in Blacks.

Wayne, G. F. and G. N. Connolly (2004). "Application, function, and effects of menthol in cigarettes: a survey of tobacco industry documents." Nicotine Tob Res 6: S43-S54.

Menthol cigarettes are the only cigarette market category identified by use of a flavor additive and constitute more than a quarter of the overall market. Menthol also is used at reduced levels in many nonmenthol brands. Public health research has suggested patterns of use of mentholated brands as a potential explanation for the health disparities between Black (largely menthol) and White (largely nonmenthol) smokers and has explored the effects of menthol on smoker behavior, consumption patterns, and consequent delivery of smoke constituents. However, relatively few published studies have directly examined the physiological impact and function of menthol delivery in cigarettes. In this study, we review internal tobacco industry documents to assess industry research on function and effects of menthol in cigarettes. Industry documents describe a range of physiological effects of menthol, with important implications for use and consumption patterns. These effects include altered perception of tobacco smoke and its constituents via cooling, smoothing, and anesthetic effects; increased impact through stimulation of trigeminal receptors;

interaction with nicotine controlling its perception, delivery, and uptake; and increased respiratory irritation and toxic effects. Further studies are needed to evaluate these findings. We conclude that the unique differences between menthol cigarettes and nonmenthol cigarettes must be considered in research, cessation treatment, and enactment of tobacco product regulations.

Westman, E. C., F. M. Behm, et al. (1996). "Airway sensory replacement as a treatment for smoking cessation." Drug Develop Res 38(3-4): 257-262.

Although nicotine may be a necessary component of the smoking addiction, it is obvious even to the non-expert that there is far more to smoking than the delivery of nicotine alone. Among the many aspects of smoking that smokers find pleasurable, 60% of smokers report liking of the feeling of cigarette smoke in the throat and chest. This paper summarizes several studies that strongly suggest that the airway sensations of smoking are important for at least the short-term satisfaction and craving reduction of cigarette smoking, and that these sensations can be reproduced by several other substances than cigarette smoke. Airway sensory replacement, especially in combination with nicotine replacement, may fill one of the many gaps that currently exist in smoking cessation treatment.

Cancer and Other Disease Risk

[Anon] (1956). "Menthol cigarettes." Brit Med J* 2(Nov17): 1189.

No abstract available.

[Anon] (1961). "Menthol cigarettes." Brit Med J* 2(526): 1659.

No abstract available.

Abidoye, O., M. K. Ferguson, et al. (2007). "Lung carcinoma in African Americans." Nat Clin Pract Oncol 4(2): 118-129.

Lung carcinoma is the most commonly diagnosed cancer and the leading cause of cancer deaths in the US. It accounts for 12% of all cancers diagnosed worldwide, making it the most common malignancy, other than nonmelanoma skin cancer. A new focus has emerged involving the role of race and ethnicity in lung carcinoma. Current health statistics data demonstrate striking disparities, which are most evident between African American patients and their white counterparts. This disparity is greatest among male patients, where statistically significant differences are seen not only in lung cancer incidence and risk, but also in survival and treatment outcomes. Several hypotheses that attempt to explain this disparity include genetic, cultural and socioeconomic differences, in addition to differences in tobacco use and exposure. Current evidence does not clearly identify the reasons for this observed disparity, or the role the aforementioned factors play in the development and overall outcomes of people with lung cancer in these populations. This disease continues to pose a considerable public health burden and more research is needed to improve understanding of the disparity of lung carcinoma statistics among African Americans. This review summarizes the existing body of knowledge regarding lung carcinoma in African Americans and attempts to identify promising areas for future investigation and intervention.

Alberg, A. J., J. G. Ford, et al. (2007). "Epidemiology of lung cancer - ACCP evidence-based clinical practice guidelines (2nd edition)." Chest 132(3): 29s-55s.

The objective of this study was to summarize the published literature concerning the epidemiology of lung cancer. A narrative review of published evidence was conducted, identifying and summarizing key reports that describe the occurrence of lung cancer in populations and factors that affect lung cancer risk. In the United States, lung cancer remains the leading cause of cancer death in both men and women, even though an extensive list of modifiable risk factors has long been identified. The predominant cause of lung

cancer is exposure to tobacco smoke, with active smoking causing most cases but passive smoking also contributing to the lung cancer burden. The reductions in smoking prevalence in men that occurred in the late 1960s through the 1980s will continue to drive lung cancer mortality rates downward in men during the first portion of this century, but rates in women have not yet begun to decrease. Fortunately, exposures to major occupational respiratory carcinogens have largely been controlled, but the population is still exposed to environmental causes of lung cancer, including radon, the second leading cause of lung cancer death.

Brooks, D. R., J. R. Palmer, et al. (2003). "Menthol cigarettes and risk of lung cancer." Am J Epidemiol 158(7): 609-16; discussion 617-20.

The authors analyzed data from a multihospital case-control study in the eastern United States to evaluate the hypothesis that smoking menthol cigarettes increases lung cancer risk compared with smoking nonmenthol cigarettes. Subjects included cases with lung cancer and controls admitted for conditions unrelated to smoking who were aged 40-74 years, were interviewed from 1981 to 2000, and had smoked for >or=20 years. Information was available on the brand and type of cigarette smoked most recently and for the longest time. Analyses were based on 643 cases and 4,110 controls for whom brand information was available for >or=60% of the total duration of smoking. Logistic regression was used to estimate the relative risk of lung cancer according to number of years of menthol cigarette use (>15, 1-15, 0), adjusting for demographic and smoking-related factors. The lung cancer risk for long-term smokers of menthol cigarettes was similar to that for smokers of nonmenthol cigarettes (odds ratio = 0.97, 95% confidence interval: 0.70, 1.34). Odds ratios were also close to 1.0 in separate analyses of male, female, Black, and White subjects. The results of this study do not support the hypothesis that smoking menthol cigarettes increases the risk of lung cancer relative to smoking nonmenthol cigarettes.

Camarasa, G. and A. Alomar (1978). "Menthol dermatitis from cigarettes." Contact Dermatitis 4(3): 169-70.

No abstract available.

Carpenter, C. L., M. E. Jarvik, et al. (1999). "Mentholated cigarette smoking and lung-cancer risk." Ann Epidemiol 9(2): 114-20.

Menthol smoking may lead to a greater increase in lung-cancer risk than smoking of nonmentholated cigarettes. Mentholation of cigarettes adds additional carcinogenic components to cigarette smoke and increases retention times for cigarette smoke in the lungs. Only two epidemiologic studies have been conducted on menthol smoking and lung cancer, and their results are conflicting. Of note, African American males have much higher rates of lung cancer than Caucasian males despite smoking fewer cigarettes per day. Because the consumption of menthol cigarettes is much more frequent among African Americans, it is of interest to examine the possible association between menthol smoking and lung-cancer risk in this population. We examined the association between menthol cigarette smoking and lung-cancer risk among smokers by comparing 337 incident cases of lung cancer with 478 population controls enrolled in a case-control study of lung cancer. Information on smoking

history and other known and potential risk factors for lung cancer, including dietary intake, was obtained by in-person interviews. The adjusted odds ratios did not differ appreciably between smokers of mentholated cigarettes versus exclusive nonmentholated cigarette smokers in the overall study group of smokers. The odds ratio (OR) for 32 pack-years or more of mentholated vs. nonmentholated cigarettes was 0.90 (95% confidence interval (CI) = 0.38-2.12) in African Americans and 1.06 (95% CI = 0.47-2.36) in Caucasians, and did not differ for either ethnic group (p = 0.98). Our results suggest that the lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes. Our data do not support the hypothesis that the increased risk of lung cancer among African Americans is due to the increased prevalence of menthol smoking.

Ciftci, O., M. Caliskan, et al. (2008). "Mentholated cigarette smoking induced alterations in left and right ventricular functions in chronic smokers." Anadolu Kardiyol Derg 8(2): 116-22.

The possible acute effects of smoking mentholated cigarette on left and right ventricular function are not known. The aim of the study was to compare acute effects of normal and mentholated cigarettes smoking on both ventricular diastolic functions in chronic smokers. A single-blinded, cross-over, open label and controlled study of the acute effect of smoking mentholated and regular cigarettes was conducted and evaluated. Eighteen other-than-healthy regular cigarette smokers and 20 nonsmoker control subjects were included in the study. To compare the acute effects of mentholated and regular cigarettes in each subject echocardiographic examination including tissue Doppler imaging (TDI) was performed at baseline. In the smokers group, TDI was measure 20-30 minutes after smoking two of either cigarette. In response to smoking two cigarettes, mitral E/A values declined from 1.78+/-0.44 to 1.58+/-0.41 after the regular cigarette (p=0.0043) and from 1.78+/-0.44 to 1.53+/-0.40 after the mentholated cigarette (p=0.0035). Tricuspid E deceleration time values declined from 185.28+/-20.05 ms to 222.72+/-26.47 ms after the regular cigarette (p<0.001) and 185.28+/-20.05 ms to 241.53+/-47.63 ms after the mentholated cigarette (p<0.001). Smoking of mentholated cigarette, but not regular cigarette smoking, increased tricuspid E deceleration time and right ventricular isovolumic contraction time (p=0.044; p=0.024 respectively) and decreased the right ventricular Em values (p=0.027). It was concluded that mentholated and regular cigarette smoking have acute detrimental effects on right and left ventricular systolic and diastolic function. Mentholated cigarettes cause additional unfavorable acute effects on especially right ventricular tissue Doppler velocities, relaxation and contraction indices compared to regular cigarettes.

Ciftci, O., S. Topcu, et al. (2008). "Smoking mentholated cigarettes impairs coronary microvascular function as severely as does smoking regular cigarettes." Acta Cardiol 63(2): 135-40.

Smoking mentholated cigarettes inhibits the metabolism of nicotine and increases systemic exposure to cigarette smoke toxins. However, the possible effects of smoking mentholated cigarettes on coronary microvascular functions are unknown. We sought to investigate whether smoking mentholated cigarettes impairs coronary flow reserve (CFR) more so than smoking regular cigarettes. Twenty otherwise healthy smokers of regular cigarettes

(6 women, 14 men; mean age, 25.6 +/- 6.4 years) and 22 non-smoking control subjects were included in the study. To compare the acute effects of mentholated (0.9 mg nicotine, 11 mg tar, 12 mg carbon monoxide) and regular (0.9 mg nicotine, 12 mg tar, 12 mg carbon monoxide) cigarettes on CFR, all subjects underwent an echocardiographic examination that included CFR measurements at baseline. Twenty to 30 minutes after subjects had smoked 2 regular cigarettes and 2 mentholated cigarettes, CFR was again measured in subjects in the smoking group. In response to smoking 2 regular and 2 mentholated cigarettes, CFR values declined from 2.56 +/- 0.60 to 2.06 +/- 0.38 ($P < 0.004$) and from 2.56 +/- 0.60 to 2.14 +/- 0.30 ($P < 0.005$), respectively. Smoking mentholated and regular cigarettes impaired CFR to the same degree ($P = 0.547$). When compared with smoking regular cigarettes, smoking mentholated cigarettes has similar acute detrimental effects on coronary microvascular functions.

Etzel, C. J., S. Kachroo, et al. (2008). "Development and validation of a lung cancer risk prediction model for African-Americans." Cancer Prev Res 1(4): 255-265.

Because existing risk prediction models for lung cancer were developed in white populations, they may not be appropriate for predicting risk among African-Americans. Therefore, a need exists to construct and validate a risk prediction model for lung cancer that is specific to African-Americans. We analyzed data from 491 African-Americans with lung cancer and 497 matched African-American controls to identify specific risks and incorporate them into a multivariable risk model for lung cancer and estimate the 5-year absolute risk of lung cancer. We performed internal and external validations of the risk model using data on additional cases and controls from the same ongoing multiracial/ethnic lung cancer case-control study from which the model-building data were obtained as well as data from two different lung cancer studies in metropolitan Detroit, respectively. We also compared our African-American model with our previously developed risk prediction model for whites. The final risk model included smoking-related variables [smoking status, pack-years smoked, age at smoking cessation (former smokers), and number of years since smoking cessation (former smokers)], self-reported physician diagnoses of chronic obstructive pulmonary disease or hay fever, and exposures to asbestos or wood dusts. Our risk prediction model for African-Americans exhibited good discrimination [75% (95% confidence interval, 0.67-0.82)] for our internal data and moderate discrimination [63% (95% confidence interval, 0.57-0.69)] for the external data group, which is an improvement over the Spitz model for white subjects. Existing lung cancer prediction models may not be appropriate for predicting risk for African-Americans because (a) they were developed using white populations, (b) level of risk is different for risk factors that African-American share with whites, and (c) unique group specific risk factors exist for African-Americans. This study developed and validated a risk prediction model for lung cancer that is specific to African-Americans and thus more precise in predicting their risks. These findings highlight the importance of conducting further ethnic specific analyses of disease risk.

Friedman, G. D., M. Sadler, et al. (1998). "Mentholated cigarettes and non-lung smoking related cancers in California, USA." J Epidemiol Community Health 52(3): 202.

No abstract available.

Garten, S. and R. V. Falkner (2003). "Continual smoking of mentholated cigarettes may mask the early warning symptoms of respiratory disease." Prev Med 37(4): 291-6.

The continual use of cold preparations including those containing menthol for relief from congestion, cough, or difficulty in breathing can mask the early warning symptoms of respiratory dysfunction.These products usually carry a warning label on the packaging that indicates that they are not for continuous use and may mask the early warning symptoms of a more serious condition. Menthol can be delivered in many dosage forms including the smoke of a mentholated cigarette. Literature searches of the NLM databases (e.g., MEDLINE from 1966, TOXLINE, OLDMEDLINE (1958-1965), CANCERLIT), plus tobacco industry documents and hardcopy indices were conducted and the evidence was evaluated with application to mentholated cigarette smoking. A logical progression is presented to attempt to demonstrate that the continuous smoking of mentholated cigarettes may also mask the early warning symptoms of respiratory distress. The early warning symptoms caused by chronic irritation of the respiratory tract may be reduced in severity when the menthol found in a mentholated cigarette is continually delivered to the tract. This masking of the symptoms of an underlying respiratory disease can lead to delays in seeking medical attention resulting in a poor prognosis, additional suffering, and eventual death.

Garten, S. and R. V. Falkner (2004). "Role of mentholated cigarettes in increased nicotine dependence and greater risk of tobacco-attributable disease." Prev Med 38(6): 793-8.

Cold air stimulates upper airway cold receptors causing a reflex depressive effect on respiratory activity. Menthol, in low concentrations can also stimulate these same cold receptors causing a depressive effect on respiratory activity. Menthol cigarettes when smoked, deliver enough menthol to stimulate cold receptors resulting in the smoker experiencing a "cool sensation." The "cool sensation" experienced by the menthol smoker can result in a reflex-depressive effect on respiratory activity. Literature searches of the NLM databases (e.g., MEDLINE from 1966, TOXLINE, OLDMEDLINE (1985-1965), CANCERLIT, plus tobacco industry documents and hardcopy indices were conducted and the evidence was evaluated with application to mentholated cigarette smoking. A logical progression is presented that develops the framework to prove that menthol found in mentholated cigarettes may cause respiratory depression resulting in greater exposure to the toxic substances found in tobacco smoke. As a result of breath holding that results from the stimulation of cold receptors there is a greater opportunity for exposure and transfer of the contents of the lungs to the pulmonary circulation. For the menthol smoker this results in a greater exposure to nicotine and the particulate matter (tar) of the smoked cigarette. This exposure can result in increased nicotine dependence and greater chance of tobacco-attributable disease.

Glick, Z. R., N. Saedi, et al. (2009). "Allergic contact dermatitis from cigarettes." Dermatitis 20(1): 6-13.

Cigarettes are widely known to contain potent carcinogens, and their smoke contributes to many chronic and potentially fatal diseases. Cigarettes may also represent an underreported and underrecognized cause of allergic contact dermatitis (ACD). Potential allergens from cigarettes can be found in the filters, paper, and tobacco. This article reviews the current

literature on ACD from cigarettes to understand the clinical manifestation of ACD from cigarettes, to recognize components in cigarettes as potential sources of ACD, and to describe how to patch-test patients with suspected ACD from cigarettes. The potential allergens discussed in this article include cocoa, menthol, licorice, colophony, and formaldehyde.

Hebert, J. R. (2003). "Invited commentary: Menthol cigarettes and risk of lung cancer." Am J Epidemiol* 158(7): 617-620.

No abstract available.

Hebert, J. R. and G. C. Kabat (1988). "Menthol cigarettes and esophageal cancer." Am J Public Health 78(8): 986-7.

No abstract available.

Hebert, J. R. and G. C. Kabat (1989). "Menthol cigarette smoking and oesophageal cancer." Int J Epidemiol 18(1): 37-44.

Oesophageal cancer incidence and mortality among American blacks is over three times the rate for whites. Between 1950 and 1977 the age-adjusted oesophageal cancer mortality rate approximately doubled in non-whites while remaining virtually unchanged in whites. Between World War II and the 1970s menthol cigarette sales dramatically increased, roughly paralleling the increase in oesophageal cancer among blacks. The present study uses existing data from a large hospital-based case-control study to test whether menthol cigarette smoking is related to oesophageal cancer. Oesophageal cancer cases were current smokers. Controls were matched to the cases on age (+/- 5 years) and sex, had conditions thought not to be related to tobacco use, and were also current smokers. Tabular analyses showed no change in risk for males ever-smoking menthol versus those never smoking menthol cigarettes. For women, however, there was an increased risk. Results of logistic regression analyses performed to account for potential confounding factors showed a marginally significant (P = 0.08) decrease in risk among male short term (less than 10 years) menthol smokers versus male never-menthol smokers (OR = 0.50, 95% Cl: 0.23-1.07) but no increased risk for menthol smoking of longer duration. Duration of menthol smoking fitted as a continuous variable showed no increased risk (P = 0.9) after accounting for non-menthol cigarette smoking duration (about 2% per year increase, P = 0.02). For females, the logistic analysis produced a marginally significant (P = 0.07) increased risk for longer menthol use (OR = 2.30, 95% Cl: 0.93-5.72). Integer years of menthol smoking showed about a 5% increase in risk per year (P = 0.09) while non-menthol duration showed only a 2% increase (P = 0.15). Future studies that can more definitively test the hypothesis are recommended.

Highstein, B. and I. Zeligman (1951). "Nonthrombocytopenic purpura caused by mentholated cigarettes." J Am Med Assoc 146(9): 816.

No abstract available.

Kabat, G. C. (1996). "Aspects of the epidemiology of lung cancer in smokers and nonsmokers in the United States." Lung Cancer 15(1): 1-20.

While it is well-established that smoking is the predominant risk factor for lung cancer, it is clear that factors other than smoking and occupational exposure play a role in some lung cancers, and particularly adenocarcinoma. Data from a large, hospital-based case-control study are used to examine the association of smoking-related risk factors (amount smoked, filter status, mentholation, and differences in smoking habits between blacks and whites) and selected factors other than smoking (environmental tobacco smoke, previous primary cancer and radiotherapy, reproductive and endocrine factors, and body mass index) with lung cancer. Although smoking shows a dose-response relationship with all major lung cancer cell types, the strength of the relationship is weaker for adenocarcinoma, suggesting that other risk factors must play an important role for this cell type. In blacks and whites of both sexes, odds ratios for lung cancer increased with increasing cumulative tobacco tar intake and decreased with years since quitting smoking. Use of mentholated cigarettes was associated with no greater risk for lung cancer than that associated with the use of nonmentholated cigarettes. Exposure to environmental tobacco smoke generally showed little relation to lung cancer risk. In particular, exposure of nonsmoking wives to a husband's smoking showed no increase in risk. A history of a reproductive primary cancer and a history of radiotherapy were each associated with a fourfold increase in risk in female nonsmokers. An association of lean body mass with lung cancer was observed in current smokers, exsmokers, and female never smokers. These results are discussed in the context of existing studies. In conclusion, variation in lung cancer rates between populations may be due to: (1) differences in effective exposure to tobacco smoke carcinogens; (2) differences in factors which modify the effect of tobacco smoke, including differences in host susceptibility and metabolism of carcinogens, or (3) differences in exposure to other independent risk factors for lung cancer.

Kabat, G. C. and J. R. Hebert (1991). "Use of mentholated cigarettes and lung cancer risk." Cancer Res 51(24): 6510-3.

Black males have higher age-adjusted lung cancer incidence rates compared to white males, and blacks of both sexes have higher rates of increase in lung cancer incidence over past decades. The majority of black smokers smoke mentholated cigarettes. These observations prompted us to assess the effect of smoking mentholated cigarettes on lung cancer risk, using data from a hospital-based case-control study of tobacco-related cancers. Analysis was restricted to current cigarette smokers and was carried out on 588 male lung cancer cases and 914 male control patients and on 456 female lung cancer cases and 410 female controls interviewed between 1985 and 1990. The prevalence of menthol usage did not differ between cases and controls of either sex. No significant association was observed between either short-term (1-14 years) or long-term (15+ years) menthol use and lung cancer in logistic regression analyses adjusting for covariates. For specific histological types of lung cancer there was no indication of an association with menthol usage.

Kabat, G. C. and J. R. Hebert (1994). "Use of mentholated cigarettes and oropharyngeal cancer." Epidemiology 5(2): 183-8.

We used data from a hospital-based case-control study of tobacco-related cancers to test the hypothesis that smoking mentholated cigarettes increases the risk of cancer of the oral cavity and pharynx, a cancer with a 50% higher incidence in black Americans compared with whites. Detailed information on smoking habits and other variables, obtained in personal interviews, was available for 194 male and 82 female newly diagnosed, histologically confirmed cases of oropharyngeal cancer and 845 male and 411 female controls, all of whom were current smokers. In univariate, stratified, and multivariable analyses involving all cases and controls, menthol was not a risk factor for cancer. The odds ratio, adjusted for covariates, for smoking mentholated cigarettes for > = 15 years relative to smoking non-mentholated cigarettes only was 0.9 (95% confidence interval = 0.5-1.6) in males, and 0.7 (95% confidence interval = 0.5-1.7) in females. In analyses by subsite, menthol use was positively associated only with cancer of the pharynx in males, although the magnitude of the association was small. These results indicate that use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer.

Kumar, S. (2008). "Panmasala chewing induces deterioration in oral health and its implications in carcinogenesis." Toxicol Mech Method 18(9): 665-677.

Panmasala containing tobacco was introduced in the Indian market during the 1970s. Panmasala consists of areca nut (betel nut), catechu, lime, cardamom, spices, and unspecified flavoring agents, etc., with tobacco locally known as gutkha or without tobacco (Plain or sada), and consumed abundantly in India and also other parts of the world, predominantly in South East Asian countries. Available studies demonstrate that the habits of chewing panmasala gutkha or plain by students and adolescents are on the increase, which may lead to deterioration of oral health and other organ systems. Based on the experimental as well as clinical studies available on panmasala as well as on different components of panmasala, this review suggests that it has the potential in causation of various oral diseases such as Oral Sub Mucosis Fibrosis (OSMF) and leucoplakia which may lead to oral cancer. Studies reviewed on these chewing mixtures also reveal that it is likely to be carcinogenic, as tobacco and areca nut have carcinogenic potential and both have encompassing addictive potential leading to dependence on chewing mixture containing areca nut and tobacco. These mixtures might not only lead to cancer but may also affect other organs of the body, including oral hard tissues in the form of dental attrition and sensitivity. There is a need to consider the potential health hazards associated with the habits of these products, especially oral cancer. More research is needed to find out early changes which could be reversible and also intervention measures through education to desist people in indulging in such habits.

Miki, K., M. Miki, et al. (2003). "Early-phase neutrophilia in cigarette smoke-induced acute eosinophilic pneumonia." Internal Med 42(9): 839-845.

Although cigarette smoking is a recognized cause of acute eosinophilic pneumonia (AEP), and an increase in eosinophils in the lung is a common occurrence in AEP, early-phase neutrophilia in AEP is not well understood. We describe three cases of cigarette smoke

(menthol type)-induced AEP with neutrophilia in the lungs or blood. Increased in-vitro production of the neutrophil chemoattractant interleukin (IL)-8 by human bronchial epithelial cells (HBECs) was correlated with neutrophilia. We suggest that IL-8 released from HBECs is involved in neutrophilia in the lung in AEP, and is newly recognized as an important factor in the early phase of AEP development.

Murray, R. P., Connett, J.E., Skeans, M.A., Tashkin, D.P. (2007). "Menthol cigarettes and health risks in Lung Health Study data." Nicotine Tob Res. 9(1): 101-107.

Whether menthol cigarettes confer a higher risk of death than plain cigarettes is not known. The Lung Health Study (LHS) enrolled 5,887 adult smokers in a clinical trial of smoking cessation and ipratropium in the prevention of chronic obstructive pulmonary disease. LHS participants have been subjected to surveillance for mortality from all causes for 14 years. We examined these data for differences between self-reported smokers of menthol cigarettes versus plain cigarettes. Using proportional hazards regression methods, we found no differences in hazard ratios for coronary heart disease, cardiovascular disease, lung cancer, or death from any cause. Contrary to expectations about nicotine dependence, we found that users of menthol cigarettes had smoked fewer pack-years at baseline. We found no difference in success at smoking cessation with or without menthol. We conclude that our data contain no evidence that mentholation of cigarettes increases the hazards of smoking

Richardson, T. L. (1997). "African-American smokers and cancers of the lung and of the upper respiratory and digestive tracts. Is menthol part of the puzzle?" West J Med 166(3): 189-94.

The prevalence of cigarette smoking is higher among African Americans than among whites. African Americans have higher rates of lung cancer than whites, although they smoke fewer cigarettes. To explore this black-white difference in lung cancer rates, I examine various aspects of tobacco use in African-American smokers, including the age of initiation of smoking, quantity of cigarettes smoked, quit rates, level of nicotine dependence, biochemical differences, and brand preferences, specifically menthol brand cigarettes. I also review briefly the sequelae of patterns of tobacco use, including rates of lung and other tobacco-related cancers. A preference for mentholated cigarettes by African Americans is well documented and is one of the most striking differences between African-American and white smokers. Menthol brand preference has been investigated in an attempt to explain the black-white differences in rates of cancers of the lungs and the upper respiratory and digestive tracts. Also, studies have evaluated smoking behavior both with and without menthol and have explicitly examined the question of whether menthol use helps explain the black-white difference in lung cancer rates. The results of these studies are so far inconclusive with regard to the use of menthol and the risk of lung cancer developing. I provide practical suggestions for clinicians in counseling African-American smokers to quit smoking and to maintain a nonsmoking status.

Richie, J. P., Jr., S. G. Carmella, et al. (1997). "Differences in the urinary metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in black and white smokers." Cancer Epidemiol Biomarkers Prev 6(10): 783-90.

Incidence and mortality rates for lung cancer in the United States are significantly greater in blacks than in whites. This disparity cannot be explained by differences in smoking behavior. We hypothesize that the observed racial differences in risk may be due to differences in the metabolic activation or detoxification of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). To test this, different biomarkers of NNK exposure and metabolism, including the urinary metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and the presumed detoxification product [4-(methylnitrosamino)-1-(3-pyridyl)but-1-yl]-beta-O-D-glucosiduronic acid (NNAL-Gluc), were examined along with questionnaire data on lifestyle habits and diet in a metabolic epidemiological study of 34 black and 27 white healthy smokers. Results demonstrated that urinary NNAL-Gluc:NNAL ratios, a likely indicator of NNAL glucuronidation and detoxification, were significantly greater in whites than in blacks ($P < 0.02$). In addition, two phenotypes were apparent by probit analysis representing poor (ratio < 6) and extensive (ratio > or = 6) glucuronidation groups. The proportion of blacks falling into the former, potentially high-risk group was significantly greater than that of whites ($P < 0.05$). The absolute levels of urinary NNAL, NNAL-Gluc, and cotinine were also greater in blacks than in whites when adjusted for the number of cigarettes smoked. None of the observed racial differences could be explained by dissimilarities in exposure or other sociodemographic or dietary factors. Also, it is unlikely that the dissimilarities are due to racial differences in preference for mentholated cigarettes, because chronic administration of menthol to NNK-treated rats did not result in either increases in urinary total NNAL or decreases in NNAL-Gluc:NNAL ratios. Altogether, these results suggest that racial differences in NNAL glucuronidation, a putative detoxification pathway for NNK, may explain in part the observed differences in cancer risk.

Savitz, D. A., N. Dole, et al. (2001). "Smoking and pregnancy outcome among African-American and white women in central North Carolina." Epidemiology 12(6): 636-42.

Despite extensive research on tobacco smoking during pregnancy, few studies address risks among African-American and white women, groups that differ in brand preference and smoking habits. The Pregnancy, Infection, and Nutrition Study is a prospective cohort study that included 2,418 women with detailed information on smoking during pregnancy, including brand, number of cigarettes per day, and changes during pregnancy. We analyzed risk of preterm birth (<37 and <34 weeks' gestation) and small-for-gestational-age deliveries in relation to tobacco use. Pregnant African-American smokers differed markedly from whites in brand preference (95% vs 26% smoked menthol cigarettes) and number of cigarettes per day (1% of African-Americans and 12% of whites smoked 20+ cigarettes per day). Smoking was not related to risk of preterm birth overall, but cotinine measured at the time of delivery was (adjusted odds ratio = 2.2, 95% confidence interval = 1.1-4.5). A clear association and dose-response gradient was present for risk of fetal growth restriction (risk ratio for 20+ cigarettes/day = 2.4, 95% confidence interval = 1.4-4.0). Associations of tobacco use with preterm premature rupture of amniotic membrane resulting in preterm birth were notably stronger than the associations with other types of preterm birth.

Sidney, S., I. S. Tekawa, et al. (1995). "Mentholated cigarette use and lung cancer." Arch Intern Med 155(7): 727-32.

Menthol combustion produces carcinogenic compounds such as benzo[a]pyrenes. Mentholated cigarettes are much more commonly smoked by black individuals than by white individuals. The incidence of lung cancer is much higher (60%) in black men than in white men, but it differs little by race in women. We examined the association of mentholated cigarette use with lung cancer in men and women because mentholated cigarette use could help to explain the higher incidence rate of lung cancer in black men than in white men. The study population consisted of 11,761 members (5771 men and 3990 women) of the Northern California Kaiser Permanente Medical Care Program, Oakland, aged 30 to 89 years, who underwent a multiphasic health checkup in 1979 through 1985 and reported that they were current cigarette smokers who had smoked for at least 20 years. Data were collected about current cigarette brand, duration of mentholated cigarette use, and other smoking characteristics. Follow-up for incident lung cancer cases (n = 318) was carried out through 1991. The relative risk of lung cancer associated with mentholation compared with nonmentholated cigarettes was 1.45 in men (95% confidence interval, 1.03 to 2.02) and 0.75 in women (95% confidence interval, 0.51 to 1.11), adjusted for age, race, education, number of cigarettes smoked per day, and duration of smoking. Further adjustment for tar content and self-reported smoking intensity characteristics did not substantially alter the estimate of relative risk. A graded increase in risk of lung cancer with increasing duration of mentholated cigarette use was present in men. This study suggests that there is an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers.

Stellman, S. D., Y. Chen, et al. (2003). "Lung cancer risk in white and black Americans." Ann Epidemiol 13(4): 294-302.

The purpose of the study was to test whether differences in smoking-related lung cancer risks in blacks and whites can explain why lung cancer incidence is greater in black males than in white males but about equal in black and white females, given that a greater proportion of blacks are smokers, but smoke far fewer cigarettes per day than do whites. A hospital-based case-control study was conducted between 1984 and 1998 that included interviews with 1,710 white male and 1,321 white female cases of histologically confirmed lung cancer, 254 black male and 163 black female cases, and 8,151 controls. Relative risks were estimated via odds ratios using logistic regression, adjusted for age, education, and body mass index. We confirmed prior reports that smoking prevalence is higher but overall dosage is lower among blacks. Overall ORs were similar for blacks and whites, except among the heaviest smoking males (21+ cigarettes per day or 37.5 pack-years), in whom ORs for blacks were considerably greater than for whites. Long-term benefits of cessation were similar for white and black ex-smokers. Smokers of menthol flavored cigarettes were at no greater risk for lung cancer than were smokers of unflavored brands. Lung cancer risks were similar for whites and blacks with similar smoking habits, except possibly for blacks who were very heavy smokers, which is an unusual sub-group in the general population of African American smokers. Explanations of racial disparities in lung cancer risk may need to account for modifying factors including type of cigarette (yield, mentholation), diet, occupation, and host factors such as the ability to metabolize mainstream smoke carcinogens.

Takkouche, B. and J. J. GestalOtero (1996). "The epidemiology of lung cancer: Review of risk factors and Spanish data." Eur J Epidemiol 12(4): 341-349.

Lung cancer is the main form of cancer among men both in Spain and in the rest of europe. However, Spanish incidence rates are among the lowest of the European registries, especially for women. In this country, lung cancer mortality increased much more rapidly for men than for women between the fifties and the eighties. This increase was larger for lung cancer than for any other site. The trend of incidence, in Spain as well as in the greatest part of the world, is entirely explained by tobacco consumption, which remains the major risk factor for lung cancer. Occupational radon and asbestos exposures are other important but less extended determinants of lung cancer. Genetic factors could also play a role in the occurrence of the disease. On the other side, a high consumption of fruit and vegetables is protective, but, so far, no single dietary component has been found to be preventive. In this article, we review the major risk factors of lung cancer with an emphasis on Spanish and European data.

Trimble, G. X. (1962). "Menthol cigarettes." BritiMed J* (5276): 500.

No abstract available.

Werley, M. S., C. R. Coggins, et al. (2007). "Possible effects on smokers of cigarette mentholation: a review of the evidence relating to key research questions." Regul Toxicol Pharmacol 47(2): 189-203.

Menthol (2-isopropyl-5-methyl-cyclohexan-1-ol) is used in food, pharmaceutical, and tobacco products. Despite its long usage history and GRAS status, scientific literature on effects of cigarette mentholation is limited. Because African-American men have high lung cancer rates and predominantly smoke mentholated cigarettes, and because menthol's cooling effect might affect puffing and smoke inhalation, possible adverse effects of cigarette mentholation have been suggested. We review the evidence on the effects of mentholation on smokers, and we also identify areas for further study. Five large epidemiological studies provide no evidence that cigarette mentholation increases lung cancer risk. Mentholation cannot explain the higher risk for lung cancer in African-American male smokers, who also predominantly smoke mentholated cigarettes. Limited data on other cancers also suggest no risk from mentholation. The scientific literature suggests that cigarette mentholation does not increase puff number or puff volume of smoked cigarettes, and has little or no effect on heart rate, blood pressure, uptake of carbon monoxide, tar intake or retention, or blood cotinine concentration. Mentholation has little effect on other smoke constituents, and no apparent effect on nicotine absorption, airway patency and smoking initiation, dependency or cessation. Any toxicological effects of cigarette mentholation on adult smokers are probably quite limited.

In Vitro and In Vivo Studies

Abanses, J. C., S. Arima, et al. (2009). "Vicks VapoRub induces mucin secretion, decreases ciliary beat frequency, and increases tracheal mucus transport in the ferret trachea." Chest 135(1): 143-148.

Vicks VapoRub (VVR) [Proctor and Gamble; Cincinnati, OH] is often used to relieve symptoms of chest congestion. We cared for a toddler in whom severe respiratory distress developed after VVR was applied directly under her nose. We hypothesized that VVR induced inflammation and adversely affected mucociliary function and tested this hypothesis in an animal model of airway inflammation by employing the following methods: [1] Trachea specimens excised from 15 healthy ferrets were incubated in culture plates lined with 200 mg of VAT, and the mucin secretion was compared to those from controls without VAT. Tracheal mucociliary transport velocity (MCTV) was measured by timing the movement of 4 mu L of mucus across the trachea. Ciliary beat frequency (CBF) was measured using video microscopy. [2] Anesthetized and intubated ferrets inhaled a placebo or VVR that was placed at the proximal end of the endotracheal tube. We evaluated both healthy ferrets and animals in which we first induced tracheal inflammation with bacterial endotoxin (it lipopolysaccharide [LPS]). Mucin secretion was measured using an enzyme-linked lectin assay, and lung water was measured by weight ratios. The results indicated: [1] Mucin secretion was increased by 63% over the controls in the NAIR in vitro group ($p < 0.01$). CBF was decreased by 35% ($p < 0.05$) in the VVR group. [2] Neither LPS nor VVR increased lung water, hot LPS decreased MCTV in both normal airways (31%) and VVR-exposed airways (30%; $p = 0.03$), and VVR increased MCTV by 34% in LPS-inflamed airways ($p = 0.002$). It was concluded that VVR stimulates mucin secretion and MCTV in the LPS-inflamed ferret airway. This set of findings is similar to the acute inflammatory stimulation observed with exposure to irritants, and may lead to mucus obstruction of small air-ways and increased nasal resistance.

Abeele, F. V., A. Zholos, et al. (2006). "Ca2+-independent phospholipase A(2)-dependent gating of TRPM8 by lysophospholipids." J Biol Chem 281(52): 40174-40182.

TRPM8 represents an ion channel activated by cold temperatures and cooling agents, such as menthol, that underlies the cold-induced excitation of sensory neurons. Interestingly, the only human tissue outside the peripheral nervous system, in which the expression of TRPM8 transcripts has been detected at high levels, is the prostate, a tissue not exposed to any essential temperature variations. Here we show that the TRPM8 cloned from human prostate and heterologously expressed in HEK-293 cells is regulated by the Ca2+-independent phospholipase A(2) (iPLA(2)) signaling pathway with its end products, lysophospholipids (LPLs), acting as its endogenous ligands. LPLs induce prominent prolongation of

TRPM8 channel openings that are hardly detectable with other stimuli (e.g. cold, menthol, and depolarization) and that account for more than 90% of the total channel open time. Down-regulation of iPLA(2) resulted in a strong inhibition of TRPM8-mediated functional responses and abolished channel activation. The action of LPLs on TRPM8 channels involved either changes in the local lipid bilayer tension or interaction with the critical determinant(s) in the transmembrane channel core. Based on this, we propose a novel concept of TRPM8 regulation with the involvement of iPLA2 stimulation. This mechanism employs chemical rather than physical (temperature change) signaling and thus may be the main regulator of TRPM8 activation in organs not exposed to any essential temperature variations, as in the prostate gland.

Alakayak, J. and C. Knall (2008). "Mentholated and non-mentholated cigarettes alter transepithelial electrical resistance of calu-3 human bronchial epithelial cells." Ethnic Dis 18(2 Suppl 1): S145-146.

A quarter of all smokers in the US smoke mentholated cigarettes with the frequency of use especially high among African Americans. Although African Americans smoke fewer cigarettes per day, they have a higher incidence of smoking related diseases. The reason for this is unknown. Tight junctions between lung epithelial cells are structures that act as a blockade against inhaled foreign particles. Lung cells from smokers exposed to cigarette smoke show an alteration in tight junction function as measured by reduced electrical resistance of the epithelial monolayer. This allows foreign matter a greater chance of passing through the lung barrier. We hypothesized that the smoke from mentholated cigarettes would have a greater effect on lung epithelial cells compared to non-mentholated cigarettes. To test this hypothesis, we exposed Calu-3 human bronchial epithelial cells to cigarette smoke using an in vitro air-liquid interface exposure system. Smoke from either mentholated or non-mentholated cigarettes was generated using the Federal Trade Commission smoking profile. After exposing Calu-3 cells to smoke from either mentholated or non-mentholated cigarettes, transepithelial electrical resistance (TER) was measured to determine the effect menthol has on the tight junctions of the Calu-3 cells. Although smoke from mentholated cigarettes caused a significant decrease in TER compared to air alone, the decrease in TER was not significantly different from that seen with non-mentholated cigarettes. Therefore, the data suggest that any increased risk from mentholated cigarettes is not due to a greater effect on TER compared to non-mentholated cigarettes.

Ashby, J. and R. W. Tennant (1991). "Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP." Mutat Res – Rev Genet 257(3): 229-306.

An analysis is presented in which are evaluated correlations among chemical structure, mutagenicity to Salmonella, and carcinogenicity to rats and mice among 301 chemicals tested by the U.S. NTP. Overall, there was a high correlation between structural alerts to DNA reactivity and mutagenicity, but the correlation of either property with carcinogenicity was low. If rodent carcinogenicity is regarded as a singular property of chemicals, then neither structural alerts nor mutagenicity to Salmonella are effective in its prediction. Given this,

the database was fragmented and new correlations sought between the derived sub-groups. First, the 301 chemicals were segregated into six broad chemical groupings. Second, the rodent cancer data were partially segregated by target tissue. Using the previously assigned structural alerts to DNA reactivity (electrophilicity), the chemicals were split into 154 alerting chemicals and 147 non-alerting chemicals. The alerting chemicals were split into three chemical groups; aromatic amino/nitro-types, alkylating agents and miscellaneous structurally-alerting groups. The non-alerting chemicals were subjectively split into three broad categories; non-alerting, non-alerting containing a non-reactive halogen group, and non-alerting chemicals with minor concerns about a possible structural alert. The tumor data for all 301 chemicals are re-presented according to these six chemical groupings. The most significant findings to emerge from comparisons among these six groups of chemicals were as follows: (a) Most of the rodent carcinogens, including most of the 2-species and/or multiple site carcinogens, were among the structurally alerting chemicals. (b) Most of the structurally alerting chemicals were mutagenic; 84% of the carcinogens and 66% of the non-carcinogens. 100% of the 33 aromatic amino/nitro-type 2-species carcinogens were mutagenic. Thus, for structurally alerting chemicals, the Salmonella assay showed high sensitivity and low specificity (0.84 and 0.33, respectively). (c) Among the 147 non-alerting chemicals <5% were mutagenic, whether they were carcinogens or non-carcinogens (sensitivity 0.04). From these facts we conclude that the concepts of genotoxic and non-genotoxic rodent carcinogenicity are worthy of continued attention. Also, that it is meaningless to discuss the sensitivity/specificity of the Salmonella assay without defining the broad chemical classes under discussion. This last conclusion is important to any model for screening environmental chemicals for potential carcinogens. Some rodent tissues, such as the lung and Zymbal's gland, are uniquely associated with genotoxic carcinogenesis, while others are equally susceptible to non-genotoxic carcinogenesis. Four such tissues are currently studied as possible sites of non-genotoxic carcinogenicity, and these were separately considered; male rat kidney-specific carcinogenic effects, rodent leukaemogens, rodent thyroid gland carcinogens and mouse liver carcinogens (the latter being the largest group, 97 of the 301 chemicals having increased tumor incidences in this tissue). Chemicals inducing tumors in these tissues were of disparate chemical classes and were predominantly non-mutagenic. These facts, together with the specificity of the carcinogenic effects is indicative of carcinogenicity resulting from a specific interaction between the chemical and the tissue, rather than it being an intrinsic and unique property of the chemical. Even when tumours in these four tissues were eliminated from the database, the Salmonella assay was only positive for 67% of the remaining 113 carcinogens (derived from a total of 162 carcinogens in the database). This indicates that a range of additional sites are subject to tissue-specific carcinogenesis by putative non-genotoxins. A distibution chart is presented which represents the 301 chemicals according to the 6 chemical groupings and the level of carcinogenic effect. From this it becomes apparent that the NTP database is dominated by two major groups of chemicals. First, a group of struc urally-alerting and mutagenic carcinogens that are predominantly active in both species and/or multiple sites, and second a group of non-alerting, non-mutagenic non-carcinogens. In between these two groups is a diffusely spread group of species/sex/tissue specific carcinogens, only some of which are mutagenic and/or structurally alerting. It is among the last group of carcinogens that research is required to understand their mechanism of action and their significance to man.

The in vitro mammalian cell genotoxicity database of the NTP failed to distinguish these last carcinogens from the non-carcinogens, and this endorses that research into the mode of action of these carcinogens should not be concerned with their genotoxicity.

Azzi, C., J. Zhang, et al. (2006). "Permeation and reservoir formation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and benzo[a]pyrene (B[a]P) across porcine esophageal tissue in the presence of ethanol and menthol." Carcinogenesis 27(1): 137-45.

Environmental influences may affect carcinogen absorption and residency in the tissues of the aero-digestive tract. We quantified the effect of ethanol and menthol on the rates of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and benzo[a]pyrene (B[a]P) absorption using a fully validated in vitro diffusion system, capable of accurately and precisely quantifying tobacco carcinogen permeation and reservoir formation in porcine esophageal mucosa. Confocal microscopy was employed to visualize the location of B[a]P in the exposed membranes. Markedly different extents of permeation and reservoir formation for the tobacco carcinogens were recorded in the presence of ethanol and menthol. The water-soluble NNK permeated the membrane rapidly, while the lipophilic B[a]P did not appreciably diffuse through the tissue. Significantly different extents of reservoir formation were observed for the different carcinogens and in the presence of the different penetration-enhancer solvents. Alcohol (at 5% concentration) did not influence the permeation or reservoir formation of NNK. A mentholated donor solution (0.08%) both decreased the flux of NNK and significantly increased the tissue reservoir formation. The magnitude of the reservoir formed by B[a]P was relatively extensive (even though membrane permeation rates were negligible), being greatest in the presence of both ethanol and menthol. This suggests synergy between the two penetration-enhancer species acting on this carcinogen. Confocal microscopy studies confirmed that there was an appreciable intra-cellular, and specifically nuclear, association of the B[a]P species during the reservoir formation process. The aqueous solubility of the diffusing species and the presence of penetration enhancers appeared to be key factors in the absorption and cellular binding processes. The results presented support the hypothesis that the use of mentholated cigarettes, or the concomitant consumption of alcohol while smoking, may have marked effects on the fate of tobacco chemicals. This finding may help to explain elevated rates of esophageal squamous cell carcinoma in African Americans.

Beck, B., G. Bidaux, et al. (2007). "Prospects for prostate cancer imaging and therapy using high-affinity TRPM8 activators." Cell Calcium 41(3): 285-94.

One of the best-studied temperature-gated channels is transient receptor potential melastatin 8 (TRPM8), which is activated by cold and cooling agents, such as menthol. Besides inducing a cooling sensation in sensory neurons, TRPM8 channel activation also plays a major role in physiopathology. Indeed, TRPMP8 expression increases in early stages of prostate cancer and its involvement in prostate cell apoptosis has recently been demonstrated. Thus, as TRPM8 is a tumor marker with significant potential use in diagnosis, as well as a target for cancer therapy, there is a need for new TRPM8-specific ligands. In this

study, we investigated the action of "WS" compounds on TRPM8 channels. We compared the affinity of these molecules to that of menthol and icilin. This enabled us to identify new TRPM8 agonists. The menthol analog with the highest affinity, WS-12, had an EC(50) value about 2000 times lower than that of menthol and is, therefore, the highest-affinity TRPM8 ligand known to date. Finally, incorporating a fluorine atom in the WS-12 retained 75% of the activity of the parent compound. The high affinity of this new TRPM8 ligand and the possibility of incorporating a radiohalogen could thus be useful for diagnosis, monitoring and, perhaps, even therapy of prostate cancer.

Bernhardt, G., B. Biersack, et al. (2008). "Terpene conjugates of diaminedichloridoplatinum(II) complexes: antiproliferative effects in HL-60 leukemia, 518A2 melanoma, and HT-29 colon cancer cells." Chem Biodivers 5(8): 1645-59.

Twenty-eight [6-(aminomethyl)nicotinate]dichloridoplatinum(II) complexes 1 esterified with various terpene alcohols either directly or via alkyl spacers were tested for antiproliferative activity in human 518A2 melanoma and HL-60 leukemia cells. Generally, conjugates with menthanes and polycyclic sesquiterpenes attached via propane-1,2-diyl spacers were most active. In the melanoma cells, the propane-1,2-diyl-spacered conjugates of (-)-menthol (1a(2')), (+)-neomenthol (1b(2')), (-)-carvomenthol (1h(2')), and (-)-isolongifolol (1n(2')) displayed growth inhibition at IC(50)<4 microM which is ten times smaller than that of cisplatin. The stationary diamino ligand was also crucial. The (-)-menthyl ester complexes with 2,3-diaminopropanoate (9a) and 2,4-diaminobutanoate (10a) ligands caused a greater and persistent growth inhibition in HT-29 colon cancer cells upon long-term exposure when compared to the 6-(aminomethyl)nicotinate analogue 1a. The cedrenyl ester 1l and the menthoxyisopropyl ester 1a(2') proved most efficacious in all three tumor cell lines. The DNA binding of complexes 1 was assessed by electrophoretic band-shift experiments and found correlated to the terpene structure but not to the observed antiproliferative activities.

Bernson, V. S. and B. Pettersson (1983). "The toxicity of menthol in short-term bioassays." Chem Biol Interact 46(2): 233-46.

The toxicity of menthol was studied on 4 different in vitro systems covering organ, cellular and subcellular levels. The 50% inhibitory concentration (IC50) for the cellular and subcellular systems ranged from 0.32 mM to 0.76 mM. At a concentration of 0.5 mM menthol the receptor mediated respiratory stimulation of isolated brown adipocytes was markedly inhibited while the intracellular mitochondrial functions were still unaffected. However, using isolated rat liver mitochondria 0.5 mM menthol was found to cause increase in the 'state 4' respiratory rate and osmotic swelling, indicating a leakage of the mitochondrial membrane. We therefore suggest that one effect of menthol is a deterioration of biological membranes. For the determination of the cellular toxicity of foreign compounds isolated brown adipocytes represents a convenient and sensitive model, providing the possibility to localize the primary site of action in terms of mitochondrial or extramitochondrial level.

Bodding, M., U. Wissenbach, et al. (2007). "Characterisation of TRPM8 as a pharmacophore receptor." Cell Calcium 42(6): 618-28.

Some proteins of the transient receptor potential (TRP) family form temperature sensitive ion channels. One member of the melastatin (M) group, namely TRPM8 is activated by cold and cooling compounds such as menthol and icilin, and its gene is up-regulated in prostate cancer and other malignancies. Here we characterise the effects of the carboxamides WS-12, CPS-113, CPS-369, the carboxylic acid WS-30 and the phosphine oxide WS-148 by Ca2+ imaging experiments and whole-cell patch-clamp recordings on TRPM8 expressing human embryonic kidney (HEK), lymph node prostate cancer (LNCaP) and dorsal root ganglia (DRG) cells. The cooling compounds introduced in this study, show a dose-dependent and reversible activation of TRPM8 with EC50 values in the nM to low microM range. The carboxamide WS-12 is most potent in activating TRPM8. It is selective, since other TRP proteins are not stimulated at muM concentrations and its efficacy with respect to TRPM8 is similar to the one of icilin. In summary, the compounds described in this study represent new tools to dissect TRPM8 functions and may serve as chemical leads for the development of additional TRPM8 agonists and novel antagonists. Such compounds may be beneficial for preventing noxious cold perception. They could also be useful in diagnosis and treatment of most common cancers in which the TRPM8 gene is up-regulated in comparison to the corresponding normal tissue.

Boyd, E. M. and E. P. Sheppard (1969). "A bronchomucotropic action in rabbits from inhaled menthol and thymol." Arch Int Pharmacodyn Ther 182(1): 206-14.

No abstract available.

Chen, H., X. Chang, et al. (2004). "A study of microemulsion systems for transdermal delivery of triptolide." J Control Release 98(3): 427-36.

Triptolide possesses immunosuppressive, anti-fertility and anti-cancer activities. Due to its severe toxicity, microemulsions with controlled, sustained and prolonged delivery of triptolide via a transdermal route are expected to reduce its adverse side effects. The purpose of the present study was to investigate the microemulsions for transdermal delivery of triptolide. The pseudo-ternary phase diagrams were developed and various microemulsion formulations were prepared using oleic acid as an oil, Tween 80 as a surfactant and propylene glycol as a cosurfactant. The droplet size of microemulsions was characterized by photocorrelation spectroscopy. The transdermal ability of triptolide from microemulsions was evaluated in vitro using Franz diffusion cells fitted with mouse skins and triptolide was analyzed by high-performance liquid chromatography. The effect of menthol as a permeation enhancer, and the loading dose of triptolide in microemulsions on the permeation rate were also evaluated. The triptolide-loaded microemulsions showed an enhanced in vitro permeation through mouse skins compared to an aqueous solution of 20% propylene glycol containing 0.025% triptolide. The permeation of microemulsions accorded with the Fick's first diffusion law. No obvious skin irritation was observed for the studied microemulsion ME6, but the aqueous solution of 20% propylene glycol containing 0.025% triptolide revealed the significant skin irritation. The results indicate that the studied microemulsion systems, especially ME6, may be promising vehicles for the transdermal delivery of triptolide.

Chen, L. J., E. H. Lebetkin, et al. (2001). "Metabolism of (R)-(+)-pulegone in F344 rats." Drug Metab Dispos 29(12): 1567-77.

(R)-(+)-Pulegone, a monoterpene ketone, is a major component of pennyroyal oil. Ingestion of high doses of pennyroyal oil has caused severe toxicity and occasionally death. Studies have shown that metabolites of pulegone were responsible for the toxicity. Previous metabolism studies have used high, near lethal doses and isolation and analysis techniques that may cause degradation of some metabolites. To clarify these issues and further explore the metabolic pathways, a study of (14)C-labeled pulegone in F344 rats at doses from 0.8 to 80 mg/kg has been conducted. High-pressure liquid chromatography (HPLC) analysis of the collected urine showed the metabolism of pulegone to be extensive and complex. Fourteen metabolites were isolated by HPLC and characterized by NMR, UV, and mass spectroscopy. The results demonstrated that pulegone was metabolized by three major pathways: 1) hydroxylation to give monohydroxylated pulegones, followed by glucuronidation or further metabolism; 2) reduction of the carbon-carbon double bond to give diastereomeric menthone/isomenthone, followed by hydroxylation and glucuronidation; and 3) Michael addition of glutathione to pulegone, followed by further metabolism to give diastereomeric 8-(N-acetylcystein-S-yl)menthone/isomenthone. This 1,4-addition not only took place in vivo but also in vitro under catalysis of glutathione S-transferase or mild base. Several hydroxylated products of the two mercapturic acids were also observed. Contrary to the previous study, all but one of the major metabolites characterized in the present study are phase II metabolites, and most of the metabolites in free forms are structurally different from those previously identified phase I metabolites.

Chiyotani, A., J. Tamaoki, et al. (1994). "Stimulation by menthol of Cl secretion via a Ca(2+)-dependent mechanism in canine airway epithelium." Br J Pharmacol 112(2): 571-5.

To investigate the effect of menthol on airway epithelial ion transport function, we studied the bioelectrical properties of canine cultured tracheal epithelium by Ussing's short-circuit technique in vitro. The addition of menthol (10(-3) M) to the mucosal but not the submucosal solution increased the short-circuit current (Isc) from 6.2 +/- 0.9 to 14.0 +/- 2.2 microA cm-2 ($P < 0.001$), and this effect was accompanied by increases in transepithelial potential difference and conductance. The response was dose-dependent, with the maximal increase from the baseline value and the concentration required to produce a half-maximal effect (EC50) being 6.4 +/- 0.9 microA cm-2 ($P < 0.001$) and 40 microM, respectively. Other cyclic alcohols, including menthone and cyclohexanol, had no effect on the electrical properties. The menthol-induced increase in Isc was not altered by pretreatment of the cells with amiloride, indomethacin, or propranolol but was abolished by diphenylamine-2-carboxylate, furosemide or substitution of Cl with iodide in the medium. Menthol (10(-3) M) increased cytosolic levels of free calcium ([Ca2+]i) from 98 +/- 12 to 340 +/- 49 nM ($P < 0.01$) in fura-2-loaded tracheal epithelium but did not affect the intracellular adenosine 3',5'-cyclic monophosphate content. These results suggest that menthol stimulates Cl secretion across airway epithelium, probably through a Ca(2+)-dependent mechanism, and might thus influence mucociliary transport in the respiratory tract.

Clapham, D. E., D. Julius, et al. (2005). "International Union of Pharmacology. XLIX. Nomenclature and structure-function relationships of transient receptor potential channels." Pharmacol Rev 57(4): 427-450.

The TRP channels are a family of ion channel proteins that permeate Na + and Ca2+ and, in several cases, Mg2+. Most cells contain several to many TRP subunits, complicating the separation of monomeric and heteromeric channel characteristics. The multipotent phosphatidylinositol pathway is involved in most TRP channel regulation, but the details of this regulation are just beginning to be elucidated. At this time there is no unifying theme in their mechanism for activation. Since TRPs are intimately linked with intracellular Ca2+ signaling, they are implicated in the control of cell cycle progression, cell migration, and programmed cell death. TRP channels also seem to be important in epithelial uptake of divalent ions. Genetic approaches combined with robust assays have most clearly established their roles in sensory functions. Tables 1 through 28 summarize the molecular, physiological, and pharmacological properties of these ion channels in more detail.

Colvin, L. A., P. R. Johnson, et al. (2008). "From bench to bedside: a case of rapid reversal of bortezomib-induced neuropathic pain by the TRPM8 activator, menthol." J Clin Oncol 26(27): 4519-20.

No abstract available.

Das, P. K., R. S. Rathor, et al. (1970). "Effect on ciliary movements of some agents which come in contact with the respiratory tract." Indian J Physiol Pharmacol 14(4): 297-303.

No abstract available.

De Petrocellis, L., K. Starowicz, et al. (2007). "Regulation of transient receptor potential channels of melastatin type 8 (TRPM8): Effect of cAMP, cannabinoid CB, receptors and endovanilloids." Exp Cell Res 313(9): 1911-1920.

The transient receptor potential channel of melastatin type 8 (TRPM8), which is gated by low (< 25 degrees C) temperature and chemical compounds, is regulated by protein kinase C-mediated phosphorylation in a way opposite to that observed with the transient receptor potential channel of vanilloid type 1 (TRPV1), i.e. by being desensitized and not sensitized. As TRPV1 is sensitized also by protein kinase A (PKA)-mediated phosphorylation, we investigated the effect of two activators of the PKA pathway, 8-Br-cAMP and forskolin, on the activity of menthol and icilin at TRPM8 in HEK-293 cells stably overexpressing the channel (TRPM8-HEK-293 cells). We also studied the effect on TRPM8 of (1) a series of compounds previously shown to activate or antagonize TRPV1, and (2) co-stimulation of transiently co-expressed cannabinoid CB, receptors. Both 8-Br-cAMP (100 mu M) and forskolin (10 mu M) right-shifted the dose-response curves for the TRPM8-mediated effect of icilin and menthol on intracellular Ca2+. The inhibitory effects of 8-Br-cAMP and forskolin were attenuated by the selective PKA inhibitor Rp-cAMP-S. Stimulation of human CB, receptors transiently co-expressed in TRPM8-HEK-293 cells also inhibited TRPM8 response to icilin. Finally, some TRPV1 agonists and antagonists, but not iodinated

antagonists, antagonized icilin- and much less so menthol-, induced TRPM8 activation. Importantly, the endovanilloids/endocannabinoids, anandamide and NADA, also antagonized TRPM8 at submicromolar concentrations. Although these findings need to be confirmed by experiments directly measuring TRPM8 activity in natively TRPM8-expressing cells, they support the notion that the same regulatory events have opposing actions on TRPM8 and TRPV1 receptors and identify anandamide and NADA as the first potential endogenous functional antagonists of TRPM8 channels.

De Petrocellis, L., V. Vellani, et al. (2008). "Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8." J Pharmacol Exp Ther 325(3): 1007-15.

The plant cannabinoids (phytocannabinoids), cannabidiol (CBD), and Delta(9)-tetrahydrocannabinol (THC) were previously shown to activate transient receptor potential channels of both vanilloid type 1 (TRPV1) and ankyrin type 1 (TRPA1), respectively. Furthermore, the endocannabinoid anandamide is known to activate TRPV1 and was recently found to antagonize the menthol- and icilin-sensitive transient receptor potential channels of melastatin type 8 (TRPM8). In this study, we investigated the effects of six phytocannabinoids [i.e., CBD, THC, CBD acid, THC acid, cannabichromene (CBC), and cannabigerol (CBG)] on TRPA1- and TRPM8-mediated increase in intracellular Ca2+ in either HEK-293 cells overexpressing the two channels or rat dorsal root ganglia (DRG) sensory neurons. All of the compounds tested induced TRPA1-mediated Ca2+ elevation in HEK-293 cells with efficacy comparable with that of mustard oil isothiocyanates (MO), the most potent being CBC (EC(50) = 60 nM) and the least potent being CBG and CBD acid (EC(50) = 3.4-12.0 microM). CBC also activated MO-sensitive DRG neurons, although with lower potency (EC(50) = 34.3 microM). Furthermore, although none of the compounds tested activated TRPM8-mediated Ca2+ elevation in HEK-293 cells, they all, with the exception of CBC, antagonized this response when it was induced by either menthol or icilin. CBD, CBG, THC, and THC acid were equipotent (IC(50) = 70-160 nM), whereas CBD acid was the least potent compound (IC(50) = 0.9-1.6 microM). CBG inhibited Ca2+ elevation also in icilin-sensitive DRG neurons with potency (IC(50) = 4.5 microM) similar to that of anandamide (IC(50) = 10 microM). Our findings suggest that phytocannabinoids and cannabis extracts exert some of their pharmacological actions also by interacting with TRPA1 and TRPM8 channels, with potential implications for the treatment of pain and cancer.

De-Oliveira, A. C., A. A. Fidalgo-Neto, et al. (1999). "In vitro inhibition of liver monooxygenases by beta-ionone, 1,8-cineole, (-)-menthol and terpineol." Toxicology 135(1): 33-41.

The present study was undertaken to investigate the inhibitory effects of beta-ionone, (-)-menthol, 1,8-cineole and alpha-terpineol on liver microsomal enzymes involved in the biotransformation of xenobiotic substances. The effects of beta-ionone and the foregoing monoterpenoid compounds on the activity of pentoxyresorufin-O-dependentilase (PROD), a selective marker for CYP2B1, were determined in a pool of liver microsomes prepared from phenobarbital-treated rats. On the other hand, the inhibitory effects of these substances on the activities of ethoxyresorufin-O-deethylase (EROD), a marker for CYP1A1, and methoxyresorufin-O-demethylase (MROD), a marker for CYP1A2, were investigated

in a pool of hepatic microsomes from beta-naphthoflavone-treated rats. Beta-ionone caused a concentration-related reduction of PROD activity with an IC50 value as low as 0.03 microM. The analysis of alterations produced by beta-ionone on PROD kinetic parameters (Lineweaver-Burk double-reciprocal plot) suggested that inhibition is non-competitive (Ki = 89.9 nM). Although being less potent than beta-ionone, 1,8-cineole (IC50 = 4.7 microM), (-)-menthol (IC50 = 10.6 microM) and terpineol (IC50 = 14.8 microM) also proved to be in vitro inhibitors of PROD reaction. Results also revealed that beta-ionone was a weak inhibitor of EROD (IC50 >100 microM) and MROD (IC50 >200 microM). Neither 1,8-cineole nor terpineol--tested in concentrations up to 150 microM--caused any decrease of EROD activity while (-)-menthol, at a concentration as high as 160 microM, produced only a slight reduction of the reaction rate. Terpineol (up to 150 microM) did not induce any reduction of MROD activity while 1,8-cineole (IC50 >300 microM) and (-)-menthol (IC50 >300 microM) caused only slight decreases of the reaction rate. The potent inhibitory effects on CYP2B1 suggest that beta-ionone, and the other monoterpenoids tested, may interfere with the metabolism of xenobiotics which are substrates for this isoenzyme.

Doolittle, D. J., C. K. Lee, et al. (1990). "Comparative studies on the genotoxic activity of mainstream smoke condensate from cigarettes which burn or only heat tobacco." Environ Mol Mutagen 15(2): 93-105.

The in vitro genotoxic activity of mainstream cigarette smoke condensate (CSC) from cigarettes which heat but do not burn tobacco was compared to that of CSC from cigarettes which burn tobacco. CSCs from five cigarettes were compared. Three of the cigarettes [the Kentucky reference research cigarette (1R4F), a commercially available ultra-low tar brand (ULT) and a commercially available ultra-low tar menthol brand (ULT-menthol]) burn tobacco while two of the cigarettes [a regular (TEST) and a menthol (TEST-menthol]) heat tobacco. CSC from all cigarettes were collected by identical standard techniques, which involved collecting mainstream smoke particulate matter on Cambridge filter pads under FTC smoking conditions. The pads were extracted with DMSO, and the CSCs obtained [10 mg total particulate matter (TPM)/ml DMSO] were evaluated at identical concentrations in an in vitro genetic toxicology test battery. CSCs from 1R4F, ULT, and ULT-menthol cigarettes were mutagenic in Ames bacterial strains TA98, TA100, TA1537, and TA1538 in the presence of metabolic activation (S9 from Aroclor-induced rat liver) but negative in strain TA1535. In the absence of metabolic activation, 1R4F, ULT, and ULT-menthol CSCs were not mutagenic except for a weak response in strain TA1537 for the 1R4F and ULT CSCs. TEST and TEST-menthol CSCs were nonmutagenic in all five bacterial strains, both with and without metabolic activation. CSCs from 1R4F, ULT, and ULT-menthol cigarettes were positive in the CHO-chromosomal aberration assay and in the CHO—sister chromatid exchange assay both with and without metabolic activation while TEST and TEST-menthol CSCs were negative in both assays, either with or without metabolic activation. CSCs from 1R4F, ULT, and ULT-menthol cigarettes were weakly positive in inducing DNA repair in cultured rat hepatocytes while TEST and TEST-menthol CSCs were negative in this assay. All five CSCs were nonmutagenic in the CHO-HGPRT assay both with and without metabolic activation. CSCs from the 1R4F, ULT, and ULT-menthol cigarettes were cytotoxic in the CHO-HGPRT assay, both with and without metabolic

activation, while TEST and TEST-menthol CSCs were not cytotoxic under either condition. These results demonstrate that mainstream CSCs from the TEST and TEST-menthol cigarettes are neither genotoxic nor cytotoxic under conditions where CSCs from 1R4F, ULT, and ULT-menthol cigarettes are genotoxic and/or cytotoxic in a concentration-dependent manner.

Doolittle, D. J., C. K. Lee, et al. (1990). "Genetic toxicology studies comparing the activity of sidestream smoke from cigarettes which burn or only heat tobacco." Mutat Res 240(2): 59-72.

The results of in vitro genetic toxicology studies of sidestream cigarette smoke (SSCS) from cigarettes which heat but do not burn tobacco were compared to those of sidestream smoke from cigarettes which burn tobacco. SSCSs from 5 cigarettes were compared. Three of the cigarettes, the Kentucky reference research cigarette (1R4F), a commercially available ultra-low-tar brand (ULT) and a commercially available ultra-low-tar menthol brand (ULT-menthol) burn tobacco while two of the cigarettes, a regular (TEST) and a menthol (TEST-menthol) heat tobacco. SSCSs from all cigarettes were prepared by identical techniques, which involved collecting sidestream smoke particulate matter on Cambridge filter pads and combining the particulate matter with the vapor-phase materials collected by bubbling the smoke exiting the Cambridge pad through DMSO. The SSCSs obtained (equivalent to 0.4 cigarettes/ml DMSO) were evaluated at identical concentrations in an in vitro genetic toxicology test battery. SSCS from 1R4F, ULT and ULT-menthol cigarettes produced positive results in Ames bacterial strains TA98, TA100, TA1537 and TA1538 in the presence of metabolic activation (S9 from Aroclor-induced rat liver) but negative results in strain TA1535. In the absence of metabolic activation, 1R4F, ULT and ULT-menthol SSCSs were not significantly mutagenic. TEST and TEST-menthol SSCSs produced negative results in all 5 bacterial strains, both with and without metabolic activation. SSCS from 1R4F, ULT and ULT-menthol cigarettes produced positive results in the CHO chromosomal aberration assay and in the CHO sister-chromatid exchange assay both with and without metabolic activation while TEST and TEST-menthol SSCSs produced negative results in both assays, either with or without metabolic activation. The SSCSs from 1R4F, ULT and ULT-menthol cigarettes were weakly positive in inducing DNA repair in cultured rat hepatocytes while TEST and TEST-menthol SSCSs were negative in this assay. All 5 SSCSs were nonmutagenic in the CHO-HGPRT assay both with and without metabolic activation. SSCSs from the 1R4F, ULT and ULT-menthol cigarettes were cytotoxic in the CHO-HGPRT assay, both with and without metabolic activation, while TEST and TEST-menthol SSCSs were not cytotoxic under either condition. These results demonstrate that sidestream smoke from cigarettes which heat but do not burn tobacco (TEST and TEST-menthol) was neither genotoxic nor cytotoxic under conditions where sidestream smoke from cigarettes which burn tobacco (1R4F, ULT and ULT-menthol) was genotoxic and/or cytotoxic in a concentration-dependent manner.

Edris, A. E. and E. S. Farrag (2003). "Antifungal activity of peppermint and sweet basil essential oils and their major aroma constituents on some plant pathogenic fungi from the vapor phase." Nahrung 47(2): 117-21.

The vapors of peppermint oil and two of its major constituents (menthol and menthone), and sweet basil oil and two of its major constituents (linalool and eugenol), were tested against Sclerotinia sclerotiorum (Lib.), Rhizopus stolonifer (Ehrenb. exFr.) Vuill and Mucor sp. (Fisher) in a closed system. These fungi cause deterioration and heavy decay of peach fruit during marketing, shipping and storage. The essential oils, their major individual aroma constituents and blends of the major individual constituents at different ratios inhibited the growth of the fungi in a dose-dependent manner. Menthol was found to be the individual aroma constituent responsible for the antifungal properties of peppermint essential oil, while menthone alone did not show any effect at all doses. In the case of basil oil, linalool alone showed a moderate antifungal activity while eugenol showed no activity at all. Mixing the two components in a ratio similar to their concentrations in the original oil was found to enhance the antifungal properties of basil oil indicating a synergistic effect.

Edwards, D. A., R. A. Mather, et al. (1988). "Spatial variation in response to odorants on the rat olfactory epithelium." Experientia 44(3): 208-11.

We have measured the electro-olfactogram produced by four odorants, nicotine, i-pentyl acetate, i-pentanoic acid and cineole from twelve positions on an in vitro preparation of rat olfactory tissue. Each odorant shows a different pattern of response over the twelve positions which can be explained by differences in olfactory receptor populations between regions of the rat olfactory epithelium. The result for nicotine is further evidence that there are olfactory receptors which are stimulated by nicotine when it is presented as a vapour.

Egashira, T. and W. J. Waddell (1984). "Histochemical localization of primary and secondary alcohol dehydrogenases in whole-body, freeze-dried sections of mice." Histochem J 16(9): 931-40.

Whole-body sagittal sections of frozen, C57BL/6J, adult, male mice were used for the localization of primary and secondary alcohol dehydrogenases in most tissues of the body. The reduction of Nitro BT with NAD+ as coenzyme, as described originally by Hardonk (1965), was utilized for the generation of coloured final reaction deposits. Ethanol was used as a substrate for primary alcohol dehydrogenase; 2-propanol, alpha-methylbenzyl alcohol and 2-butanol were used as substrates for secondary alcohol dehydrogenase. Liver and bronchial epithelium showed the highest activities for both enzymes; oesophageal and upper gastric epithelium showed a high activity of primary alcohol dehydrogenase. Pyrazole, indazole and imidazole inhibited primary, but not secondary, alcohol dehydrogenase. Dimethylsulphoxide and menthol slightly inhibited both enzymes. Oleic acid, sulphydryl agents, p-chloromercuribenzoate, and copper sulphate also inhibited both enzymes. Slight inhibition of secondary dehydrogenase was observed on co-administration of several alcohols. As expected, N-nitrosonornicotine did not function as a substrate for alcohol dehydrogenases. When this compound was present in the histochemical incubation media, no activity was seen at any of the usual sites of these enzymes. The distribution of the alcohol dehydrogenase activities

found in this study correlates with the distribution of radioactivity in oesophagus, bronchi and liver after administration of [14C]nitrosonornicotine. This suggests that the alcohol dehydrogenases may be involved in the metabolism of hydroxylated nitrosonornicotine, a metabolite of the most abundant known carcinogen in cigarette smoke.

Ertel, A., R. Eng, et al. (1991). "The differential effect of cigarette smoke on the growth of bacteria found in humans." Chest 100(3): 628-30.

The effect of cigarette smoke on growth of those species of bacteria that are considered common potential human pathogens was examined in vitro. Smoke from both mentholated and nonmentholated cigarettes inhibited the growth of Gram-positive cocci to a greater degree than that of Gram-negative rods. Staphylococcus aureus, Streptococcus pneumoniae, and a variety of other streptococci were inhibited at a smoke solution dilution of 1:8. Enteric bacteria such as Klebsiella, Enterobacter, and Pseudomonas were not affected by a 1:1 dilution of the solution. As with the Gram-positive cocci, the Neisseria species and Branhamella were also inhibited at a dilution of 1:8. Culture results of the mouth of 15 smokers and 15 nonsmokers showed that the smokers have a propensity to develop heavy Gram-negative bacterial colonization.

Fajardo, O., V. Meseguer, et al. (2008). "TRPA1 channels: novel targets of 1,4-dihydropyridines." Channels 2(6): 429-438.

Transient receptor potential type A1 (TRPA1) channels are cation permeable channels activated by irritant chemicals and pungent natural compounds. Their location in peptidergic sensory terminals innervating the skin and blood vessels makes them important effectors of vasodilator responses of neural origin. 1,4-dihydropyridines are a class of L-type calcium channel antagonists commonly used in the treatment of hypertension and ischemic heart disease. Here we show that four different 1,4-dihydropyridines (nifedipine, nimodipine, nicardipine and nitrendipine), and the structurally related L-type calcium channel agonist BayK8644, exert powerful excitatory effects on TRPA1 channels. The activation does not depend on elevated Ca2+ levels and cross-desensitizes with that produced by other TRPA1 agonists. The activation produced by nifedipine was reduced by camphor and the selective TRPA1 antagonist HC03001. In a subclass of mouse nociceptors expressing TRPA1 channels, assessed by responses to the TRPA1 agonist mustard oil, nifedipine also produced large elevations in [Ca2+](i). These responses were fully abrogated in TRPA1(-/-) mice. These findings identify TRPA1 channels as a new molecular target for the 1,4-dihydropyridine class of calcium channel modulators.

Foureman, P., J. M. Mason, et al. (1994). "Chemical mutagenesis testing in Drosophila. IX. Results of 50 coded compounds tested for the national toxicology program." Environ Mol Mutagen 23(1): 51-63.

Fifty chemicals were tested for mutagenic activity in post-meiotic and meiotic germ cells of male Drosophila melanogaster using the sex-linked recessive lethal (SLRL) assay. As in the previous studies in this series, feeding was chosen as the first route of administration. If the compound failed to induce mutations by this route, injection exposure was used.

One gaseous chemical (1,3-butadiene) was tested only by inhalation. Those chemicals that were mutagenic in the sex-linked recessive lethal assay were further tested for the ability to induce reciprocal translocations. Eleven of the 50 chemicals tested were mutagenic in the SLRL assay. These included bis(2-chloroethyl) ether, 1,4-butanediol diglycidyl ether, 1-chloro-2- propanol, dimethyl methylphosphonate, dimethyl morpholinophosphoramidate, dimethyloldihydroxyethylene urea, 2,2-dimethyl vinyl chloride, hexamethylphosphoramide, isatin-5-sulfonic acid (Na salt), isopropyl glycidyl ether, and urethane. Five of these, including 1,4-butanediol diglycidyl ether, 2,2-dimethyl vinyl chloride, hexamethylphosphoramide, isopropyl glycidyl ether, and urethane, also induced reciprocal translocations.

Galeotti, N., L. Di Cesare Mannelli, et al. (2002). "Menthol: a natural analgesic compound." Neurosci Lett 322(3): 145-8.

Menthol, after topical application, causes a feeling of coolness due to stimulation of 'cold' receptors by inhibiting Ca++ currents of neuronal membranes. Since Ca++ channel blockers are endowed with analgesic properties, the aim of the present study was to investigate the potential antinociceptive effect of menthol. (-)-Menthol produced a dose-dependent increase in the pain threshold in the mouse hot-plate (3-10 mg kg(-1) p.o.) and abdominal constriction (3-10 mg kg(-1) p.o.; 10 microg per mouse intracerebroventricularly (i.c.v.)) tests. The antinociceptive effect of (-)-menthol was antagonised by the unselective opioid antagonist naloxone and by the selective kappa-antagonist nor-NBI. Conversely, CTOP (mu-antagonist), 7-benzylidenenal-trexone (delta(1) antagonist) and naltriben (delta(2) antagonist) did not prevent (-)-menthol antinociception. In both tests, (+)-menthol (10-50 mg kg(-1) p.o.; 10-30 microg per mouse i.c.v.) was unable to modify the pain threshold. These results indicate that (-)-menthol is endowed with analgesic properties mediated through a selective activation of kappa-opioid receptors.

Gaworski, C. L., M. M. Dozier, et al. (1997). "13-week inhalation toxicity study of menthol cigarette smoke." Food Chem Toxicol 35(7): 683-92.

Menthol is a common pharmaceutical, food and tobacco flavouring ingredient used for its minty characteristics and cooling effects. A 13-wk comparative nose-only smoke inhalation toxicity study was conducted using an American-style, cellulose acetate-filtered, non-menthol reference cigarette and a similarly blended test cigarette containing 5000 ppm synthetic l-menthol tobacco. Male and female Fischer 344 rats were exposed for 1 hr/day, 5 days/wk for 13 wk at target mainstream smoke particulate concentrations of 200, 600 or 1200 mg/m3, while control rats were exposed to filtered air. Internal dose biomarkers (blood carboxyhaemoglobin, serum nicotine and serum continine) indicated equivalent exposures were obtained for the two cigarettes. Effects typically noted in rats exposed to high levels of mainstream tobacco smoke were similar for both cigarette types and included reduced body weights (males slightly more affected than females), increased heart-to-body weight ratios and lung weights, and histopathological changes in the respiratory tract. Rats exposed to reference cigarette smoke displayed a dose-related increase in nasal discharge that was not observed in menthol smoke-exposed rats. All smoke-related effects diminished significantly during a 6-wk non-exposure recovery period. The results of this 13-wk smoke inhalation study indicated that the addition of 5000 ppm menthol to tobacco had no

substantial effect on the character or extent of the biological responses normally associated with inhalation of mainstream cigarette smoke in rats.

Gaworski, C. L., J. D. Heck, et al. (1999). "Toxicologic evaluation of flavor ingredients added to cigarette tobacco: Skin painting bioassay of cigarette smoke condensate in SENCAR mice." Toxicology 139(1-2): 1-17.

Four comparative two-stage SENCAR mouse skin painting bioassays were conducted with cigarette smoke condensate (CSC) preparations to evaluate the effect of common American cigarette flavoring ingredients on tumor promotion. Each independent study employed a unique flavoring combination applied to tobacco at exaggerated levels, and in total resulted in an evaluation of 150 ingredients. Groups of 30-50 female SENCAR mice each were initiated topically with 50 Î¼g of 7,12-dimethylbenz(a)anthracene (DMBA), and promoted thrice weekly for 26 weeks with either 10 or 20 mg of CSC from test cigarettes containing ingredient mixtures. For comparison, separate groups of mice received concurrent treatment with CSC from reference cigarettes prepared without added ingredients. Negative and positive controls were treated with acetone or 12-0-tetradecanoyl-phorbol-13-acetate (TPA) as a promoter, respectively. CSC-only groups served as promotion controls. Tumors developed in >80% of the TPA-treated mice by study week 11, with a <3% background tumor formation in the acetone treated controls at termination. Tumor incidence in CSC-only promotion control groups was <20%, with no apparent difference between reference and test CSC groups. Approximately 70% of the DMBA-initiated mice promoted with 20 mg CSC developed tumors. Tumors first appeared around week 9, with about five tumors/tumor bearing animal. Tumor incidence, latency and multiplicity were CSC dose related, with a lower tumor incidence (approximately 50%), longer latency (12 weeks), and reduced tumor burden (four tumors/tumor bearing animal) at the 10 mg CSC dose level. While tumor incidence, latency and multiplicity data occasionally differed between test and comparative reference CSC groups, all effects appeared to be within normal variation for the model system. Furthermore, none of the changes appeared to be substantial enough to conclude that the tumor promotion capacity of CSC obtained from cigarettes containing tobacco with ingredients was discernibly different from the CSC obtained from reference cigarettes containing tobacco processed without ingredients.

Gordon, W. P., A. J. Forte, et al. (1982). "Hepatotoxicity and pulmonary toxicity of pennyroyal oil and its constituent terpenes in the mouse." Toxicol Appl Pharm 65(3): 413-424.

Pennyroyal oil, an aromatic mint-like oil used as a flavoring and fragrance agent and as a herbal medicine, caused acute hepatic and lung damage at doses of 400 mg/kg, ip, and higher in male Swiss-Webster mice. Cellular necrosis was localized to the centrilobular regions of the liver and bronchiolar epithelial cells of the lung. Capillary gas chromatographic analysis of samples of pennyroyal oil that were obtained from health food stores showed the presence of several monoterpene constituents. R-(+)-Pulegone was the major terpene and constituted greater than 80% of the constituent terpenes in the oils that were examined. Pulegone and two other constituent terpenes, isopulegone and menthofuran, were found to be both hepatotoxic and lung toxic. Based on results of histologic scoring of necrosis, plasma GPT elevations, and hepatic glutathione depletion, R-(+)-pulegone is

the terpene primarily responsible for the tissue necrosis. Furthermore, results of toxicity tests with several congeners of R-(+)-pulegone, including the enantiomeric S-(-)-pulegone, strongly implicated the Î±-isopropylidene ketone group as the structural unit required for eliciting hepatotoxicity, although the configurational orientation of the methyl group can modulate the hepatoxic response.

Ito, S., H. Kume, et al. (2008). "Inhibition by the cold receptor agonists menthol and icilin of airway smooth muscle contraction." Pulm Pharmacol Ther 21(5): 812-7.

Menthol, known as a cold receptor agonist, has widely been used in the relief of respiratory symptoms such as coughing and chest congestion. Previous studies have demonstrated that menthol reduces bronchoconstriction and airway hyperresponsiveness. The aim of this study was to examine the effects of menthol and icilin, another cold receptor agonist, on airway smooth muscle contraction. Isometric force was monitored using epithelium-denuded tracheal smooth muscle tissues isolated from guinea pigs. Intracellular Ca(2+) concentrations were assessed by fura-2 fluorescence. (-)Menthol (0.01-1mM) inhibited contraction induced by methacholine (MCh, 0.01-10microM) and high extracellular K(+) concentrations (20-60mM) in a concentration-dependent manner. Moreover, the increases of intracellular Ca(2+) concentrations induced by MCh or high K(+) were significantly reduced by (-)menthol. Icilin (100microM) also significantly attenuated contraction induced by MCh or high K(+). The inhibitory effect of 1mM (-)menthol on MCh-induced contraction was significantly higher at cool temperature (24-26 degrees C) than at 37 degrees C. The present results demonstrate that inhibition of Ca(2+) influx plays an important role in the menthol-mediated inhibition of contraction in airway smooth muscle. Furthermore, our findings indicate that stimulation of unknown cold receptors may be involved in these mechanisms. These findings suggest that the use of menthol is beneficial for reducing respiratory symptoms because of its inhibitory effects on airway smooth muscle contraction.

Johnson, C. D., D. Melanaphy, et al. (2009). "Transient receptor potential melastatin 8 (TRPM8) channel involvement in the regulation of vascular tone." Am J Physiol Heart Circ Physiol 296(6):H1868-77.

The transient receptor potential melastatin 8 (TRPM8) channel has been characterized as a cold and menthol receptor expressed in a subpopulation of sensory neurons, but was recently identified in other tissues, including respiratory tract, urinary system, and vasculature. Thus, TRPM8 may play multiple functional roles, likely to be in a tissue- and activation state-dependent manner. We examined TRPM8 channel presence in large arteries from rats and functional consequences of their activation. We also aimed to examine whether these channels contribute to control of conscious human skin blood flow. TRPM8 mRNA and protein were detected in rat tail, femoral and mesenteric arteries and thoracic aorta. This was confirmed in single isolated vascular myocytes by immunocytochemistry. Isometric contraction studies on endothelium-denuded relaxed rat vessels found small contractions on application of TRPM8-specific agonist, menthol (300microM). However, both menthol and another agonist, icilin (50microM) caused relaxation of vessels precontracted with KCl (60mM) or alpha-adrenoceptor agonist, phenylephrine (2microM), and a reduction in sympathetic nerve-mediated contraction. These effects were antagonized

by bromoenol lactone treatment suggesting involvement of iPLA2 activation in TRPM8-mediated vasodilatation. In thoracic aorta with intact endothelium, menthol-induced inhibition of KCl-induced contraction was enhanced. This was unaltered by pre-incubation with either Nomega-nitro-l-arginine methyl ester (L-NAME, 100nM), a nitric oxide synthase inhibitor, or acetylcholine receptor antagonist, atropine (1microM). Application of menthol (3% solution, topical application) to skin caused increased blood flow in conscious humans, measured by laser Doppler fluximetry. Vasodilatation was markedly reduced or abolished by prior application of L-NAME (passive application, 10mM) or atropine (iontophoretic application, 100nM, 30 sec @ 70microA). We conclude that TRPM8 channels are present on rat artery vascular smooth muscle and on activation cause vasoconstriction or vasodilatation, dependent on previous vasomotor tone. TRPM8 channels may also contribute to human cutaneous vasculature control, likely with the involvement of additional neuronal mechanisms. Key words: TRPM8, human, rat, artery.

Juergens, U. R., M. Stober, et al. (1998). "Antiinflammatory effects of euclyptol (1.8-cineole) in bronchial asthma: inhibition of arachidonic acid metabolism in human blood monocytes ex vivo." Eur J Med Res 3(9): 407-12.

Monoterpenes are prescribed to treat chronic obstructive airway disorders mainly because of their familiar secretolytic properties. The aim of this study was to investigate the effect of 1.8-cineole (Soledum) on arachidonic acid (AA) metabolism in blood monocytes of patients with bronchial asthma. Patients with bronchial asthma (n = 10) and healthy test subjects (n = 12) were included in the study. Production of the representative AA-metabolites LTB4 and PGE2 from isolated monocytes stimulated with the calcium ionophore A23187 were measured ex vivo before therapy with 1.8-cineole (3 x 200 mg/day), after three days of treatment (day 4) and four days after discontinuation of 1. 8-cineole (day 8). The production of LTB4 and PGE2 from monocytes ex vivo was significantly inhibited on day 4 in patients with bronchial asthma (-40.3%, n = 10 and -31.3%, p = 0.1, n = 3 respectively) as well as in healthy volunteers (-57.9%, n = 12 and -42.7%, n = 8 respectively). In conclusion, 1.8-cineole was shown to inhibit LTB4 and PGE2, both pathways of AA-metabolism. Further studies are needed to show that 1.8-cineole is suitable in the treatment of bronchial asthma.

Juergens, U. R., M. Stober, et al. (1998). "The anti-inflammatory activity of L-menthol compared to mint oil in human monocytes in vitro: a novel perspective for its therapeutic use in inflammatory diseases." Eur J Med Res 3(12): 539-45.

The anti-inflammatory efficacy of monoterpenes is still unknown. In order to evaluate the potential role of L-menthol and mint oil as an anti-inflammatory drug, preclinical in vitro-investigations were performed using LPS-stimulated monocytes from healthy volunteers. Arachidonic acid metabolism was assessed by measuring LTB subset4 and PGE subset2 as indicators for both the lipoxygenase and the cyclooxygenase pathways respectively. In addition, the anti-inflammatory effects of the two terpenes on IL-1beta production were analysed. - L-menthol significantly suppressed the production of each of the three inflammation mediators by monocytes in vitro. LTB subset4 decreased by -64.4 +/- 10%, PGE subset2 by -56.6 +/- 8%, and IL-1beta by -64.2 +/- 7% respectively at L-menthol concentrations

within the presumed therapeutic range of about 10 superset-7 g/ml. In contrast, mint oil had a bimodal effect on PGE subset2 production: lower concentrations of 10 superset-10 to 10 superset-8 g/ml increased PGE subset2 up to 6-fold compared to baseline but concentrations of 10 superset-7 g/ml suppressed PGE subset2 production by approximately 50%. Mint oil had similar effects on LTB subset4 and IL-1beta as its main constituent, L-menthol, although the degree of suppression was by comparison smaller at lower concentrations. Paraffin oil, which served as a solvent, did not affect arachidonic acid metabolism and IL-1beta production. - These results obtained with human monocytes suggest preferable anti-inflammatory effects of L-menthol compared to mint oil at therapeutically relevant concentrations supplied in enteric coated capsules. Therefore, clinical trials investigating the potential therapeutic efficacy of L-menthol for treatment of chronic inflammatory disorders such as bronchial asthma, colitis and allergic rhinitis seem worthwhile.

Juergens, U. R., M. Stober, et al. (1998). "Inhibition of cytokine production and arachidonic acid metabolism by eucalyptol (1.8-cineole) in human blood monocytes in vitro." Eur J Med Res 3(11): 508-10.

Cineole (eucalyptol) is the isolated active agent of eucalyptus oil. Traditionally, it is recommended for treating the symptoms of airway diseases exacerbated by infection. We have examined the inhibitory effect of 1.8-cineole on LPS-and IL1beta-stimulated mediator production by human monocytes in vitro. For the first time, we report on a dose-dependent and highly significant inhibition of production of tumor necrosis factor-alpha, interleukin-1beta, leukotriene B4 and thromboxane B2 by 1.8-cineole. In summary, this is the first report on a new mechanism of action of monoterpenes suggesting 1.8-cineole as a strong inhibitor of cytokines that might be suitable for longterm treatment of airway inflammation in bronchial asthma and other steroid-sensitive disorders.

Kim, S. H., J. H. Nam, et al. (2009). "Menthol regulates TRPM8-independent processes in PC-3 prostate cancer cells." Biochim Biophys Acta 1792(1): 33-8.

Menthol, a naturally occurring compound from peppermint oil, binds and activates the TRPM8 Ca(2+)-permeable channel that exhibits abnormal expression patterns in prostate cancer, suggesting that TRPM8 links Ca(2+) transport pathways to tumor biology. We thus investigated the cellular responses of prostate cancer cells to menthol. Here we found that menthol increases [Ca(2+)](i) via Ca(2+) influx mechanism(s) independent of TRPM8 in PC-3 cells. We demonstrated that menthol induces cell death at supramillimolar concentrations in PC-3 cells and the cell death is not suppressed by low extracellular Ca(2+) condition which indicates that menthol-induced cell death is not associated with Ca(2+) influx pathways. In addition, we showed that menthol increases a phosphorylated form of c-jun N-terminal kinase (JNK) in PC-3 cells through TRPM8-independent mechanisms. Thus, our data indicate that there is an apparent lack of causality between TRPM8 activation and menthol-induced cell death and that menthol can regulate TRPM8-independent Ca(2+)-transport and cellular processes.

Kotan, R., S. Kordali, et al. (2007). "Screening of antibacterial activities of twenty-one oxygenated monoterpenes." Z Naturforsch [C] 62(7-8): 507-13.

Plant essential oils are widely used as fragrances and flavours in the cosmetic, perfume, drug and food industries. Oxygenated monoterpenes are widespread components of the essential oils, usually occurring in high amount. In this paper, the antibacterial activities of twenty-one oxygenated monoterpenes (borneol, borneol acetate, camphor, carvone, 1,8-cineole, citronellal, beta-citronellol, dihydrocarvone, fenchol, fenchone, geraniol acetate, isomenthol, limonene oxide, linalool, linalool acetate, nerol, nerol acetate, terpinen-4-ol, alpha-terpineol, menthol and menthone) and penicillin (standard antibiotic) were determined using a disc diffusion method (in vitro) against 63 bacterial strains, belonging to 37 different genera and 54 species (plant, food and clinic origins). The results showed that the oxygenated monoterpenes exhibited a variable degree of antibacterial activities. These compounds also inhibited the growth of bacterial strains by producing a weak zone of inhibition from 7 to 11 mm in diameter, depending on the susceptibility of the tested bacteria. Among the tested compounds, nerol, linalool alpha-terpineol, fenchol and terpinen-4-ol showed antibacterial activity at a broad spectrum. However, their antibacterial activities were lower than those of penicillin. In contrast to these compounds, camphor and 1,8-cineole exhibited no inhibition effects on the growth of all tested bacteria.

Kuhn, F. J. P., C. Kuhn, et al. (2009). "Inhibition of TRPM8 by icilin distinct from desensitization induced by menthol and menthol derivatives." J Biol Chem 284(7): 4102-4111.

TRPM8 is a cation channel activated by cold temperatures and the chemical stimuli menthol and icilin. Both compounds use different mechanisms of current activation; amino acid residues within the S2-S3 linker have been identified critical for current activation by icilin but not by menthol. Current decline in the course of menthol stimulation reflects Ca2+-dependent desensitization attributed to phosphatidylinositol 4,5-bisphosphate depletion. Carboxyamide derivatives chemically resembling menthol have been described as activators of TRPM8 analogous to icilin. Our aim was a detailed analysis of whether differences exist between all these substances with respect to their activation and inactivation of currents. We studied wildtype TRPM8 as well as an s3-TRPM8 mutant with mutations in the S2-S3 linker region that could not be activated by icilin. Menthol and menthol derivatives behaved indistinguishable in evoking currents through both channels in a Ca2+-independent manner as well as inducing Ca2+-dependent desensitization. Icilin, in contrast, activated currents only in wild type TRPM8 and in the presence of Ca2+. Moreover, it completely reversed currents induced by menthol, menthol derivatives, and cold temperatures in wild type TRPM8 and s3-TRPM8; this current inhibition was independent of Ca2+. Finally, icilin suppressed current activation by the other agonists. None of the inhibiting effects of icilin occurred in the cation channel TRPA1 that is also stimulated by both menthol and icilin. Thus, icilin specifically inhibits TRPM8 independently of its interaction site within the S2-S3 linker through a process distinct from desensitization.

Kunta, J. R., V. R. Goskonda, et al. (1997). "Effect of menthol and related terpenes on the percutaneous absorption of propranolol across excised hairless mouse skin." J Pharm Sci 86(12): 1369-73.

The potential use of terpenes/terpenoids as penetration enhancers in the transdermal delivery of propranolol hydrochloride (PL) was investigated. PL was chosen for the reasons of its extensive first-pass metabolism and short elimination half-life. The terpenes studied included L-menthol, (+)-limonene, (+/-)-linalool, and carvacrol at 1%, 5%, and 10% w/v concentrations. The diffusion of PL across excised hairless mouse skin was determined using side-by-side diffusion cells. Flux, permeability coefficient (Pm), and lag time (tL) were calculated. PL showed comparable lag times with menthol at all three concentration levels. At a 1% level of carvacrol, PL exhibited a 2.4- and 2.2-fold increase in lag time compared with 5 and 10% levels of enhancer, respectively. In the presence of limonene, PL had shown maximum lag time (between 3.0 and 3.3 h) at all three levels. In the case of linalool, the lag times for PL with 5 and 10% levels of enhancer were 7.0- and 5.2-fold less compared with 1% level. A significant ($p < 0.05$) concentration effect was observed only with linalool. Hydrogel-based patches were formulated with or without menthol as enhancer. Release profiles from the hydrogel formulations obeyed zero-order kinetics. The permeability of propranolol was significantly higher ($p < 0.05$) from the test patch than the control (no enhancer) patch across the mouse skin. The mechanism of permeation enhancement of menthol could involve its distribution preferentially into the intercellular spaces of stratum corneum and the possible reversible disruption of the intercellular lipid domain. The results suggest the potential use of menthol as effective penetration enhancer in the delivery of significant amounts of PL through skin.

Laude, E. A., A. H. Morice, et al. (1994). "The antitussive effects of menthol, camphor and cineole in conscious guinea-pigs." Pulm Pharmacol 7(3): 179-84.

Menthol and other aromatic vapours have been widely used in the symptomatic treatment of upper respiratory tract infections, although there is little objective evidence as to their benefit. We have investigated the action of aromatic vapours on the cough reflex in conscious guinea-pigs. Animals (n = 13) were pretreated with air or test vapours for 5 min at a rate of 1 l/min. One minute later the animal was challenged with aerosolized citric acid for 2 min. Control responses to air pretreatment were not significantly different throughout the procedures. Three concentrations of each aromatic vapour were used (3, 10 and 30 micrograms/l menthol, 50, 133 and 500 micrograms/l camphor and 0.8, 2.7 and 8 mg/l cineole). Menthol proved the most effective antitussive—10 and 30 micrograms/l produced a significant 28 and 56% reduction in cough frequency—500 micrograms/l camphor gave a significant 33% reduction, while cineole, at the concentrations used, had no significant effect. An increase in cough latency coincided with a reduction in cough frequency. These results demonstrate the efficacy of aromatic vapours as antitussives in chemically induced cough.

Leclerc, S., J. M. Heydel, et al. (2002). "Glucuronidation of odorant molecules in the rat olfactory system. Activity, expression and age-linked modifications of UDP-glucuronosyltransferase isoforms, UGT1A6 and UGT2A1, and relation to mitral cell activity." Mol Brain Res 107(2): 201-213.

The aim of the present study was to examine the glucuronidation of a series of odorant molecules by homogenates prepared either with rat olfactory mucosa, olfactory bulb or brain. Most of the odorant molecules tested were efficiently conjugated by olfactory mucosa, whereas olfactory bulb and brain homogenates displayed lower activities and glucuronidated only a few molecules. Important age-related changes in glucuronidation efficiency were observed in olfactory mucosa and bulb. Therefore, we studied changes in expression of two UDP-glucuronosyltransferase isoforms, UGT1A6 and UGT2A1, in 1-day, 1- and 2-week-, 3-, 12- and 24-month-old rats. UGT1A6 was expressed at the same transcriptional level in the olfactory mucosa, bulb and brain, throughout the life period studied. UGT2A1 mRNA was expressed in both olfactory mucosa and olfactory bulb, in accordance with previous results [Mol. Brain Res. 90 (2001) 83], but UGT2A1 transcriptional level was 400-4000 times higher than that of UGT1A6. Moreover, age-dependent variations in UGT2A1 mRNA expression were observed. As it has been suggested that drug metabolizing enzymes could participate in olfactory function, mitral cell electrical activity was recorded during exposure to different odorant molecules in young, adult and old animals. Age-related changes in the amplitude of response after stimulation with several odorant molecules were observed, and the highest responses were obtained with molecules that were not efficiently glucuronidated by olfactory mucosa. In conclusion, the present work presents new evidence of the involvement of UGT activity in some steps of the olfactory process. Â© 2002 Elsevier Science B.V. All rights reserved.

Lee, C. K., D. J. Doolittle, et al. (1990). "Comparative genotoxicity testing of mainstream whole smoke from cigarettes which burn or heat tobacco." Mutat Res 242(1): 37-45.

The genotoxic potential of mainstream whole smoke (MWS) from cigarettes which heat tobacco (TEST) was compared to the genotoxic potential of MWS from a cigarette which burns tobacco (REFERENCE). MWS was collected from a University of Kentucky 1R4F cigarette (REFERENCE) and two, TEST cigarettes, one with regular flavor and the other with menthol flavor. All cigarettes were smoked on a smoking machine and the particulate phase was collected on Cambridge filter pads. The vapor phase, which passed through the pad, was bubbled into a dimethyl sulfoxide (DMSO) trap. The filter pad was extracted with the DMSO in the trap and additional DMSO to obtain MWS. MWS representing an identical number of cigarettes was tested to make a per-cigarette comparison of their genotoxic potential. REFERENCE MWS was mutagenic and cytotoxic in the Ames assay in the presence of metabolic activation while it was cytotoxic but not mutagenic in the absence of metabolic activation. Statistically significant increases in frequency of both sister-chromatid exchanges and chromosomal aberrations were observed in Chinese hamster ovary cells exposed to REFERENCE MWS with and without metabolic activation. MWS from the TEST cigarettes, with either regular or menthol flavor, was neither cytotoxic nor mutagenic in any of these assays. In summary, MWS from the 2 TEST cigarettes was neither genotoxic nor cytotoxic under conditions where MWS from the REFERENCE cigarettes was genotoxic and/or cytotoxic in a concentration-dependent manner.

Li, S., J. Westwick, et al. (2003). "Transient receptor potential (TRP) channels as potential drug targets in respiratory disease." Cell Calcium 33(5-6): 551-558.

Calcium-permeable channels have traditionally been thought of as therapeutic targets in excitable cells. For instance, voltage-operated Ca2+ channels in neurones and smooth muscle cells for neurological and cardiovascular diseases although calcium-permeable channels are also functionally important in electrically non-excitable cells. In the lung, calcium channels play a pivotal role in the activation of all the cell types present, whether resident cells such as airway smooth muscle cells and macrophages or migratory cells such as neutrophils or lymphocytes. Previously, research in this area has been hindered by the lack of obvious molecular identity. More recently, the emergence of the transient receptor potential (TRP) cation family has yielded promising candidates which may underpin the different receptor-operated calcium influx pathways. The challenge now, is to ascribe function to the TRP channels expressed in each cell type as a first step in identifying which TRP channels may be potential drug targets for asthma and chronic obstructive pulmonary disease (COPD) (Fig. 1).

Lin, J. P., K. C. Cheng, et al. (2003). "Effects of (-)-menthol on the distribution and metabolism of 2-aminofluorene in various tissues of Sprague-Dawley rats." In Vivo 17(5): 441-455.

The purpose of the present study was to examine whether or not (-)-Menthol affects the distribution and metabolism of 2-aminofluorene (AF) in Sprague-Dawley rats. The AF, acetylated AF and AF metabolites were determined by using high performance liquid chromatography. AF was administered orally alone, with (-)-Menthol at the same time, and after 24-hour (-)-Menthol pretreatment and then urine, stool, blood and tissues from liver, kidneys, stomach, colon and bladder were collected and assayed for AF and its metabolites. Compared to the control group, (-)-Menthol caused an increase of the metabolites excreted in the urine and stool. The major metabolite excreted both in the urine and in the stool was 9-OH-AAF. The liver was the major metabolism center and the major residual metabolite ofAF in the liver was 9-OH-AAE When AF was given for 24 hours with (-)- Menthol to SD rats, the rate of carcinogen acetylation is decreased in bladder, blood, colon, kidney and liver tissues.

Lin, J. P., Y. C. Li, et al. (2001). "Effects of (-)-menthol on arylamine N-acetyltransferase activity in human liver tumor cells." Am J Chin Med 29(2): 321-9.

To evaluate whether or not (-)-menthol affects arylamine N-acetyltransferase (NAT) activity, we selected human liver tumor cell line (J 5) for examination. By using high performance liquid chromatography, NAT activity for acetylation of 2-aminofluorene (AF) was determined. (-)-Menthol displayed a dose-dependent inhibition to cytosolic NAT activity. Time-course experiments showed that NAT activity measured from intact human liver tumor cells was inhibited by (-)-menthol for up to 24 hrs. But in human liver tumor intact cells, the low doses (0.0032 and 0.032 mM) of (-)-menthol promoted the NAT activity and the high doses (3.2 and 32 mM) of (-)-menthol inhibited NAT activity and the 0.32 mM (-)-menthol did not show any significant differences between control and (-)-menthol

treated groups. Using standard steady-state kinetic analysis, it was demonstrated that (-)-menthol was a possible uncompetitive inhibitor (decrease Km and Vmax) to NAT activity in cytosols. This report is the first demonstration which showed (-)-menthol affect on human liver tumor cells NAT activity.

Lin, J. P., H. F. Lu, et al. (2005). "(-)-Menthol inhibits DNA topoisomerases I, II alpha and beta and promotes NF-kappaB expression in human gastric cancer SNU-5 cells." Anticancer Res 25(3B): 2069-74.

It has been reported that (-)-Menthol can inhibit the growth of rat liver epithelial tumor cells and is a potent chemopreventive agent. The purpose of the present experiment was to examine and identify cellular processes leading to cell death which are affected by (-)-Menthol in human gastric SNU-5 cancer cells. Cell death (cytotoxicity) was examined and analyzed by trypan blue stain and flow cytometric methods. It was shown that (-)-Menthol inhibited the proliferation of the cells in a dose- and time-dependent manner, inhibited topoisomerase I, IIa and IIbeta, but promoted the levels of NF-kappaB gene expression based on the Western blot and polymerase chain reaction (PCR) and cDNA microarray methods. These data suggest that (-)-Menthol may induce cytotoxicity through inhibiting gene expression of topoisomerase I, IIalpha and IIbeta and promoting the gene expression of NF-kappaB in SNU-5 cells.

Lu, H. F., S. C. Hsueh, et al. (2006). "The role of Ca2+ in (-)-menthol-induced human promyelocytic leukemia HL-60 cell death." In Vivo 20(1): 69-75.

A human promyelocytic leukemia HL-60 cell line was selected to examine the effect of (-)-Menthol on cell death. Based on the results from morphological changes and the percentage of viable cells in HL-60 cells after treatment with various concentrations of (-)-Menthol, it was shown that (-)-Menthol induced cell death through necrosis, not apoptosis. No cell cycle arrest was found in HL-60 cells examined by flow cytometry analysis. Also, the DNA gel electrophoresis method showed that (-)-Menthol did not induce apoptosis in HL-60 cells. However, it was found that (-)-Menthol induced the production of Ca2+ in these examined cells, dose-dependently. When HL-60 cells were pretreated with the chelator (BAPTA) of Ca2+ for 3 hours before addition of (-)-Menthol to the culture, a decrease of Ca2+ production was observed. Under the same conditions, the percentage of viable HL-60 cells was increased. Apparently Ca2+ production is associated with the induction of (-)-Menthol-induced cell death.

Lu, H. F., J. Y. Liu, et al. (2007). "(-)-Menthol inhibits WEHI-3 leukemia cells in vitro and in vivo." In Vivo 21(2): 285-9.

(-)-Menthol ([1-alpha]-5-methyl-2-[1-methylethyl]-cyclohexanol), is a widely used flavoring ingredient in mouthwash, foods, toothpaste and cigarettes. The studies reported here revealed that (-)-menthol induced cytotoxicity against murine leukemia WEHI-3 cells in vitro in a dose-dependent manner. The effects of (-)-menthol on WEHI-3 cells in vivo (BALBIc mice) were also examined, and it was observed that the Mac-3 and CD11b markers were decreased, indicating inhibition of differentiation of the precursor of macrophage and

granulocyte. The weights of liver and spleen samples from mice treated with (-)-menthol were found to be decreased compared to untreated animals.

Ma, S., G. G, et al. (2008). "Menthol derivative WS-12 selectively activates transient receptor potential melastatin-8 (TRPM8) ion channels." Pak J Pharm Sci 21(4): 370-8.

Transient receptor potential melastatin-8 (TRPM8), a cationic ion channel is involved in detection of normal cooling-sensation in mammals. TRPM8 activation by cooling or chemical agonists have been shown to produce profound, mechanistically novel analgesia in chronic pain states such as neuropathic pain in rodents. Known TRPM8 agonists such as menthol and icilin have a relatively low potency and cross-activate nociceptors like TRPA1; thus bearing a limited therapeutic usefulness. For that reason, characterising ligands, which selectively activate TRPM8, presents a clinical need. Using Xenopus laevis oocytes as expression system, we evaluated WS-12, a menthol derivative, for its potential interaction with all six thermo-sensitive TRP ion channels. Oocytes were injected with cRNA of gene of interest and incubated for 3-5 days (at 16 degrees C) before testing for functional characterisation of the recombinant ion channels. Oocytes were superfused with the test and standard substances respectively. Responses were measured by two-electrode voltage clamp technique and the amplitudes of evoked currents were compared with baseline values. WS-12 robustly activated TRPM8 in low micromolar concentrations (EC50 12+/-5 microM) thereby displaying a higher potency and efficacy compared to menthol (EC50 196+/-22 microM). Any of the other described thermo-sensitive TRP ion channel including TRPV1, TRPV2, TRPV3, TRPV4 and TRPA1 were not activated at a concentration (1 mM) optimally effective for TRPM8 responses; a characteristic which is in sharp contrast to menthol as it activates TRPA1 and TRPV3 in addition to TRPM8. Unlike icilin (75% reduction; $p<0.001$, n=6), WS-12 does not induce tachyphylaxis (4+/-2.3% increase in responses; $p<0.08$, n=6) of TRPM8 mediated currents to repeated exposure of 1 mM doses. In addition, acidosis or variations in extracellular calcium have no influence on potency/efficacy of WS-12 for TRPM8. The selectivity profile of WS-12, its several-fold higher potency and around two-fold increase in efficacy compared to menthol warrants its potential utility for therapy in chronic neuropathic pain states and as a diagnostic probe in prostate cancer.

MacDougall, J. M., K. Fandrick, et al. (2003). "Inhibition of human liver microsomal (S)-nicotine oxidation by (-)-menthol and analogues." Chem Res Toxicol 16(8): 988-93.

(-)-Menthol is a widely used flavoring ingredient present in mouthwash, foods, toothpaste, and cigarettes; yet, the pharmacological effects of menthol have not been widely studied. Mentholated cigarette smoking may increase the risk for lung cancer. Many African American smokers smoke mentholated cigarettes, and African Americans have a significantly higher incidence of lung cancer as compared with whites. There may be a relationship between the incidence of lung cancer and the type of cigarette smoked because the use of mentholated cigarettes by white smokers is significantly less and the incidence of lung cancer is less. The mechanism whereby (-)-menthol could increase the health risk of smoking is not known. The results of our in vitro studies herein show that (-)-menthol and synthetic congeners inhibit the microsomal oxidation of nicotine to cotinine and the P450 2A6-mediated 7-hydroxylation of coumarin. Replacement of the alcohol oxygen atom of

menthol with other heteroatoms increased the potency of P450 2A6 inhibition. Thus, the K(i) value of (-)-menthol for inhibition of microsomal nicotine oxidation was 69.7 micro M but neomenthyl thiol possesses a K(i) value of 13.8 micro M. Menthylamine inhibited nicotine oxidation with a K(i) value of 49.8 micro M, but its hydroxylamine derivative gave an IC(50) value of 2.2 micro M. A series of 16 menthol derivatives and putative metabolites were procured or chemically synthesized and tested as inhibitors of P450 2A6. While highly potent inhibition of P450 2A6 was not observed for the menthol analogues examined, it is nevertheless possible that smoking mentholated cigarettes leads to inhibition of nicotine metabolism and allows the smoker to achieve a certain elevated dose of nicotine each day. This may be another example of self-medication to obtain the desired effect of nicotine.

Mahieu, F., G. Owsianik, et al. (2007). "TRPM8-independent menthol-induced Ca2+ release from endoplasmic reticulum and Golgi." J Biol Chem 282(5): 3325-3336.

Menthol, a secondary alcohol produced by the peppermint herb, Mentha piperita, is widely used in the food and pharmaceutical industries as a cooling/ soothing compound and odorant. It induces Ca2+ influx in a subset of sensory neurons from dorsal root and trigeminal ganglia, due to activation of TRPM8, a Ca2+-permeable, cold-activated member of the TRP superfamily of cation channels. Menthol also induces Ca2+ release from intracellular stores in several TRPM8-expressing cell types, which has led to the suggestion that TRPM8 can function as an intracellular Ca2+-release channel. Here we show that menthol induces Ca2+ release from intracellular stores in four widely used cell lines (HEK293, lymph node carcinoma of the prostate (LNCaP), Chinese hamster ovary (CHO), and COS), and provide several lines of evidence indicating that this release pathway is TRPM8-independent: 1) menthol-induced Ca2+ release was potentiated at higher temperatures, which contrasts to the cold activation of TRPM8; 2) overexpression of TRPM8 did not enhance the menthol-induced Ca2+ release; 3) menthol-induced Ca2+ release was mimicked by geraniol and linalool, which are structurally related to menthol, but not by the more potent TRPM8 agonists icilin or eucalyptol; and 4) TRPM8 expression in HEK293 cells was undetectable at the protein and mRNA levels. Moreover, using a novel TRPM8-specific antibody we demonstrate that both heterologously expressed TRPM8 (in HEK293 cells) and endogenous TRPM8 (in LNCaP cells) are mainly localized in the plasma membrane, which contrast to previous localization studies using commercial anti-TRPM8 antibodies. Finally, aequorin-based measurements demonstrate that the TRPM8-independent menthol-induced Ca2+ release originates from both endoplasmic reticulum and Golgi compartments.

Malkia, A., R. Madrid, et al. (2007). "Bidirectional shifts of TRPM8 channel gating by temperature and chemical agents modulate the cold sensitivity of mammalian thermoreceptors." J Physiol-London 581(1): 155-174.

TRPM8, a member of the melastatin subfamily of transient receptor potential (TRP) cation channels, is activated by voltage, low temperatures and cooling compounds. These properties and its restricted expression to small sensory neurons have made it the ion channel with the most advocated role in cold transduction. Recent work suggests that activation of TRPM8 by cold and menthol takes place through shifts in its voltage-activation curve, which cause the channel to open at physiological membrane potentials. By contrast, little

is known about the actions of inhibitors on the function of TRPM8. We investigated the chemical and thermal modulation of TRPM8 in transfected HEK293 cells and in cold-sensitive primary sensory neurons. We show that cold-evoked TRPM8 responses are effectively suppressed by inhibitor compounds SKF96365,4-(3-chloro-pyridin-2-yl)-piperazine-1-carboxylic acid (4-tert-butyl-phenyl)-amide (BCTC) and 1,10-phenanthroline. These antagonists exert their effect by shifting the voltage dependence of TRPM8 activation towards more positive potentials. An opposite shift towards more negative potentials is achieved by the agonist menthol. Functionally, the bidirectional shift in channel gating translates into a change in the apparent temperature threshold of TRPM8-expressing cells. Accordingly, in the presence of the antagonist compounds, the apparent response-threshold temperature of TRPM8 is displaced towards colder temperatures, whereas menthol sensitizes the response, shifting the threshold in the opposite direction. Co-application of agonists and antagonists produces predictable cancellation of these effects, suggesting the convergence on a common molecular process. The potential for half maximal activation of TRPM8 activation by cold was similar to 140 mV more negative in native channels compared to recombinant channels, with a much higher open probability at negative membrane potentials in the former. In functional terms, this difference translates into a shift in the apparent temperature threshold for activation towards higher temperatures for native currents. This difference in voltage-dependence readily explains the high threshold temperatures characteristic of many cold thermoreceptors. The modulation of TRPM8 activity by different chemical agents unveils an important flexibility in the temperature-response curve of TRPM8 channels and cold thermoreceptors.

Marlowe, K. F. (2003). "Urticaria and asthma exacerbation after ingestion of menthol-containing lozenges." Am J Health Syst Pharm 60(16): 1657-9.

No abstract available.

Mergler, S., M. Z. Strowski, et al. (2007). "Transient receptor potential channel TRPM8 agonists stimulate calcium influx and neurotensin secretion in neuroendocrine tumor cells." Neuroendocrinology 85(2): 81-92.

TRPM8 is a member of the melastatin-type transient receptor potential ion channel family. Activation by cold or by agonists (menthol, icilin) induces a transient rise in intracellular free calcium concentration ([Ca(2+)](i)). Our previous study demonstrated that Ca(2+)-permeable cation channels play a role in IGF-1-induced secretion of chromogranin A in human neuroendocrine tumor (NET) cell line BON [Mergler et al.: Neuroendocrinology 2006;82:87-102]. Here, we extend our earlier study by investigating the expression of TRPM8 and characterizing its impact on [Ca(2+)](i) and the secretion of neurotensin (NT). We identified TRPM8 expression in NET BON cells by RT-PCR, Western blotting and immunofluorescence staining. Icilin increased [Ca(2+)](i) in TRPM8-transfected human embryonic kidney cells (HEK293) but not in mock-transfected cells. Icilin and menthol induced Ca(2+) transients in BON cells as well as in primary NET cell cultures of two different pancreatic NETs as detected by single cell fluorescence imaging. Icilin increased non-selective cation channel currents in BON cells as detected by patch-clamp recordings. This activation was associated with increased NT secretion. Taken together, this study

demonstrates for the first time the expression TRPM8 in NET cells and its role in regulating [Ca(2+)](i) and NT secretion. The regulation of NT secretion in NETs by TRPM8 may have a potential clinical implication in diagnosis or therapy.

Miki, K., M. Miki, et al. (2003). "Early-phase neutrophilia in cigarette smoke-induced acute eosinophilic pneumonia." Intern Med 42(9): 839-45.

Although cigarette smoking is a recognized cause of acute eosinophilic pneumonia (AEP), and an increase in eosinophils in the lung is a common occurrence in AEP, early-phase neutrophilia in AEP is not well understood. We describe three cases of cigarette smoke (menthol type)-induced AEP with neutrophilia in the lungs or blood. Increased in-vitro production of the neutrophil chemoattractant interleukin (IL)-8 by human bronchial epithelial cells (HBECs) was correlated with neutrophilia. We suggest that IL-8 released from HBECs is involved in neutrophilia in the lung in AEP, and is newly recognized as an important factor in the early phase of AEP development.

Mo, H. and C. E. Elson (2004). "Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention." Exp Biol Med (Maywood) 229(7): 567-85.

Pools of farnesyl diphosphate and other phosphorylated products of the mevalonate pathway are essential to the post-translational processing and physiological function of small G proteins, nuclear lamins, and growth factor receptors. Inhibitors of enzyme activities providing those pools, namely, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase and mevalonic acid-pyrophosphate decarboxylase, and of activities requiring substrates from the pools, the prenyl protein transferases, have potential for development as novel chemotherapeutic agents. Their potentials as suggested by the clinical responses recorded in Phase I and II investigations of inhibitors of HMG CoA reductase (the statins), of mevalonic acid-pyrophosphate decarboxylase (sodium phenylacetate and sodium phenylbutyrate), and of farnesyl protein transferase (R115777, SCH66336, BMS-214662, Tipifarnib, L-778,123, and, prematurely, perillyl alcohol) are dimmed by dose-limiting toxicities. These nondiscriminant growth-suppressive agents induce G1 arrest and initiate apoptosis and differentiation, effects attributed to modulation of cell signaling pathways either by modulating gene expression, suppressing the post-translational processing of signaling proteins and growth factor receptors, or altering diacylglycerol signaling. Diverse isoprenoids and the HMG CoA reductase inhibitor, lovastatin, modulate cell growth, induce cell cycle arrest, initiate apoptosis, and suppress cellular signaling activities. Perillyl alcohol, the isoprenoid of greatest clinical interest, initially was considered to inhibit farnesyl protein transferase; follow-up studies revealed that perillyl alcohol suppresses the synthesis of small G proteins and HMG CoA reductase. In sterologenic tissues, sterol feedback control, mediated by sterol regulatory element binding proteins (SREBPs) 1a and 2, exerts the primary regulation on HMG CoA reductase activity at the transcriptional level. Secondary regulation, a nonsterol isoprenoid-mediated fine-tuning of reductase activity, occurs at the levels of reductase translation and degradation. HMG CoA reductase activity in tumors is elevated and resistant to sterol feedback regulation, possibly as a consequence of aberrant SREBP activities. Nonetheless, tumor reductase remains sensitive to isoprenoid-mediated

post-transcriptional downregulation. Farnesol, an acyclic sesquiterpene, and farnesyl homologs, gamma-tocotrienol and various farnesyl derivatives, inhibit reductase synthesis and accelerate reductase degradation. Cyclic monoterpenes, d-limonene, menthol and perillyl alcohol and beta-ionone, a carotenoid fragment, lower reductase mass; perillyl alcohol and d-limonene lower reductase mass by modulating translational efficiency. The elevated reductase expression and greater demand for nonsterol products to maintain growth amplify the susceptibility of tumor reductase to isoprenoids, therein rendering tumor cells more responsive than normal cells to isoprenoid-mediated growth suppression. Blends of lovastatin, a potent nondiscriminant inhibitor of HMG CoA reductase, and gamma-tocotrienol, a potent isoprenoid shown to post-transcription-ally attenuate reductase activity with specificity for tumors, synergistically affect the growth of human DU145 and LNCaP prostate carcinoma cells and pending extensive preclinical evaluation, potentially offer a novel chemotherapeutic strategy free of the dose-limiting toxicity associated with high-dose lovastatin and other nondiscriminant mevalonate pathway inhibitors.

Mucciarelli, M., W. Camusso, et al. (2001). "Effect of (+)-pulegone and other oil components of Mentha x Piperita on cucumber respiration." Phytochemistry 57(1): 91-8.

Peppermint (Mentha x piperita L.) essential oil and main components were assessed for their ability to interfere with plant respiratory functions. Tests were conducted on both root segments and mitochondria isolated by etiolated seedlings of cucumber (Cucumis sativus L.). Total essential oil inhibited 50% of root and mitochondrial respiration (IC50) when used at 324 and 593 ppm, respectively. (+)-Pulegone was the most toxic compound, with a 0.08 and 0.12 mM IC50 for root and mitochondrial respiration, respectively. (-)-Menthone. followed (+)-pulegone in its inhibitory action (IC50 values of 1.11 and 2.30 mM for root and mitochondrial respiration respectively), whereas (-)-menthol was the less inhibitory compound (IC50 values of 1.85 and 3.80 mM respectively). A positive correlation was found for (+)-pulegone, (-)-menthone and (-)-menthol between water solubility and respiratory inhibition. The uncoupling agent. carbonyl-cyanide-m-chlorophenyl-hydrazone (CCCP), lowered (-)-menthol and (-)menthone inhibition and annulled (+)-pulegone inhibition of mitochondrial respiration, whereas salicyl-hydroxamic acid (SHAM) 2-hydroxybenzohydroxamic acid, the alternative oxidase (AO) inhibitor, increased (-)-menthone inhibition and annulled both (+)-pulegone and (-)-menthol inhibitory activity. The possible interaction of (-)-pulegone and (-)-menthol with AO and the mechanism of action of(+)-pulegone, (-)-menthone and (-)-menthol on mitochondrial respiration are discussed.

Nassenstein, C., K. Kwong, et al. (2008). "Expression and function of the ion channel TRPA1 in vagal afferent nerves innervating mouse lungs." J Physiol 586(6): 1595-604.

Transient receptor potential (TRP) A1 and TRPM8 are ion channels that have been localized to afferent nociceptive nerves. These TRP channels may be of particular relevance to respiratory nociceptors in that they can be activated by various inhaled irritants and/or cold air. We addressed the hypothesis that mouse vagal sensory nerves projecting to the airways express TRPA1 and TRPM8 and that they can be activated via these receptors. Single cell RT-PCR analysis revealed that TRPA1 mRNA, but not TRPM8, is uniformly expressed in lung-labelled TRPV1-expressing vagal sensory neurons. Neither TRPA1 nor TRPM8

mRNA was expressed in TRPV1-negative neurons. Capsaicin-sensitive, but not capsaicin-insensitive, lung-specific neurons responded to cinnamaldehyde, a TRPA1 agonist, with increases in intracellular calcium. Menthol, a TRPM8 agonist, was ineffective at increasing cellular calcium in lung-specific vagal sensory neurons. Cinnamaldehyde also induced TRPA1-like inward currents (as measured by means of whole cell patch clamp recordings) in capsaicin-sensitive neurons. In an ex vivo vagal innervated mouse lung preparation, cinnamaldehyde evoked action potential discharge in mouse vagal C-fibres with a peak frequency similar to that observed with capsaicin. Cinnamaldehyde inhalation in vivo mimicked capsaicin in eliciting strong central-reflex changes in breathing pattern. Taken together, our results support the hypothesis that TRPA1, but not TRPM8, is expressed in vagal sensory nerves innervating the airways. TRPA1 activation provides a mechanism by which certain environmental stimuli may elicit action potential discharge in airway afferent C-fibres and the consequent nocifensor reflexes.

Nigam, S. K., A. Kumar, et al. (2001). "Toxicological evaluation of pan masala in pure inbred Swiss mice: A preliminary report on long-term exposure study." Current Science* 80(10): 1306-1309.

Pan masala, a product similar to betel quid in powder form, is stated to be a combination of ingredients like betel nut, catechu, lime, sandal oil, menthol, cardamom, flavour spices, fennel seeds, sugar, waxes, til seeds, colours, etc. Pan masalas are consumed abundantly even by those who generally refrain from smoking or with other tobacco addictions. Use of pan masala is considered to be harmless. In this study, the carcinogenic potential of pan masala was determined by exposing pure inbred Swiss mice of both sexes to pan masala mixed in feed in 2% concentration for eighty weeks in total, but the schedule of sacrifice of 6 animals from each group was started after 16 and 56 weeks of exposure, in order to find out the earlier tumour recurrence, if any, in these groups. Pan masala in 2% concentration in feed fed for 16 weeks could not produce any tumour, but after 56 weeks of exposure in sada pan masala group, 4 out of 12 animals were observed with tumours. But, in the group having tobacco as one of the constituents, 7 out of 12 animals showed tumours primarily affecting lungs, stomach, liver, testis, ovary and adrenal. In the control group, 1 out of 12 animals developed tumours, suggesting that the pan masala may be carcinogenic and habitual pan masala use in humans may exert carcinogenic influence.

Nishino, T., J. W. Anderson, et al. (1993). "Effects of halothane, enflurane, and isoflurane on laryngeal receptors in dogs." Respiration Physiology 91(2-3): 247-260.

The effects of halothane, enflurane, and isoflurane on laryngeal receptors were investigated in 6 anesthetized dogs breathing spontaneously through a tracheostomy. Single unit action potentials were recorded from the peripheral cut end of the superior laryngeal nerve (SLN) while different concentrations of volatile anesthetics (1.25, 2.5, 5.0%) were administered in the expiratory direction at a constant air-flow (6 l/min) for 1 min through the functionally isolated upper airway. A total of 21 respiratory-modulated mechanoreceptors, 18 ''irritant'' receptors, and 7 cold receptors were studied. The overall results obtained from the 16 respiratory-modulated mechanoreceptors challenged with the 3 anesthetic gases disclosed a prevalent inhibitory effect and halothane proved to be the most effective of the 3 gases. The

activity during both the inspiratory and expiratory phase was significantly reduced only by halothane (inspiratory phase, $P < 0.01$; expiratory phase, $P < 0.05$), while neither isoflurane nor enflurane caused significant changes in receptor activity. Of the 18 irritant receptors, 14 receptors increased their activity in a dose-related manner in response to one or more of the anesthetics although the effect of halothane was more pronounced than those of enflurane and isoflurane. All of the 7 cold receptors consistently increased their activity in a dose-related manner in response to halothane whereas 3 of 7 receptors were insensitive to enflurane and 4 of 7 receptors were insensitive to isoflurane. Our results indicate that, while all three commonly used anesthetics can have an effect on different types of laryngeal receptors, the effects of halothane are more pronounced than those of the other two gases in terms of changes in receptor activity.

Orani, G. P., J. W. Anderson, et al. (1991). "Upper airway cooling and l-menthol reduce ventilation in the guinea pig." J Appl Physiol 70(5): 2080-6.

Cooling of the upper airway, which stimulates specific cold receptors and inhibits laryngeal mechanoreceptors, reduces respiratory activity in unanesthetized humans and anesthetized animals. This study shows that laryngeal cooling affects the pattern of breathing in the guinea pig and assesses the potential role of cold receptors in this response by using a specific stimulant of cold receptors (l-menthol). The response to airflows (30 ml/s, 10-s duration) through the isolated upper airway was studied in 23 anesthetized (urethan, 1 g/kg ip) guinea pigs breathing through a tracheostomy. Respiratory airflow, tidal volume, laryngeal temperature, and esophageal pressure were recorded before the challenges (control), during cold airflows (25 degrees C, 55% relative humidity), and during warm airflows (37 degrees C, saturated) with or without the addition of l-menthol. Whereas warm air trials had no effect, cold air trials, which lowered laryngeal but not nasal temperature, reduced ventilation (VE) to 85% of control, mainly by prolonging expiratory time (TE, 145% of control), an effect abolished by laryngeal anesthesia. Addition of l-menthol to the warm airflow caused a greater reduction in VE (41% of control) by prolonging TE (1,028% of control). Nasal anesthesia markedly reduced the apneogenic effect of l-menthol but did not affect the response to cold air trials. In conclusion, both cooling of the larynx and l-menthol in the laryngeal lumen reduce ventilation. Exposure of the nasal cavity to l-menthol markedly enhances this ventilatory inhibition; considering the stimulatory effect of l-menthol on cold receptors, these results suggest a predominant role of nasal cold receptors in this response.

Park, E. J., S. H. Kim, et al. (2009). "Menthol enhances an antiproliferative activity of 1alpha,25-dihydroxyvitamin D(3) in LNCaP cells." J Clin Biochem Nutr 44(2): 125-30.

1alpha,25-dihydroxyvitamin D(3) [1alpha,25(OH)(2)D(3)], the most active form of vitamin D(3), and its analogues have therapeutic benefits for prostate cancer treatment. However, the development of hypercalcemia is an obstacle to clinical applications of 1alpha,25(OH)(2)D(3) for cancer therapy. In this study, we provide evidence that menthol, a key component of peppermint oil, increases an anti-proliferation activity of 1alpha,25(OH)(2)D(3) in LNCaP prostate cancer cells. We found that menthol per se does not exhibit antiproliferative activity, but it is able to enhance 1alpha,25(OH)(2)D(3)-mediated growth inhibition in

LNCaP cells. Fluorometric assays using Fura-2 showed that 1alpha,25(OH)(2)D(3) does not induce acute Ca(2+) response, whereas menthol evokes an increase in [Ca(2+)](i), which suggests that cross-talks of menthol-induced Ca(2+) signaling with 1alpha,25(OH)(2)D(3)-mediated growth inhibition pathways. In addition, Western blot analysis revealed that 1alpha,25(OH)(2)D(3) and menthol cooperatively modulate the expression of bcl-2 and p21 which provides the insight into the molecular mechanisms underlying the enhanced 1alpha,25(OH)(2)D(3)-mediated growth inhibition by menthol. Thus, our findings suggest that menthol may be a useful natural compound to enhance therapeutic effects of 1alpha,25(OH)(2)D(3).

Perraud, A. L., H. M. Knowles, et al. (2004). "Novel aspects of signaling and ion-homeostasis regulation in immunocytes - The TRPM ion channels and their potential role in modulating the immune response." Mol Immunol 41(6-7): 657-673.

In just a few years, the discovery and subsequent characterization of several members of the TRPM family of cation channels have provided us with surprising new insights into unknown aspects of cellular ion-homeostasis regulation. This includes reports about ADP-ribose functioning as a novel intracellular second messenger and gating molecule of the Ca2+-permeable TRPM2 channel, studies demonstrating the central role of mouse TRPM5 in taste signaling, as well as the unexpected involvement of TRPM6 and TRPM7 in regulating Mg2+-homeostasis, or the cool properties of TRPM8 acting as a cold and menthol sensor in sensory neurons. At least four of the eight known TRPM proteins have been shown to be present in the immune context: TRPM1 (melastatin), TRPM2, TRPM4 and TRPM7. Although we currently lack animal models allowing a detailed assessment of the potential involvement of TRPM family members in modulating the immune response, the powerful combination of molecular and cellular biology, biochemistry, and electrophysiology have provided the first clues as to how these molecules could contribute to immunity.

Pettersson, B., M. Curvall, et al. (1982). "Effects of tobacco smoke compounds on the ciliary activity of the embryo chicken trachea in vitro." Toxicology 23(1): 41-55.

The ciliotoxicity of 316 individual compounds representative of the gaseous and semivolatile phases of tobacco smoke has been investigated using chicken tracheal organ cultures. When examined at 5 mM concentration and measuring the time to complete ciliostasis, 36% of the compounds were found to cause ciliostasis within 15 min, while about 50% had no visible effect on the ciliary activity during a 60-min exposure. The majority of the ciliotoxic compounds were either alkylated phenylethers, benzonitriles, benzaldehydes, phenols, benzenes, naphthalenes and indoles, or Î±,Î²-unsaturated ketones and aldehydes or C6-C10 aliphatic alcohols, aldehydes, acids and nitriles. Most of the compounds classified as benzoic acids, esters, polyaromatic hydrocarbons, amines and N-heterocycles, except indoles, were found to be inactive.

Rachakonda, V. K., K. M. Yerramsetty, et al. (2008). "Screening of chemical penetration enhancers for transdermal drug delivery using electrical resistance of skin." Pharm Res 25(11): 2697-704.

A novel technique is presented for identifying potential chemical penetration enhancers (CPEs) based on changes in the electrical resistance of skin. Specifically, a multi-well resistance chamber was designed and constructed to facilitate more rapid determination of the effect of CPEs on skin resistance. The experimental setup was validated using nicotine and decanol on porcine skin in vitro. The multi-well resistance chambers were capable of operating at 37 degrees C in order to simulate the physiological temperature of the human body. Further, the utility of the multi-well resistance chamber technique was validated using standard Franz diffusion cells. Electrical resistance measurements were used to evaluate the potency of seven new potential CPEs, identified using virtual screening algorithms. From the resistance measurements, the chemicals 1-dodecyl-2-pyrrolidinone (P), menthone (M) and R(+)-3-amino-1-hydroxy-2-pyrrolidinone (C) were identified as the better penetration enhancers among the seven tested. Further, traditional permeation experiments were performed in Franz diffusion cells to confirm our findings. The permeation test results indicated that, of the three CPEs deemed potentially viable using the newly-developed resistance screening technique, both P and M increased the permeation of the test drug (melatonin) through skin in 48 h. In summary, this resistance technique can be used to effectively pre-evaluate potential CPEs, thereby reducing the time required to conduct the permeability studies.

Rakieten, N., M. L. Rakieten, et al. (1954). "Effects of menthol vapor on the intact animal with special reference to the upper respiratory tract." J Am Pharm Assoc Am Pharm Assoc (Baltim) 43(7): 390-2.

No abstract available.

Rakieten, N., M. L. Rakieten, et al. (1952). "Mammalian ciliated respiratory epithelium; studies with particular reference to effects of menthol, nicotine, and smoke of mentholated and nonmentholated cigarettes." AMA Arch Otolaryngol 56(5): 494-503.

No abstract available.

Ruch, R. J. and K. Sigler (1994). "Growth inhibition of rat liver epithelial tumor cells by monoterpenes does not involve Ras plasma membrane association." Carcinogenesis 15(4): 787-9.

The role of altered ras oncoprotein (Ras) farnesylation and membrane association in the growth inhibitory effects of several monoterpenes (limonene, perillic acid, perillyl alcohol, menthol, pinene and cineole) was investigated in rat liver epithelial cells. All of the above compounds except cineole inhibited the growth of viral Ha-ras-transformed rat liver epithelial cells (WB-ras cells) at concentrations of 0.25-2.5 mM. These cells, however, were not necessarily more sensitive to these compounds compared to non-transformed and viral raf-transformed rat liver epithelial cells. Growth inhibition by limonene, perillic acid and

pinene was only partially restored (20-50%) by supplementing the culture medium with 2 mM mevalonic acid. Western blot analyses of cytosolic and membranous fractions of WB-ras cells treated with monoterpenes indicated no change in Ras distribution. In contrast, lovastatin, a potent inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase and Ras farnesylation, specifically reduced WB-ras cell growth and increased cytosolic levels of Ras. Thus, monoterpene-induced growth inhibition of rat liver epithelial cells was dissimilar to lovastatin and did not appear to involve altered Ras plasma membrane association.

Ruskin, D. N., R. Anand, et al. (2007). "Menthol and nicotine oppositely modulate body temperature in the rat." Eur J Pharmacol 559 (2-3): 161-4.

Menthol is a prominent additive in many tobacco products. To investigate possible interactions with nicotine, (-)-menthol (200 or 400 mg/kg) and (-)-nicotine (0.5 mg/kg) were injected subcutaneously in rats, and body temperature, which is modulated by brain nicotinic acetylcholine receptors, was measured. Nicotine caused robust (-1.6 degrees C) hypothermia, the magnitude and time course of which was not altered by menthol pretreatment. Menthol alone produced mild (0.4-0.8 degrees C) hyperthermia, which was not secondary to locomotor activation. Nicotine and menthol influence body temperature independently and oppositely; menthol does not appear to influence the function of the central nicotinic receptors that control body temperature.

Ruskin, D. N., R. Anand, et al. (2008). "Chronic menthol attenuates the effect of nicotine on body temperature in adolescent rats." Nicotine Tob Res 10(12): 1753-9.

Menthol is a commonly used additive in tobacco products. Smoking cessation may be more difficult for smokers of mentholated cigarettes, particularly adolescent smokers. Evidence indicates that menthol can influence neurotransmitter receptors and nicotine metabolism. We investigated the effects of chronic menthol using body temperature as a bioassay for the effects of acute nicotine in vivo. Male rats (34-36 days, adolescent; 53-58 days, young adult; 9-10 months, full adult) were injected with menthol (100 mg/kg) or vehicle once daily for 4 days. On day 5, animals were injected with nicotine (0.5 mg/kg) and body temperature was measured for the next 70 min. We found no effect of chronic menthol treatment or of age on baseline temperature. Nicotine quickly produced vasodilatory hypothermia in all animals. Chronic menthol treatment had significant effects only in adolescent rats, diminishing nicotine-induced hypothermia. Nicotine treatment was repeated on day 6 to test for tolerance. Equivalent tolerance was found in all ages, and the attenuating effect of menthol was still present and was still limited to adolescent rats. In adolescents, acute menthol injection (400 mg/kg) 30 min prior to nicotine also attenuated nicotine-induced hypothermia but with a smaller effect size. Also in adolescents, we found no effect of chronic or acute menthol on hypothermia induced by hydralazine, a peripherally acting vasodilator. These data demonstrate that menthol diminishes the influence of nicotine on body temperature in adolescents, suggesting a greater susceptibility of youthful physiology to menthol.

Russin, W. A., J. D. Hoesly, et al. (1989). "Inhibition of rat mammary carcinogenesis by monoterpenoids." Carcinogenesis 10(11): 2161-4.

We have previously demonstrated the cancer chemopreventive activities of the monocyclic unsaturated monoterpene d-limonene. In the present work we report data evaluating the chemopreventive effects of limonene and five other monoterpenes with various chemical structures using a 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary carcinogenesis model. The terpenes tested include: oxygenated [(-)-menthol] and non-oxygenated (d-limonene) monocyclic forms, oxygenated (1,8-cineole) and non-oxygenated [(+/-)-alpha-pinene] bicyclic forms and oxygenated [(+/-)-linalool] and non-oxygenated (beta-myrcene) acyclic forms. Dietary additions of each of the monocyclic terpenes, d-limonene or (-)-menthol resulted in a significant inhibition of mammary carcinogenesis. Furthermore, menthol was found to be a more potent chemopreventive agent than limonene during the DMBA initiation of rat mammary tumors. The acyclic and bicyclic terpenes had no significant chemopreventive activities at the dose levels used in these studies.

Sabnis, A. S., C. A. Reilly, et al. (2008). "Increased transcription of cytokine genes in human lung epithelial cells through activation of a TRPM8 variant by cold temperatures." Am J Physiol Lung Cell Mol Physiol 295(1): L194-200.

Recognition of temperature is a critical element of sensory perception and allows mammals to evaluate both their external environment and internal status. The respiratory epithelium is constantly exposed to the external environment, and prolonged inhalation of cold air is detrimental to human airways. However, the mechanisms responsible for adverse effects elicited by cold air on the human airways are poorly understood. Transient receptor potential melastatin family member 8 (TRPM8) is a well-established cold- and menthol-sensing cation channel. We recently discovered a functional cold- and menthol-sensing variant of the TRPM8 ion channel in human lung epithelial cells. The present study explores the hypothesis that this TRPM8 variant mediates airway cell inflammatory responses elicited by cold air/temperatures. Here, we show that activation of the TRPM8 variant in human lung epithelial cells leads to increased expression of several cytokine and chemokine genes, including IL-1alpha, -1beta, -4, -6, -8, and -13, granulocyte-macrophage colony-stimulating factor (GM-CSF), and TNF-alpha. Our results provide new insights into mechanisms that potentially control airway inflammation due to inhalation of cold air and suggest a possible role for the TRPM8 variant in the pathophysiology of asthma.

Sabnis, A. S., M. Shadid, et al. (2008). "Human lung epithelial cells express a functional cold-sensing TRPM8 variant." Am J Respir Cell Mol Biol 39(4): 466-74.

Several transient receptor potential (TRP) ion channels sense and respond to changes in ambient temperature. Chemical agonists of TRP channels, including menthol and capsaicin, also elicit sensations of temperature change. TRPM8 is a cold- and menthol-sensing ion channel that converts thermal and chemical stimuli into neuronal signals and sensations of cooling/cold. However, the expression and function of TRPM8 receptors in non-neuronal cells and tissues is a relatively unexplored area. Results presented here document the expression and function of a truncated TRPM8 variant in human bronchial epithelial cells.

Expression of the TRPM8 variant was demonstrated by RT-PCR, cloning, and immunohistology. Receptor function was characterized using the prototypical TRPM8 agonist, menthol, and exposure of cells to reduced temperature (18 degrees C). The TRPM8 variant was expressed primarily within endoplasmic reticulum membranes of lung epithelial cells and its activation was attenuated by thapsigargin, the cell-permeable TRPM8 antagonist N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide, and shRNA-induced suppression of TRPM8 expression. Activation of the TRPM8 variant in lung cells was coupled with enhanced expression of the inflammatory cytokines IL-6 and IL-8. Collectively, our results suggest that this novel TRPM8 variant receptor may function as a modulator of respiratory physiology caused by cold air, and may partially explain asthmatic respiratory hypersensitivity to cold air.

Sant'Ambrogio, F. B., J. W. Anderson, et al. (1991). "Effect of l-menthol on laryngeal receptors." J Appl Physiol 70(2): 788-93.

We have studied the effect of l-menthol on laryngeal receptors. Experiments have been conducted in 11 anesthetized dogs that breathed through a tracheostomy. We have recorded the activity of 23 laryngeal cold receptors and 19 mechanoreceptors. Constant flows of air, 15-50 ml/s (low) and 100-150 ml/s (high), passing for 10 s through the isolated upper airway in the expiratory direction, lowered laryngeal temperature and activated the cold receptors. This cold-induced discharge promptly ceased upon withdrawal of the airflow. Addition of l-menthol to the airflow evoked, for a similar decrease in temperature, a greater peak activation of the cold receptors than airflow alone (low flows 164%, high flows 111%); statistical significance was reached only for the lower flow. This activity outlasted the cessation of airflow by 30-120 s, even at a time when laryngeal temperature had returned to control (low flow 237%, high flow 307% of similar trials with airflow alone). Four laryngeal cold receptors were also tested with l-menthol added to a warm, humidified airflow that did not change laryngeal temperature; all of them were stimulated with a long-lasting discharge. Nine cold receptors were also tested with d-neomenthol and d-isomenthol; both isomers stimulated the receptors. None of the 19 mechano-receptors tested was affected by l-menthol. We conclude that l-menthol constitutes a specific stimulant of laryngeal cold receptors and could provide a useful tool for the study of their reflex effects.

Sant'Ambrogio, F. B., J. W. Anderson, et al. (1992). "Menthol in the upper airway depresses ventilation in newborn dogs." Respir Physiol 89(3): 299-307.

Upper airway cooling depresses ventilation in the newborn dog. Since airway cooling stimulates laryngeal cold receptors and inhibits laryngeal mechanoreceptors, the type of afferent ending responsible for this reflex cannot be easily identified. l-menthol, a specific stimulant of cold receptors in the absence of any cooling, has been used to ascertain the discrete role of upper airway cold receptors in this ventilatory depression. Experiments were carried out in 8 anesthetized 7-14-day-old dogs breathing through a tracheostomy with the upper airway functionally isolated. Constant flows of warm air (37 degrees C), with and without addition of l-menthol, and cold air (25 degrees C) were delivered through the upper airway in the expiratory direction. As compared to warm air trials, cold air and warm air + l-menthol trials greatly reduced ventilation (57.5 +/- 10.7% and 52.8 +/-

11.7% of control, respectively; P less than 0.01) mostly due to a prolongation of Te (291.2 +/- 106.4% and 339.2 +/- 90.0%, respectively, P less than 0.01). Section of the superior laryngeal nerve abolished the response to cold air. However, a residual depressive effect of l-menthol was still present in 3 of 5 animals and was abolished by nasal anesthesia, suggesting the involvement of nasal cold receptors. The results suggest that in the newborn dog stimulation of laryngeal cold receptors, without any concurrent inhibition of laryngeal mechanoreceptors, is a sufficient stimulus to cause respiratory depression.

Sekizawa, S. I., H. Tsubone, et al. (1996). "Nasal receptors responding to cold and l-menthol airflow in the guinea pig." Resp Physiol 103(3): 211-219.

The aim of this study was to demonstrate the presence of nasal 'cold' receptors, through recordings of action potentials from the ethmoidal nerve (EN), in guinea pigs and to characterize their responsiveness to l-menthol and capsaicin. Constant flows (400 ml/min) of room air (20Â°C), warm air (45Â°C), room air containing l-menthol, and cold air (5Â°C) were directed into the nasal cavity in the inspiratory direction via a nasopharyngeal catheter in the anesthetized guinea pigs breathing spontaneously through a tracheostomy. The ethmoidal afferent activity was increased by cold air, and to a greater extent by l-menthol but hardly by warm air. After topical anesthesia of the nasal cavity with 2% lidocaine, cold air and l-menthol no longer stimulated the EN. L-menthol noticeably stimulated the EN even after repeated capsaicin instillation into the nose, but these values were lower than those following the l-menthol stimulus before the 1st capsaicin treatment. These results suggest that the ethmoidal nerve in guinea pigs has cold-sensitive receptors which consist of both small myelinated fibers and C-fiber endings.

Sherkheli, M. A., G. Gisselmann, et al. (2008). "Menthol derivative WS-12 selectively activates transient receptor potential melastatin-8 (TRPM8) ion channels." Pak J Pharm Sci 21(4): 370-378.

Transient receptor potential melastatin-8 (TRPM8), a cationic ion channel is involved in detection of normal cooling-sensation in mammals. TRPM8 activation by cooling or chemical agonists have been shown to produce profound, mechanistically novel analgesia in chronic pain states such as neuropathic pain in rodents. Known TRPM8 agonists such as menthol and icilin have a relatively low potency and cross-activate nociceptors like TRPA1; thus bearing a limited therapeutic usefulness. For that reason, characterising ligands, which selectively activate TRPM8, presents a clinical need. Using Xenopus laevis oocytes as expression system, we evaluated WS-12, a menthol derivative, for its potential interaction with all six thermo-sensitive TRP ion channels. Oocytes were injected with cRNA of gene of interest and incubated for 3-5 days (at 16 degrees C) before testing for functional characterisation of the recombinant ion channels. Oocytes were superfused with the test and standard substances respectively. Responses were measured by two-electrode voltage clamp technique and the amplitudes of evoked currents were compared with baseline values. WS-12 robustly activated TRPM8 in low micromolar concentrations (EC50 12+/-5 microM) thereby displaying a higher potency and efficacy compared to menthol (EC50 196+/-22 microM). Any of the other described thermo-sensitive TRP ion channel including TRPV1, TRPV2, TRPV3, TRPV4 and TRPA1 were not activated at a concentration

(1 mM) optimally effective for TRPM8 responses; a characteristic which is in sharp contrast to menthol as it activates TRPA1 and TRPV3 in addition to TRPM8. Unlike icilin (75% reduction; p<0.001, n=6), WS-12 does not induce tachyphylaxis (4+/-2.3% increase in responses; p<0.08, n=6) of TRPM8 mediated currents to repeated exposure of 1 mM doses. In addition, acidosis or variations in extracellular calcium have no influence on potency/efficacy of WS-12 for TRPM8. The selectivity profile of WS-12, its several-fold higher potency and around two-fold increase in efficacy compared to menthol warrants its potential utility for therapy in chronic neuropathic pain states and as a diagnostic probe in prostate cancer.

Shojaei, A. H., M. Khan, et al. (1999). "Transbuccal permeation of a nucleoside analog, dideoxycytidine: effects of menthol as a permeation enhancer." Int J Pharm 192(2): 139-46.

The use of a safe and effective permeation enhancer is paramount to the success of a buccal drug delivery system intended for systemic drug absorption. The enhancing effects of menthol (dissolved in an aqueous buffer in the absence of co-enhancers) on buccal permeation of a model hydrophilic nucleoside analog, dideoxycytidine (ddC), were investigated. In vitro transbuccal permeation of ddC was examined using freshly obtained porcine buccal mucosa. The experiments were carried out in side-bi-side flow through diffusion cells. Permeation enhancement studies were performed with varying concentrations of l-menthol dissolved in Krebs buffer solutions containing ddC. Partition coefficient experiments were carried out to probe into the mechanism of permeation enhancing properties of l-menthol and DSC studies were conducted to determine if there is a eutectic formation between ddC and l-menthol at various concentrations. Permeation of ddC increased significantly (P<0.05) in the presence of l-menthol independent of the concentration of the terpene. The apparent 1-octanol/buffer partition coefficient (log K(p)) of ddC was significantly (P<0.05) increased in presence of l-menthol and was also independent of the enhancer concentration. However, the tissue/buffer partition coefficient (log K'(p)) data showed a concentration dependent increase of log K'(p) in presence of l-menthol. Since log K'(p) is a measure of drug binding to the tissue in addition to drug partitioning, binding of ddC to the buccal tissue may provide an explanation for the concentration dependent increase in these values.

Sidell, N., T. Taga, et al. (1991). "Retinoic acid-induced growth inhibition of a human myeloma cell line via down-regulation of IL-6 receptors." J Immunol 146(11): 3809-14.

In this report we demonstrate that retinoic acid (RA) down-regulated the number of IL-6R on human leukocyte cell lines, including the myeloma cell line AF10, and two B cell hybridomas that correspond to cells at earlier stages of B cell development. Using AF10 cells, whose growth was determined to be mediated by the autocrine action of IL-6, we found that RA reduction of IL-6R was concentration-dependent over a range of 10(-11) to 10(-5) M and corresponded to the ability of the retinoid to inhibit cell proliferation. The down-regulation of IL-6R number by RA was accompanied by reduced IL-6R mRNA expression. RA did not affect endogeneous IL-6 synthesis or secretion from AF10 cells. However, addition of exogenous rIL-6 could overcome RA-induced growth inhibition. Menthol, a structurally unrelated compound to RA, also suppressed IL-6R expression and, correspondingly,

inhibited cell growth. Taken together, our results suggest that the antiproliferative action of RA on AF10 cells is caused by reduction of IL-6R expression and subsequent inhibition of IL-6-mediated autocrine growth. These findings suggest the possibility that down-regulation of IL-6R is a means by which RA can modulate immune function.

Sidell, N., M. A. Verity, et al. (1990). "Menthol blocks dihydropyridine-insensitive Ca2+ channels and induces neurite outgrowth in human neuroblastoma cells." J Cell Physiol 142(2): 410-9.

Voltage-gated Ca2+ channels were identified in LA-N-5 human neuroblastoma cells using the Ca2+ sensitive fluorescent probe, fura-2. Using a variety of "classical" Ca2+ channel blockers, we have demonstrated the presence of both dihydropyridine (DHP)-sensitive and -insensitive channel types that can be activated by depolarization of the cells with either high K+ or gramicidin in the bathing solution. Brief exposure of LA-N-5 cells to menthol blunted the depolarization-induced Ca2+ influx though both DHP-sensitive and DHP-insensitive channels. This effect is concentration dependent (50% maximal blocking effect with 0.25 mM menthol), rapid in onset, and readily reversible. The specificity of the Ca2(+)-channel blocking effect of menthol was demonstrated in parallel studies using compounds with similar structures: menthone blocked Ca2+ channels with about half the potency of menthol, while cyclohexanol was without effect. Addition of either menthol or menthone to LA-N-5 cultures induced neurite outgrowth, cellular clustering, and reduction of cell growth in a dose-dependent fashion that correlated with the ability of these compounds to inhibit the DHP-insensitive Ca2+ influx. Cyclohexanol had no biologic activity. Taken together, the parallel potency for blockade of DHP-insensitive Ca2+ influx with the biologic activity of menthol suggests a role for certain types of Ca2+ channels in triggering growth and morphologic changes in LA-N-5 cells.

Slominski, A. (2008). "Cooling skin cancer: menthol inhibits melanoma growth. Focus on "TRPM8 activation suppresses cellular viability in human melanoma." Am J Physiol Cell Physiol 295(2): C293-5.

No abstract available.

Stich, H. F. and W. Stich (1982). "Chromosome-damaging activity of saliva of betel nut and tobacco chewers." Cancer Lett 15(3): 193-202.

Saliva of volunteers chewing betel quid, cured betel nut (Areca catechu), betel leaves (Piper betle), a mixture of quid ingredients (dried betel nut flakes, catechu, cardamon, lime, copra and menthol) and Indian tobacco was collected and examined for its genotoxic activity. Chromosome aberrations (chromatid breaks and chromatid exchanges) in Chinese hamster ovary (CHO) cells were used to estimate the genotoxic effect. No detectable levels of clastogenic activity were observed in the saliva of non-chewing individuals. After 5 min of chewing betel quid, betel nut, betel leaves, quid ingredients and Indian tobacco, the saliva samples showed relatively potent clastogenic activities. The addition of transition metals Mn2+ and Cu2+ to the saliva samples of betel nut and Indian tobacco chewers enhanced their clastogenic activities, whereas Fe3+ increased the clastogenicity of the betel nut saliva

but decreased the genotoxic effect of the saliva of Indian tobacco chewers. After removal of the betel quid or its components from the mouth, the clastogenic activity disappeared within 5 min. The western-type chewing tobacco did not produce a genotoxic activity in the saliva of chewers. A possible association between the genotoxicity in the saliva of betel quid chewers and the development of oral, pharyngeal and esophageal carcinomas is discussed.

Story, G. M. (2006). "The emerging role of TRP channels in mechanisms of temperature and pain sensation." Curr Neuropharmacol 4(3): 183-196.

Pain is universal and vital to survival. It is an essential component of our sense of touch; together, touch and pain have evolved to enable our awareness of the intricacies of our environment and to warn us of danger and possible injury. There is a clear link between temperature sensation and pain - painful temperature sensations occur acutely and are a hallmark of inflammatory and chronic pain disorders of the nervous system. Mounting evidence suggests a subset of Transient Receptor Potential (TRP) ion channels activated by temperature (thermoTRPs) are important molecular players in acute, inflammatory and chronic pain states. Varying degrees of heat activate four of these channels (TRPV1-4), while cooling temperatures ranging from pleasant to painful activate two distantly related thermoTRP channels (TRPM8 and TRPA1). ThermoTRP channels are also chemosensitive, being activated and or modulated by plant-derived small molecules and endogenous inflammatory mediators. All thermoTRPs are expressed in tissues essential to cutaneous thermal and pain sensation. This review examines the contribution of thermoTRP channels to our understanding of temperature and pain transduction at the molecular level.

Tatman, D. and H. Mo (2002). "Volatile isoprenoid constituents of fruits, vegetables and herbs cumulatively suppress the proliferation of murine B16 melanoma and human HL-60 leukemia cells." Cancer Letters 175(2): 129-139.

Substantial evidence from epidemiological studies supports the inverse association between the intake of fruits, vegetables and other plant products and cancer incidence. Cancer-preventive constituents of fruits and vegetables may inhibit carcinogen activation, enhance carcinogen detoxification, prevent carcinogens from interacting with critical target sites, or impede tumor progression. These activities, however, are achievable only when levels of individual bioactive constituents reach beyond those attainable from a normal balanced diet. Isoprenoids, a broad class of mevalonate-derived phytochemicals ubiquitous in the plant kingdom, suppress the proliferation of tumor cells and the growth of implanted tumors. A search for volatile isoprenoid constituents of food products spanning seven plant families identified 179 isoprenoids. Of these, 41 purchased from commercial sources were screened for efficacy in suppressing the proliferation of murine B16 melanoma cells. Individual isoprenoids suppressed the proliferation of B16 and HL-60 promyelocytic leukemia cells with varying degrees of potency. Cell cycle arrest at the G0-G1 phase and apoptosis account, at least in part, for the suppression. Blends of isoprenoids suppressed B16 and HL-60 cell proliferation with efficacies equal to the sum of the individual impacts. These findings suggest that the cancer-protective property of fruits, vegetables, and related products is partly conferred by the cumulative impact of volatile isoprenoid constituents.

Thebault, S., L. Lemonnier, et al. (2005). "Novel role of cold/menthol-sensitive transient receptor potential melastatine family member 8 (TRPM8) in the activation of store-operated channels in LNCaP human prostate cancer epithelial cells." J Biol Chem 280(47): 39423-35.

Recent cloning of a cold/menthol-sensitive TRPM8 channel (transient receptor potential melastatine family member 8) from rodent sensory neurons has provided the molecular basis for the cold sensation. Surprisingly, the human orthologue of rodent TRPM8 also appears to be strongly expressed in the prostate and in the prostate cancer-derived epithelial cell line, LNCaP. In this study, we show that despite such expression, LNCaP cells respond to cold/menthol stimulus by membrane current (I(cold/menthol)) that shows inward rectification and high Ca(2+) selectivity, which are dramatically different properties from "classical" TRPM8-mediated I(cold/menthol). Yet, silencing of endogenous TRPM8 mRNA by either antisense or siRNA strategies suppresses both I(cold/menthol) and TRPM8 protein in LNCaP cells. We demonstrate that these puzzling results arise from TRPM8 localization not in the plasma, but in the endoplasmic reticulum (ER) membrane of LNCaP cells, where it supports cold/menthol/icilin-induced Ca(2+) release from the ER with concomitant activation of plasma membrane (PM) store-operated channels (SOC). In contrast, GFP-tagged TRPM8 heterologously expressed in HEK-293 cells target the PM. We also demonstrate that TRPM8 expression and the magnitude of SOC current associated with it are androgen-dependent. Our results suggest that the TRPM8 may be an important new ER Ca(2+) release channel, potentially involved in a number of Ca(2+)- and store-dependent processes in prostate cancer epithelial cells, including those that are important for prostate carcinogenesis, such as proliferation and apoptosis.

Tsujimura, K., M. Asamoto, et al. (2006). "Prediction of carcinogenic potential by a toxicogenomic approach using rat hepatoma cells." Cancer Science 97(10): 1002-1010.

The long-term rodent bioassay is the standard method to predict the carcinogenic hazard of chemicals for humans. However, this assay is costly, and the results take at least two years to produce. In the present study, we conducted gene expression profiling of cultured cells exposed to carcinogenic chemicals with the aim of providing a basis for rapid and reliable prediction of carcinogenicity using microarray technology. We selected 39 chemicals, including 17 rat hepatocarcinogens and eight compounds demonstrating carcinogenicity in organs other than the liver. The remaining 14 were non-carcinogens. When rat hepatoma cells (MH1C1) were treated with the chemicals for 3 days at a non-toxic dose, analysis of gene expression changes with our in-house microarray allowed a set of genes to be identified differentiating hepatocarcinogens from non-carcinogens, and all carcinogens from non-carcinogens, by statistical methods. Moreover, optimization of the two gene sets for classification with an SVM and LOO-CV resulted in selection of 39 genes. The highest predictivity was achieved with 207 genes for differentiation between non-hepatocarcinogens and non-carcinogens. The overlap between the two selected gene sets encompassed 26 genes. This gene set contained significant genes for prediction of carcinogenicity, with a concordance of 84.6% by LOO-CV SVM. Using nine external samples, correct prediction of carcinogenicity by SVM was 88.9%. These results indicate that short-term bioassay systems for carcinogenicity using gene expression profiling in hepatoma cells have great promise.

Umezu, T. and M. Morita (2005). "Behavioral pharmacology of plant-derived substances (14): Interaction between menthol and nicotine on ambulation in mice." J Pharmacol Sci* 97: 91p-91p.

No abstract available.

Umezu, T., A. Sakata, et al. (2001). "Ambulation-promoting effect of peppermint oil and identification of its active constituents." Pharmacol Biochem Behav 69(3-4): 383-90.

Various plant-derived essential oils (EOs) have traditionally been used in the treatment of mental disorders, despite a lack of scientific evidence. In a previous study, we demonstrated that certain EOs possess behavioral effects, a finding that supports our original hypotheses that EOs possess psychoactive actions. The present study was conducted in order to obtain further evidence to support our hypothesis. Peppermint oil, a type of EO, is believed to be effective for treating mental fatigue. When the oil was administered intraperitoneally to ICR mice, the ambulatory activity of mice increased dramatically. We identified alpha-pinene, beta-pinene, (R)-(+)-limonene, 1,8-cineol, isomenthone, menthone, menthol, (R)-(+)-pulegone, menthyl acetate and caryophyllene as constituent elements of peppermint oil by GC-MS analysis. We then examined the effect of each constituent element of peppermint oil on ambulatory activity in mice. Intraperitoneal administration of 1,8-cineol, menthone, isomenthone, menthol, (R)-(+)-pulegone, menthyl acetate and caryophyllene significantly increased ambulatory activity in mice, suggesting that these chemicals are the behaviorally active elements of peppermint oil. Intravenous administration of these substances to mice induced a significant increase in ambulatory activity at much lower doses. The present study provides further evidence demonstrating that EOs possess pharmacological actions on behavior. In addition, our finding revealed that the action of peppermint oil comes from its constituent elements.

Vanden Abeele, F., A. Zholos, et al. (2006). "Ca2+-independent phospholipase A2-dependent gating of TRPM8 by lysophospholipids." J Biol Chem 281(52): 40174-82.

TRPM8 represents an ion channel activated by cold temperatures and cooling agents, such as menthol, that underlies the cold-induced excitation of sensory neurons. Interestingly, the only human tissue outside the peripheral nervous system, in which the expression of TRPM8 transcripts has been detected at high levels, is the prostate, a tissue not exposed to any essential temperature variations. Here we show that the TRPM8 cloned from human prostate and heterologously expressed in HEK-293 cells is regulated by the Ca(2+)-independent phospholipase A(2) (iPLA(2)) signaling pathway with its end products, lysophospholipids (LPLs), acting as its endogenous ligands. LPLs induce prominent prolongation of TRPM8 channel openings that are hardly detectable with other stimuli (e.g. cold, menthol, and depolarization) and that account for more than 90% of the total channel open time. Down-regulation of iPLA(2) resulted in a strong inhibition of TRPM8-mediated functional responses and abolished channel activation. The action of LPLs on TRPM8 channels involved either changes in the local lipid bilayer tension or interaction with the critical determinant(s) in the transmembrane channel core. Based on this, we propose a novel concept of TRPM8 regulation with the involvement of iPLA(2) stimulation. This mechanism

employs chemical rather than physical (temperature change) signaling and thus may be the main regulator of TRPM8 activation in organs not exposed to any essential temperature variations, as in the prostate gland.

Vanscheeuwijck, P. M., A. Teredesai, et al. (2002). "Evaluation of the potential effects of ingredients added to cigarettes. Part 4: Subchronic inhalation toxicity." Food Chem Toxicol 40(1): 113-131.

Mainstream smoke from blended research cigarettes with (test) and without (control) the addition of ingredients to the tobacco was assayed for inhalation toxicity. In total, 333 ingredients commonly used in cigarette manufacturing were assigned to three different groups. Each group of ingredients was introduced at a low and a high level to the test cigarettes. Male and female Sprague-Dawley rats were exposed nose-only either to fresh air (sham) or diluted mainstream smoke from the test, the control, or the Reference Cigarette 1R4F at a concentration of 150 Î¼g total particulate matter/l for 90 days, 6 h/day, 7 days/week. A 42-day post-inhalation period was included to evaluate reversibility of possible findings. There were no remarkable differences in in-life observations or gross pathology between test and control groups. An increase in activity of liver enzymes, known to be due to the high smoke dose, revealed no toxicologically relevant differences between the test and control groups. No toxicological differences were seen between the test and control groups for smoke-related hematological changes, such as a decrease in total leukocyte count. The basic smoke-related histopathological effects, which were more pronounced in the upper respiratory tract than in the lower respiratory tract, were hyperplasia and squamous metaplasia of the respiratory epithelium, squamous metaplasia and atrophy of the olfactory epithelium, and accumulation of pigmented alveolar macrophages. There were no relevant qualitative or quantitative differences in findings in the respiratory tract of the rats exposed to the smoke from the control and test cigarettes. The data indicate that the addition of these 333 commonly used ingredients, added to cigarettes in three groups, did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used.

Varnai, P., B. Thyagarajan, et al. (2006). "Rapidly inducible changes in phosphatidylinositol 4,5-bisphosphate levels influence multiple regulatory functions of the lipid in intact living cells." J Cell Biol 175(3): 377-82.

Rapamycin (rapa)-induced heterodimerization of the FRB domain of the mammalian target of rapa and FKBP12 was used to translocate a phosphoinositide 5-phosphatase (5-ptase) enzyme to the plasma membrane (PM) to evoke rapid changes in phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P(2)) levels. Rapa-induced PM recruitment of a truncated type IV 5-ptase containing only the 5-ptase domain fused to FKBP12 rapidly decreased PM PtdIns(4,5)P(2) as monitored by the PLCdelta1PH-GFP fusion construct. This decrease was paralleled by rapid termination of the ATP-induced Ca(2+) signal and the prompt inactivation of menthol-activated transient receptor potential melastatin 8 (TRPM8) channels. Depletion of PM PtdIns(4,5)P(2) was associated with a complete blockade of transferrin uptake and inhibition of epidermal growth factor internalization. None of these changes were observed upon rapa-induced translocation of an mRFP-FKBP12 fusion protein that was used as a control. These data demonstrate that rapid inducible depletion of PM

PtdIns(4,5)P(2) is a powerful tool to study the multiple regulatory roles of this phospholipid and to study differential sensitivities of various processes to PtdIns(4,5)P(2) depletion.

Voets, T., G. Owsianik, et al. (2007). "TRPM8." Handb Exp Pharmacol (179): 329-44.

Originally cloned as a prostate-specific protein, TRPM8 is now best known as a cold- and menthol-activated channel implicated in thermosensation. In this chapter we provide a brief review of current knowledge concerning the biophysical properties, gating mechanisms, pharmacology and (patho)physiology of this TRP channel.

Wakai, J., K. Yoshizaki, et al. (2008). "Expression of Fos protein in brainstem after application of l-menthol to the rat nasal mucosa." Neurosci Lett 435(3): 246-50.

There are two functional pathways for the nasotrigeminal reflex: the spinal nucleus of trigeminal nerve (SPV) to the Kolliker-Fuse (KF) nucleus and the nucleus of solitary tract (NTS) to the lateral parabrachial nucleus (PBl). Although stimulation of the nasal mucosa by cool temperature induces respiratory depression, it is still unknown whether these nuclei are activated. In the present study, we examined the expression of Fos protein in rat brainstem neurons after nasal application of l-menthol, which is known to activate cold-sensitive nasal receptors. Application of l-menthol, but not paraffin oil, decreased the respiratory rate from 99.7+/-15.6 to 78.5+/-7.3 min(-1). Furthermore, a significantly higher density of Fos-immunoreactive cells was observed in the SPV and KF in the l-menthol rats than in the controls. In the SPV, the density of Fos-immunoreactive cells was highest at approximately 0.5mm rostral to the obex in both the l-menthol (48.5+/-11.5 cells/section) and paraffin oil (26.0+/-9.6 cells/section) groups. In the KF, the mean density of Fos-immunoreactive cells was highest at approximately 5.0mm rostral to the obex in both groups (l-menthol: 67.8+/-14.0 cells/section, control: 41.0+/-12.7 cells/section). The present study suggests that the SPV-KF pathway is important for the cold-induced respiratory depression.

Wang, Y., R. P. Erickson, et al. (1993). "Selectivity of lingual nerve fibers to chemical stimuli." J Gen Physiol 101(6): 843-66.

The cell bodies of the lingual branch of the trigeminal nerve were localized in the trigeminal ganglion using extracellular recordings together with horseradish peroxidase labeling from the tongue. Individual lingual nerve fibers were characterized with regard to their conduction velocities, receptive fields, and response to thermal, mechanical, and chemical stimuli. Fibers were classified as C, A delta, A beta, cold, and warm. The chemical stimuli included NaCl, KCl, NH4Cl, CaCl2, menthol, nicotine, hexanol, and capsaicin. With increasing salt concentration the latency of the response decreased and the activity increased. The responses elicited by salts (to 2.5 M), but not nonpolar stimuli such as menthol, were reversibly inhibited by 3.5 mM of the tight junction blocker, LaCl3. These data suggest that salts diffuse into stratified squamous epithelia through tight junctions in the stratum corneum and stratum granulosum, whereupon they enter the extracellular space. 11 C fibers were identified and 5 were characterized as polymodal nociceptors. All of the C fibers were activated by one or more of the salts NaCl, KCl, or NH4Cl. Three C fibers were activated by nicotine (1 mM), but none were affected by CaCl2 (1 M), menthol (1 mM), or hexanol

(50 mM). However, not all C fibers or even the subpopulation of polymodals were activated by the same salts or by nicotine. Thus, it appears that C fibers display differential responsiveness to chemical stimuli. A delta fibers also showed differential sensitivity to chemicals. Of the 35 characterized A delta mechanoreceptors, 8 responded to NaCl, 9 to KCl, 9 to NH-4Cl, 0 to CaCl2, menthol, or hexanol, and 2 to nicotine. 8 of 9 of the cold fibers (characterized as A delta's) responded to menthol, none responded to nicotine, 8 of 16 were inhibited by hexanol, 9 of 19 responded to 2.5 M NH4Cl, 5 of 19 responded to 2.5 M KCl, and 1 of 19 responded to 2.5 M NaCl. In summary, lingual nerve fibers exhibit responsiveness to chemicals introduced onto the tongue. The differential responses of these fibers are potentially capable of transmitting information regarding the quality and quantity of chemical stimuli from the tongue to the central nervous system.

Wattenberg, L. W. (1991). "Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol)." Carcinogenesis 12(1): 151-2.

The inhibitory capacities of four terpenes on azoxymethane (AOM)-induced neoplasia of the large bowel and duodenum was studied in male F344 rats. A complete course of AOM administrations was given and 3 days later the rats were fed a semipurified diet containing 5 mg/g of the test compounds, i.e. 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol), beta-citronellol, (+/-)-linalool and (1R,2S,5R)-(-)-menthol or a corresponding control diet. The experiment was terminated 22 weeks after the last dose of AOM. Under these conditions, nerolidol showed an inhibitory effect on carcinogenesis of the large bowel. The number of rats bearing large bowel neoplasms (adenomas) was reduced from 82% in the controls to 33% in rats fed nerolidol and the number of tumors/rat from 1.5 in the controls to 0.7 in the nerolidol group. A reduction in adenocarcinomas of the duodenum was found but the data are not statistically significant. The effects of nerolidol are of interest in terms of the identification of a new inhibitor of carcinogenesis of the large bowel. The chemical structure of nerolidol suggests the possibility that the compound might have an impact on protein prenylation or some other aspect of the mevalonate pathway, but this remains to be established.

Wondergem, R., T. W. Ecay, et al. (2008). "HGF/SF and menthol increase human glioblastoma cell calcium and migration." Biochem Biophys Res Commun 372(1): 210-5.

This study explored the role of transient receptor potential melastatin 8 ion channels (TRPM8) in mechanisms of human glioblastoma (DBTRG) cell migration. Menthol stimulated influx of Ca(2+), membrane current, and migration of DBTRG cells. Effects on Ca(2+) and migration were enhanced by pre-treatment with hepatocyte growth factor/scatter factor (HGF/SF). Effects on Ca(2+) also were greater in migrating cells compared with non-migrating cells. 2-Aminoethoxydiphenyl borate (2-APB) inhibited all menthol stimulations. RT-PCR and immunoblot analysis showed that DBTRG cells expressed both mRNA and protein for TRPM8 ion channels. Two proteins were evident: one (130-140 kDa) in a plasma membrane-enriched fraction, and a variant (95-100 kDa) in microsome- and plasma membrane-enriched fractions. Thus, TRPM8 plays a role in mechanisms that increase [Ca(2+)](i) needed for DBTRG cell migration.

Wright, C. E., E. A. Laude, et al. (1997). "Capsaicin and neurokinin A-induced bronchoconstriction in the anaesthetised guinea-pig: evidence for a direct action of menthol on isolated bronchial smooth muscle." Br J Pharmacol 121(8): 1645-50.

For many years, menthol has been used in the treatment of respiratory disorders, although a bronchodilator effect of menthol has yet to be described. Using the bronchoconstrictors capsaicin (acting via stimulating the release of neuropeptides from sensory afferents) and neurokinin A (NKA), we have raised airways resistance in the guinea-pig (GP) and studied the effect of menthol on both capsaicin and NKA-induced bronchoconstriction in vivo. In vitro the effect of menthol on acetylcholine (ACh) and KCl precontracted GP bronchi was also studied. GP (n = 13) were anaesthetized (urethane 1.5 g kg-1, i.p.) and a bolus injection of capsaicin (7.5 micrograms ml-1, i.v.) or infusion of NKA (1 microgram min-1, i.v.) was given either in the presence of air (0.81 min-1) or air impregnated with menthol vapour (7.5 micrograms l-1) freely breathed from a tracheal cannula via a T-piece. Airways resistance (Raw) and ventilation were measured throughout. Bronchi of mean internal diameter (1029 + 73.6 microns; n = 24) were removed from GP (n = 16) and mounted in the Cambustion myograph. Bronchial rings were maximally precontracted with 80 mM KCl or 2 mM ACh. Relaxation due to a cumulative dose of menthol (1- 3000 microM) was measured. Menthol produced a significant ($P < 0.05$) 51.3% reversal of the capsaicin-induced increase in Raw, and also inhibited the significant ($P < 0.05$) reduction in minute ventilation (Ve) associated with the capsaicin-induced increased in Raw. Menthol also caused a significant ($P < 0.05$) 41% reversal of the NKA-induced increase in Raw. The NKA-induced decrease in Ve was again significantly ($P < 0.05$) reversed with menthol inhalation. Menthol caused a significant ($P < 0.001$) dose-dependent relaxation of KCl and ACh precontracted bronchi. We have shown that menthol attenuates both capsaicin and NKA-induced bronchoconstriction in vivo and relaxes KCl and ACh preconstricted bronchi in vitro. Menthol inhibition of NKA and capsaicin-induced bronchoconstriction could be, in part, explained by a direct action of menthol on bronchial smooth muscle.

Xing, H., J. X. Ling, et al. (2008). "TRPM8 mechanism of autonomic nerve response to cold in respiratory airway." Molecular Pain 4:22.

Breathing cold air without proper temperature exchange can induce strong respiratory autonomic responses including cough, airway constriction and mucosal secretion, and can exacerbate existing asthma conditions and even directly trigger an asthma attack. Vagal afferent fiber is thought to be involved in the cold-induced respiratory responses through autonomic nerve reflex. However, molecular mechanisms by which vagal afferent fibers are excited by cold remain unknown. Using retrograde labeling, immunostaining, calcium imaging, and electrophysiological recordings, here we show that a subpopulation of airway vagal afferent nerves express TRPM8 receptors and that activation of TRPM8 receptors by cold excites these airway autonomic nerves. Thus activation of TRPM8 receptors may provoke autonomic nerve reflex to increase airway resistance. This putative autonomic response may be associated with cold-induced exacerbation of asthma and other pulmonary disorders, making TRPM8 receptors a possible target for prevention of cold-associated respiratory disorders.

Yamamura, H., S. Ugawa, et al. (2008). "TRPM8 activation suppresses cellular viability in human melanoma." Am J Physiol Cell Physiol 295(2): C296-301.

The transient receptor potential melastatin subfamily (TRPM), which is a mammalian homologue of cell death-regulated genes in Caenorhabditis elegans and Drosophila, has potential roles in the process of the cell cycle and regulation of Ca(2+) signaling. Among this subfamily, TRPM8 (also known as Trp-p8) is a Ca(2+)-permeable channel that was originally identified as a prostate-specific gene upregulated in tumors. Here we showed that the TRPM8 channel was expressed in human melanoma G-361 cells, and activation of the channel produced sustainable Ca(2+) influx. The application of menthol, an agonist for TRPM8 channel, elevated cytosolic Ca(2+) concentration in a concentration-dependent manner with an EC(50) value of 286 microM in melanoma cells. Menthol-induced responses were significantly abolished by the removal of external Ca(2+). Moreover, inward currents at a holding potential of -60 mV in melanoma cells were markedly potentiated by the addition of 300 microM menthol. The most striking finding was that the viability of melanoma cells was dose-dependently depressed in the presence of menthol. These results reveal that a functional TRPM8 protein is expressed in human melanoma cells to involve the mechanism underlying tumor progression via the Ca(2+) handling pathway, providing us with a novel target of drug development for malignant melanoma.

Yang, X. R., M. J. Lin, et al. (2006). "Functional expression of transient receptor potential melastatin- and vanilloid-related channels in pulmonary arterial and aortic smooth muscle." Am J Physiol Lung Cell Mol Physiol 290(6): L1267-76.

Transient receptor potential melastatin- (TRPM) and vanilloid-related (TRPV) channels are nonselective cation channels pertinent to diverse physiological functions. Multiple TRPM and TRPV channel subtypes have been identified and cloned in different tissues. However, their information in vascular tissue is scant. In this study, we sought to identify TRPM and TRPV channel subtypes expressed in rat deendothelialized intralobar pulmonary arteries (PAs) and aorta. With RT-PCR, mRNA of TRPM2, TRPM3, TRPM4, TRPM7, and TRPM8 of TRPM family and TRPV1, TRPV2, TRPV3, and TRPV4 of TRPV family were detected in both PAs and aorta. Quantitative real-time RT-PCR showed that TRPM8 and TRPV4 were the most abundantly expressed TRPM and TRPV subtypes, respectively. Moreover, Western blot analysis verified expression of TRPM2, TRPM8, TRPV1, and TRPV4 proteins in both types of vascular tissue. To examine the functional activities of these channels, we monitored intracellular Ca(2+) transients ([Ca(2+)](i)) in pulmonary arterial smooth muscle cells (PASMCs) and aortic smooth muscle cells (ASMCs). The TRPM8 agonist menthol (300 muM) and the TRPV4 agonist 4alpha-phorbol 12,13-didecanoate (1 muM) evoked significant increases in [Ca(2+)](i) in PASMCs and ASMCs. These Ca(2+) responses were abolished in the absence of extracellular Ca(2+) or the presence of 300 muM Ni(2+) but were unaffected by 1 muM nifedipine, suggesting Ca(2+) influx via nonselective cation channels. Hence, for the first time, our results indicate that multiple functional TRPM and TRPV channels are coexpressed in rat intralobar PAs and aorta. These novel Ca(2+) entry pathways may play important roles in the regulation of pulmonary and systemic circulation.

Zaenker, K. S., W. Toelle, et al. (1980). "Evaluation of surfactant-like effects of commonly used remedies for colds." Respiration 39(3): 150-157.

Volatile aromatics, eucalyptol, eucalyptus oil, camphor and menthol were spread on synthetic DPL films and pulmonary surfactants; the initial surface pressure of the surfactants was measured and the additional surface pressure increment recorded. Eucalyptol was allowed to be inhaled by rabbits and lung compliance was monitored. Under the experimental conditions the volatile aromatics exhibited surfactant-like effects, namely a decrease in surface tension between water and air and thus improved lung compliance values in vivo.

Zhang, L. and G. J. Barritt (2004). "Evidence that TRPM8 is an androgen-dependent Ca2+ channel required for the survival of prostate cancer cells." Cancer Res 64(22): 8365-73.

The Ca(2+)-permeable channel TRPM8 is thought to play an important role in the pathophysiology of prostate cancer. We have investigated the intracellular location of TRPM8 and its role as a Ca(2+)-permeable channel in an androgen-responsive and an androgen-insensitive prostate cancer cell line. We report evidence from immunofluorescence experiments that in the androgen-responsive LNCaP cell line, the TRPM8 protein is expressed in the endoplasmic reticulum and plasma membrane, acts as a Ca(2+)-permeable channel (assessed using Fura-2 to measure increases in the cytoplasmic Ca(2+) concentration) in each of these membranes, and is regulated by androgen. Although TRPM8 was detected in the androgen-insensitive PC-3 cell line, no evidence was obtained for regulation of its expression by androgen. The results of experiments using LNCaP cells, the TRPM8 antagonist capsazepine, and small interference RNA targeted to TRPM8 indicate that TRPM8 is required for cell survival. These results indicate that TRPM8 is an important determinator of Ca(2+) homeostasis in prostate epithelial cells and may be a potential target for the action of drugs in the management of prostate cancer.

Zhang, L. and G. J. Barritt (2006). "TRPM8 in prostate cancer cells: a potential diagnostic and prognostic marker with a secretory function?" Endocr Relat Cancer 13(1): 27-38.

During the past 5 years it has emerged that the transient receptor potential (TRP) family of Ca(2+)-and Na(+)-permeable channels plays a diverse and important role in cell biology and in pathology. One member of this family, TRPM8, is highly expressed in prostate cancer cells but the physiological and pathological functions of TRPM8 in these cells are not known. Here we address these questions, and the issue of whether or not TRPM8 is an effective diagnostic and prognostic marker in prostate cancer. TRPM8 is known to be activated by cool stimuli (17-25 degrees C) and cooling compounds such as menthol. The activation mechanism(s) involves voltage sensing of membrane potential, phosphatidylinositol 4,5-bisphosphate and Ca(2+). In addition to prostate cancer cells, TRPM8 is expressed in sensory neurons where it acts as a sensor of cold. In prostate epithelial cells, expression of TRPM8 is regulated by androgen and is elevated in androgen-sensitive cancerous cells compared with normal cells. While there is some evidence that in prostate cancer cells Ca(2+) and Na(+) inflow through TRPM8 is necessary for survival and function, including secretion at the apical membrane, the function of TRPM8 in these cells is not really known. It may well differ from the role of TRPM8 as a cool sensor in sensory nerve

cells. Androgen unresponsive prostate cancer is difficult to treat effectively and there are limited diagnostic and prognostic markers available. TRPM8 is a potential tissue marker in differential diagnosis and a potential prognostic marker for androgen-unresponsive and metastatic prostate cancer. As a consequence of its ability to convey Ca(2+) and Na(+) and its expression in only a limited number of cell types, TRPM8 is considered to be a promising target for pharmaceutical, immunological and genetic interventions for the treatment of prostate cancer.

Zhang, X. B., P. Jiang, et al. (2008). "A-type GABA receptor as a central target of TRPM8 agonist menthol." PLoS ONE 3(10).

Menthol is a widely-used cooling and flavoring agent derived from mint leaves. In the peripheral nervous system, menthol regulates sensory transduction by activating TRPM8 channels residing specifically in primary sensory neurons. Although behavioral studies have implicated menthol actions in the brain, no direct central target of menthol has been identified. Here we show that menthol reduces the excitation of rat hippocampal neurons in culture and suppresses the epileptic activity induced by pentylenetetrazole injection and electrical kindling in vivo. We found menthol not only enhanced the currents induced by low concentrations of GABA but also directly activated GABAA receptor (GABAAR) in hippocampal neurons in culture. Furthermore, in the CA1 region of rat hippocampal slices, menthol enhanced tonic GABAergic inhibition although phasic GABAergic inhibition was unaffected. Finally, the structure-effect relationship of menthol indicated that hydroxyl plays a critical role in menthol enhancement of tonic GABAAR. Our results thus reveal a novel cellular mechanism that may underlie the ambivalent perception and psychophysical effects of menthol and underscore the importance of tonic inhibition by GABAARs in regulating neuronal activity.

Pharmacology, Toxicology, and Physiological and Biological Responses for Non-Tobacco Products

[No author] (2009). "The common cold." Prescrire Int 18(99): 31-32.

Most colds are due to viruses and resolve spontaneously after a few days. Available drugs do not modify the course of a viral cold. Some drugs used to treat colds carry a risk of serious adverse effects. This includes nasal sprays, especially vasoconstrictors such as pseudoephedrine and, in young children, menthol, camphor, and terpene derivatives.

Andersson, M. and M. Hindsen (2007). "Rhinitis because of toothpaste and other menthol-containing products." Allergy 62(3): 336-337.

No abstract available.

Atul Bhattaram, V., U. Graefe, et al. (2002). "Pharmacokinetics and bioavailability of herbal medicinal products." Phytomedicine 9(SUPPL. 3): 1-33.

The use of herbs for treating various ailments dates back several centuries. Usually, herbal medicine has relied on tradition that may or may not be supported by empirical data. The belief that natural medicines are much safer than synthetic drugs has gained popularity in recent years and led to tremendous growth of phytopharmaceutical usage. Market driven information on natural products is widespread and has further fostered their use in daily life. In most countries there is no universal regulatory system that insures the safety and activity of phytopharmaceuticals. Evidence-based verification of the efficacy of HMPs (herbal medicinal products, botanicals) is still frequently lacking. However, in recent years, data on evaluation of the therapeutic and toxic activity of herbal medicinal products became available. The advances in analytical technology have led to discovery of many new active constituents and an ever-increasing list of putatively active constituents. Establishing the pharmacological basis for efficacy of HMPs is a constant challenge. Of particular interest is the question of bioavailability to assess to what degree and how fast compounds are absorbed after administration of HMPs. Of further interest is the elucidation of metabolic pathways (yielding potentially new active compounds), and the assessment of elimination

routes and their kinetics. These data become an important issue to link data from pharmacological assays and clinical effects. Of interest are currently also interactions of herbal medicinal products with synthetically derived drug products. A better understanding of the pharmacokinetics and bioavailability of phytopharmaceuticals can also help in designing rational dosage regimens. In this review, pharmacokinetic and bioavailability studies that have been conducted for some of the more important or widely used phytopharmaceuticals are critically evaluated. Furthermore, various drug interactions are discussed which show that caution should be exercised when combining phytopharmaceuticals with chemically derived active pharmaceutical ingredients.

Behrends, M., M. Beiderlinden, et al. (2005). "Acute lung injury after peppermint oil injection." Anesth Analg 101(4): 1160-1162.

We describe a case of acute lung injury following IV injection of peppermint oil. An 18-yr-old woman injected the oil and developed fulminant pulmonary edema requiring ventilator support. Within 4 h after injection her arterial oxygen tension was 8.1 kPa (60 mm Hg) at an inspired oxygen fraction (FIO2) of 0.7 (P/F ratio: 85) despite a positive end expiratory pressure (PEEP) of 20 mbar, therefore meeting criteria for acute respiratory distress syndrome (ARDS). Mean pulmonary artery pressures and pulmonary artery wedge pressures were within normal limits throughout the case (<25 mm Hg and <10 mm Hg, respectively). Ventilation with high PEEP and diuresis resulted in a P/F ratio of 265 after 24 h. The patient was successfully weaned from the ventilator on the 9th day. This report is the first description of the sequelae of IV peppermint oil injection. The injection resulted in pulmonary edema and acute lung injury, presumably due to direct toxicity and a resultant increase in pulmonary vascular permeability.

Broderick, A., E. Finder, et al. (1973). "The effect of a commonly used cold remedy on host antibacterial defense mechanisms of the lung." Clinical Research 21(3): 593.

No abstract available.

Carstens, E., M. I. Carstens, et al. (2002). "It hurts so good: oral irritation by spices and carbonated drinks and the underlying neural mechanisms." Food Qual Prefer* 13(7-8): 431-443.

This paper reviews neurophysiological and psychological studies of oral irritation elicited by chemicals in spicy foods and carbonated drinks. Oral irritant, thermal and textural sensations are conveyed to the brain by the trigeminal pathway, which is separate from the gustatory and olfactory systems. In humans, repetitive application of capsaicin, citric acid, or concentrated NaCl elicits oral irritation that grows in intensity across trials ("sensitization"). After a rest period, reapplication elicits less irritation ("self-desensitization"), but if given recurrently will eventually evoke a progressive rise in irritation ("stimulus-induced recovery"=SIR). In neurophysiological recordings from neurons in the trigeminal subnucleus caudalis (Vc), the first relay in the pathway for oral somatosensation, these irritants elicit a similar pattern of progressively increasing firing, followed after a rest by self-desensitization and SIR. In contrast, nicotine, menthol or mustard oil elicit irritation that

decreases across trials ("desensitization"), a pattern also observed in Vc neuronal responses to these irritants. Carbonated water elicits an oral tingling sensation and excites Vc neurons largely through its conversion to carbonic acid. The good correspondence in temporal profiles for perception and neuronal activity supports a role for Vc neurons in the mediation of oral irritation. Finally, the development of preference for foods containing aversive chemicals is addressed. This may involve mere exposure, social reinforcement, the "thrill" of the strong sensation, or physiological reinforcement associated with satiety or release of endorphins by the painful stimulus.

Cohen, B. M. and W. E. Dressler (1982). "Acute aromatics inhalation modifies the airways. Effects of the common cold." Respiration 43(4): 285-93.

No abstract available.

Cooke, C. J., M. N. Nanjee, et al. (1998). "Plant monoterpenes do not raise plasma high-density-lipoprotein concentrations in humans." Am J Clin Nutr 68(5): 1042-5.

Low plasma concentrations of HDLs are associated with an increased risk of coronary artery disease. Two uncontrolled studies suggested that plant monoterpenes may have substantial HDL-cholesterol-elevating activity in humans. Each study used a proprietary mixture of 6 monoterpenes in olive oil. The present study was undertaken to test more rigorously the hypothesis that monoterpenes raise HDL concentrations in men with hypoalphalipoproteinemia. A double-blind, placebo-controlled crossover design was used. Twenty-four men aged 58-68 y (x: 62.3 y) with plasma HDL cholesterol <1.1 mmol/L, plasma triacylglycerols <3.5 mmol/L, and plasma total cholesterol <5.5 mmol/L at recruitment were randomly assigned to 6 capsules daily of a proprietary mixture of 6 monoterpenes in olive oil or 6 capsules daily of olive oil alone for 24 wk, followed by a washout period of 8 wk, and then the alternative capsules for 24 wk.: Five men dropped out. In the others, compliance was excellent as judged by capsule counts and urinary menthol glucuronide concentrations. No significant effects were observed on plasma HDL-cholesterol or apolipoprotein A-I concentrations, nor on plasma triacylglycerol, LDL-cholesterol, or apolipoprotein B concentrations. It was concluded that plant monoterpenes have no HDL-elevating activity of potential value for coronary artery disease prevention.

De Cort, S. C., J. S. Rowe, et al. (1993). "Cardiorespiratory effects of inhalation of L-menthol in healthy humans." J Physiol 473: 54P.

No abstract available.

dos Santos, M. A., C. E. Santos Galvao, et al. (2001). "Menthol-induced asthma: a case report." J Investig Allergol Clin Immunol 11(1): 56-8.

A case of asthma due to menthol is reported in a 40-year-old woman with no history of asthma or any other allergy. During the last two years, the patient had presented dyspnea, wheezing and nasal symptoms when exposed to mentholated products such as toothpaste and candies. The etiology was suggested by the history of exposure and diagnosis was

established by skin tests and bronchial challenge with menthol. The patient achieved control of symptoms by avoiding menthol and its derivatives.

Eccles, R. (1994). "Menthol and related cooling compounds." J Pharm Pharmacol 46(8): 618-30.

Menthol and related cooling compounds such as 'coolant agent 10', are widely used in products ranging from common cold medications to toothpastes, confectionery, cosmetics and pesticides. The review brings together a range of information on production and chemistry of menthol, and its metabolism, mechanism of action, structure-activity relationships, pharmacology and toxicology. In particular, the coolant action and carminative actions of menthol are discussed in terms of actions on calcium conductance in sensory nerves and smooth muscle. The actions of menthol on the nose, respiratory reflexes, oral cavity, skin and gastrointestinal tract are reviewed.

Eccles, R. (2000). "Role of cold receptors and menthol in thirst, the drive to breathe and arousal." Appetite 34(1): 29-35.

Menthol is widely used in candy, chewing gum, toothpastes, cigarettes and common cold medications. Menthol has been shown to stimulate cold receptors in the mouth and nose. The present paper puts forward the hypothesis that menthol, by its effects on oral and nasal cold receptors, may influence thirst, the drive to breathe, and arousal. The satisfying effects of menthol on thirst and breathing, together with an effect on arousal, may explain the popularity of menthol and account for the very large amount of menthol-containing products that are consumed each day.

Eccles, R. (2003). "Menthol: effects on nasal sensation of airflow and the drive to breathe." Curr Allergy Asthma Rep 3(3): 210-4.

Menthol, in lozenges, nasal sprays, vapo-rubs, inhalers, and cough syrups, is widely used as a treatment for rhinitis that is associated with acute upper respiratory tract infection and allergy. Menthol as a plant extract has been used in traditional medicine in Asia for the treatment of respiratory diseases for hundreds of years, but it was only introduced to the West as a medicine at the end of the 19th century. With the recent discovery of a menthol receptor on the sensory nerves that modulate the cool sensation, menthol has graduated from the realms of herbal medicine into the field of molecular pharmacology. This review concerns the physiologic and pharmacologic mechanisms that underlie the widespread use of menthol as a treatment for the relief of nasal congestion associated with rhinitis and its effects on the drive to breathe and symptomatic relief of dyspnea.

Eccles, R., M. S. Jawad, et al. (1990). "The effects of oral administration of (-)-menthol on nasal resistance to airflow and nasal sensation of airflow in subjects suffering from nasal congestion associated with the common cold." J Pharm Pharmacol 42(9): 652-4.

The effects of oral administration of a lozenge containing 11 mg (-)-menthol on nasal resistance to airflow (NAR) and nasal sensation of airflow in 62 subjects suffering from

nasal congestion associated with naturally acquired common cold infection have been studied. NAR was measured by posterior rhinomanometry and nasal sensation of airflow by means of a visual analogue scale (VAS). The effects of the lozenge were compared with a candy placebo lozenge in a double blind randomized trial. NAR showed a significant increase (P less than 0.05) in both the menthol and placebo groups over the 2 h experiment with no difference between the groups at any time. The VAS scores showed significant changes of subjective improvement in nasal sensation of airflow (P less than 0.001) in the menthol-treated group 10 min after dosing whereas the placebo group showed no change. It is concluded that dosing with 11 mg menthol in subjects with common cold has no effect on NAR as measured by posterior rhinomanometry but causes a marked change in nasal sensation of airflow with a subjective sensation of nasal decongestion.

Eccles, R., M. S. M. Jawad, et al. (1989). "The effects of L-Menthol on nasal resistance to air-flow and nasal sensation of air-flow in human volunteers suffering from acute upper respiratory-tract infection." J Physiol-London* 417: P131-P131.

No abstract available.

Eccles, R. and A. S. Jones (1983). "The effect of menthol on nasal resistance to air flow." J Laryngol Otol 97(8): 705-9.

Total nasal resistance to airflow was measured in thirty-one subjects before and after five minutes' exposure to menthol vapour. Menthol inhalation had no consistent effect on nasal resistance but the majority of subjects reported an increased sensation of nasal airflow and a cooling effect of menthol. The results indicate that menthol stimulates cold receptors in the nasal mucosa to create an increased sensation of airflow. No evidence was found in support of any nasal decongestant action for menthol.

Eccles, R., B. Lancashire, et al. (1987). "The effect of aromatics on inspiratory and expiratory nasal resistance to airflow." Clin Otolaryngol Allied Sci 12(1): 11-14

No abstract available.

Eccles, R., S. Morris, et al. (1990). "The effects of menthol on reaction time and nasal sensation of airflow in subjects suffering from the common cold." Clin Otolaryngol Allied Sci 15(1): 39-42.

The effects of sucking a lozenge containing 11 mg L-menthol on reaction time and nasal sensation were investigated in a double blind trial on 60 subjects suffering from the common cold. Reaction time was determined by measuring the response time to a stimulus presented on a microcomputer screen and nasal sensation was scored on a visual analogue scale. Menthol ingestion compared to placebo caused a significant increase in nasal sensation of airflow which persisted for up to 30 min. The simple and choice reaction times measured before ingestion of the lozenge were similar to those found in healthy uninfected subjects and there was no change in reaction time after ingestion of menthol.

Elson, C. E. and A. A. Qureshi (1995). "Coupling the cholesterol- and tumor-suppressive actions of palm oil to the impact of its minor constituents on 3-hydroxy-3-methylglutaryl coenzyme a reductase activity." Prostag Leukotr Ess 52(2-3): 205-208.

The impact of palm oil on cardiovascular disease and cancer may be explained by the mevalonate-suppressive action of constituent isoprenoid end products of plant secondary metabolism. Assorted monoterpenes, sesquiterpenes, carotenoids and tocotrienols down regulate, post-transcriptionally, 3-hydroxy-3-methylglutaryl coenzyme A reductase activity thereby modestly decreasing cholesterol synthesis and concomitantly decreasing LDL cholesterol. The reductase activity in tumor tissues differs from that of liver in being resistant to sterol feedback regulation. Tumor reductase activity retains sensitivity to the post-transcriptional regulation. As a consequence, the isoprenoid-mediated suppression of mevalonate synthesis depletes tumor tissues of two intermediate products, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are incorporated post-translationally into growth control-associated proteins.

Gelal, A., P. Jacob Iii, et al. (1999). "Disposition kinetics and effects of menthol." Clin Pharmacol Ther 66(2): 128-135.

Menthol is widely used in a variety of commercial products and foods, but its clinical pharmacology is not well studied. To determine the disposition kinetics and to examine subjective and cardiovascular effects of menthol, we conducted a crossover placebo-controlled study that compared pure menthol versus placebo, along with an uncontrolled exposure to menthol in food or beverage. A novel assay for the measurement of menthol in biological fluids was also developed. Twelve subjects were studied; each received a 100 mg l-menthol capsule, a placebo capsule, and 10 mg menthol in mint candy or mint tea on three different occasions. Plasma and urine levels of menthol and conjugated menthol (glucuronide), cardiovascular measurements, and subjective effects were measured at frequent intervals. Menthol was rapidly metabolized, and only menthol glucuronide could be measured in plasma or urine. The plasma half-life of menthol glucuronide averaged 56.2 minutes (95% confidence interval [CI], 51.0 to 61.5) and 42.6 minutes (95% CI, 32.5 to 52.7) in menthol capsule and mint candy/mint tea conditions, respectively ($P < .05$). The plasma area under the plasma concentration-time curve ratios for menthol capsule to mint candy/mint tea treatment averaged 9.2 (95% CI, 8.2 to 10.1). Urinary recovery of menthol as the glucuronide averaged 45.6 and 56.6% for menthol capsule and mint candy/tea, respectively (difference not significant). After menthol capsule dosing, the decrease in heart rate was less than the decrease after placebo administration ($P < .05$). Menthol reduced subjective vigor value at 30 minutes. We conclude that pure menthol and menthol in food or beverages have a similar systemic bioavailability and that menthol has a small cardioaccelerating effect.

Gomez-Galera, S., A. M. Pelacho, et al. (2007). "The genetic manipulation of medicinal and aromatic plants." Plant Cell Rep 26(10): 1689-715.

Medicinal and aromatic plants have always been intimately linked with human health and culture. Plant-derived medicines constitute a substantial component of present day human healthcare systems in industrialized as well as developing countries. They are products of

plant secondary metabolism and are involved in many other aspects of a plant's interaction with its immediate environment. The genetic manipulation of plants together with the establishment of in vitro plant regeneration systems facilitates efforts to engineer secondary product metabolic pathways. Advances in the cloning of genes involved in relevant pathways, the development of high throughput screening systems for chemical and biological activity, genomics tools and resources, and the recognition of a higher order of regulation of secondary plant metabolism operating at the whole plant level facilitate strategies for the effective manipulation of secondary products in plants. Here, we discuss advances in engineering metabolic pathways for specific classes of compounds in medicinal and aromatic plants and we identify remaining constraints and future prospects in the field. In particular we focus on indole, tropane, nicotine, isoquinoline alcaloids, monoterpenoids such as menthol and related compounds, diterpenoids such as taxol, sequiterpenoids such as artemisinin and aromatic amino acids.

Green, B. G. and M. T. Schullery (2003). "Stimulation of bitterness by capsaicin and menthol: Differences between lingual areas innervated by the glossopharyngeal and chorda tympani nerves." Chemical Senses 28(1): 45-55.

Capsaicin is viewed as a purely chemesthetic stimulus that selectively stimulates the somatosensory system. Here we show that when applied to small areas of the tongue, capsaicin can produce a bitter taste as well as sensory irritation. In experiment 1, individuals were screened for the ability to perceive bitterness from capsaicin on the circumvallate papillae. Fifteen of 25 subjects who reported at least weak bitterness rated the intensity of taste, irritation and coolness produced by 100-320 muM capsaicin and 100-320 mM menthol applied via cotton swabs to the tip (fungiform region), the posterior edge (foliate region), and the dorsal posterior surface (circumvallate region) of the tongue. Sucrose, citric acid, sodium chloride and quinine hydrochloride were applied to the same areas to assess tastes responsiveness. On average, capsaicin and menthol produced 'moderate' bitterness (and no other significant taste qualities) in the circumvallate region, and weaker bitterness on the side and tip of the tongue. Sensory irritation from capsaicin was rated significantly higher at the tongue tip, whereas menthol coolness was rated higher in the circumvallate region. In experiment 2 we applied sucrose and quinine hydrochloride together with capsaicin to investigate the effects other taste stimuli might have on capsaicin's reported bitterness. As expected, adding quinine produced stronger bitterness in the circumvallate and fungiform regions, and adding sucrose significantly reduced the bitterness of capsaicin in the circumvallate region. Overall, the results suggest that capsaicin and menthol are capable of stimulating a subset of taste neurons that respond to bitter substances, perhaps via receptor-gated ion channels like those recently found in capsaicin- and menthol-sensitive trigeminal ganglion neurons, and that the glossopharyngeal nerve may contain more such neurons than the chorda tympani nerve. That some people fail to perceive bitterness from capsaicin further implies that the incidence of capsaicin-sensitive taste neurons varies across people as well as between gustatory nerves.

Harris, B. (2006). "Menthol: A review of its thermoreceptor interactions and their therapeutic applications." Int J Aromather 16(3-4): 117-131.

This review examines the effect of menthol on thermoreceptors, firstly from a historical viewpoint leading to the characterisation of temperature-gated transient receptor channels and then by linking this activity to specific therapeutic effects. The underlying mechanisms involved in these effects, primarily by the dermal and respiratory administration of menthol, are explored.

Hasani, A., D. Pavia, et al. (2003). "Effect of aromatics on lung mucociliary clearance in patients with chronic airways obstruction." J Altern Complement Med 9(2): 243-9.

Complementary and alternative medicine have become an increasingly topical theme in respiratory medicine. Aromatics are a commonly used ingredient in a number of proprietary medicines. It is well established that lung mucus clearance is impaired in patients with chronic airways obstruction. This study investigated whether aromatics delivered by inunction could be objectively shown to enhance lung clearance. We studied 12 patients with chronic bronchitic with a mean standard error (SE) age of 67 (2) years (mean [SE] tobacco consumption history of 64 [12] pack-years). We used a randomized, single-blinded, placebo-controlled crossover trial within patient design assessing the effect of 7.5 g of aromatics inunction (compared to a "no-treatment baseline" and to a petrolatum "placebo") on lung mucus clearance measured by a standard radioaerosol technique. Aromatic treatment significantly enhanced clearance at two time points, 30 ($p < 0.05$) and 60 ($p < 0.02$) minutes postradioaerosol inhalation, but had no demonstrable further effect over the following 5 hours despite further application of the inunction. The clearance improvement (relative to a baseline) observed during the first hour of testing was significantly correlated ($p < 0.01$) with the concentration level of aromatics. Our data, thus, provide objective evidence of a positive effect of aromatics inunction on mucus clearance in chronic airways obstruction.

Haught, J. M., D. M. Jukic, et al. (2008). "Hydroxyethyl starch-induced pruritus relieved by a combination of menthol and camphor." J Am Acad Dermatol 59(1): 151-3.

Hydroxyethyl starch is a key component of many colloid volume expanders used in hypovolemic shock and otologic disease. Pruritus is a common side effect. Histopathology reveals multiple cytoplasmic vacuoles in dermal macrophages, endothelial cells, and perineural cells with electron-dense foreign material within the said vacuoles. Although classically refractory to treatment with corticosteroids and antihistamines, some benefit has been achieved with capsaicin, ultraviolet light therapy, and oral naltrexone. We present a case responsive to menthol and camphor and discuss the possible therapeutic mechanism.

Houghton, T. M. and C. S. Beardsmore (1998). "The effect of menthol on nasal airflow, perception of nasal patency, and cough receptor sensitivity in children aged 10 and 11 years." Thorax 53(Suppl.4): A9.

Background: Menthol has been used to treat the common cold for over a century despite limited evidence for its effectiveness, especially in children in whom colds are more

prevalent. Aims: To examine the effect of menthol on nasal flow rates, perception of nasal patency and cough in children, and to see whether different effects of menthol were linked. Subjects: Forty-two healthy volunteers (13 male) aged 10 and 11 years, free from upper respiratory tract infection. Methods: Subjects performed forced vital capacity manoeuvres through the nose, completed a visual analogue scale (VAS) for perception of nasal patency and had a citric acid cough challenge test. Tests were repeated twice on each of 2 days, with the second set following a 5-min inhalation of either menthol or a eucalyptus oil placebo. Results: Flow and volume measures were not significantly changed after menthol. Subjective nasal patency increased significantly ($p<0.0002$) and cough count in response to citric acid decreased ($p<0.007$) after menthol. Placebo had no effect. Inter-subject variation in VAS readings and cough responses were considerable. There was no relationship between the effects of menthol on perception of nasal patency or cough. Conclusions: Menthol has an effect on subjective nasal patency and cough in children, indicating that it may have a role in relief of common cold symptoms.

Huang, L. J., C. H. Li, et al. (2006). "Total synthesis and biological evaluation of (+)- and (-)-Butyl ester of rosmarinic acid." J Asian Nat Prod Res 8(6): 561-566.

An efficient method for the synthesis of the natural product (+)-(R)-butyl ester of rosmarinic acid (+)-(R)-1 and its enantiomer (-)-(S)-1 has been developed by chemical resolution of its phenyl lactic acid precursors 4 with (-)-menthol. Their antioxidative and anti-tumor activities were evaluated.

Javorka, K., Z. Tomori, et al. (1980). "Protective and defensive airway reflexes in premature infants." Physiol Bohemoslov 29(1): 29-35.

The incidence of respiratory reactions to stimulation of the nasal and propharyngeal mucose was studied in 44 newborn premature infants. The inhalation of menthol fumes or the administration of drops of Mukoseptonex to the nasal mucosa caused transient respiratory arrest or a drop in the respiration rate. The heart rate rose during chemical stimulation of the nasal mucosa, possibly in association with a general arousal reaction. Mechanical stimulation of the nasal mucosal with a nylon fibre elicited an expulsive reaction in 95% of the cases. As distinct from experimental animals, sneezing was not preceded by a deep initial inspiration. Stimulation of the oropharyngeal region produced transient apnoea in 24.5% of the cases, in 18% expiratory reactions reminiscent of the expiration reflex, in 33% independent, intensive inspiratory reactions and in 24.5% cough. Cough from both the oropharyngeal and the laryngeal region had a pronounced inspiratory component. Independent inspiratory reactions may to some extent be co-responsible for the high incidence of aspirations in the neonatal period.

Kaefer, C. M. and J. A. Milner (2008). "The role of herbs and spices in cancer prevention." J Nutr Biochem 19(6): 347-361.

Historically, herbs and spices have enjoyed a rich tradition of use for their flavor enhancement characteristics and for their medicinal properties. The rising prevalence of chronic diseases worldwide and the corresponding rise in health care costs is propelling interest

among researchers and the public for multiple health benefits related to these food items, including a reduction in cancer risk and modification of tumor behavior. A growing body of epidemiological and preclinical evidence points to culinary herbs and spices as minor dietary constituents with multiple anticancer characteristics. This review focuses on the antimicrobial, antioxidant, and antitumorigenic properties of herbs and spices; their ability to influence carcinogen bioactivation; and likely anticancer contributions. While culinary herbs and spices present intriguing possibilities for health promotion, more complete information is needed about the actual exposures to dietary components that are needed to bring about a response and the molecular target(s) for specific herbs and spices. Only after this information is obtained will it be possible to define appropriate intervention strategies to achieve maximum benefits from herbs and spices without eliciting ill consequences.

Kawane, H. (1994). "Aspirin-induced asthma and artificial flavors." Chest 106(2): 654-655.

No abstract available.

Kawane, H. (1996). "Menthol and aspirin-induced asthma." Respir Med 90(4): 247.

No abstract available.

Keifer, D., C. Ulbricht, et al. (2007). "Peppermint (Mentha Ã—piperita): An evidence-based systematic review by the Natural Standard Research Collaboration." J Herbal Pharmacother 7(2): 91-143.

An evidence-based systematic review including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology and dosing.

Loza-Tavera, H. (1999). Monoterpenes in essential oils: Biosynthesis and properties. Adv Exp Med Biol. 464: 49-62.

Monoterpenes are compounds found in the essential oils extracted from many plants, including fruits, vegetables, spices and herbs. These compounds contribute to the flavor and aroma of plant from which they are extracted. Monoterpenes are acyclic, monocyclic, or bicyclic C10 compounds synthesized by monoterpene synthases using geranyl pyrophosphate (GPP) as substrate. GPP is also the precursor in the synthesis of farnesyl pyrophosphate (FPP) and geranyl-geranyl pyrophosphate (GGPP), two important compounds in cell metabolism of animals, plants and yeast. Monoterpene cyclases produce cyclic monoterpenes through a multistep mechanism involving a universal intermediate, a terpinyl cation which can be transformed to several compounds. Experimental studies, using animal cancer models, have demonstrated that some monoterpenes possess anticarcinogenic properties, acting at different cellular and molecular levels. From these discoveries it seems clear that monoterpenes could be considered as effective, nontoxic dietary antitumorigenic agents that hold promise as a novel class of anticancer drugs.

Macht, D. I. (1939). "Comparative pharmacology of menthol and its isomers." Arch Int Pharmacod T* 63: 43-58.

No abstract available.

Marlowe, K. F. (2003). "Urticaria and asthma exacerbation after ingestion of menthol-containing lozenges." Am J Health Syst Pharm 60(16): 1657-9.

No abstract available.

McCurdy, C. R. and S. S. Scully (2005). "Analgesic substances derived from natural products (natureceuticals)." Life Sciences 78(5): 476-484.

From the first recorded accounts, over 7000 years ago, various forms of natural products have been utilized to treat pain disorders. Prototypical examples of such natural products are the opium poppy (Papaver soniferum) and the bark of the willow tree (Salix spp.). It was not until the 19th century when individual compounds were isolated from these substances and were determined to posses the desired effects. The known sources of these substances have been thoroughly investigated. Over the last several decades, more analgesic substances have been purified from natural products resulting in novel structural classes and mechanisms of actions. Plants and other natural products described in historical ethnobotanical and ethnopharmacological literature have become of more recent interest in drug discovery efforts. These manuscripts and reports are being utilized to aid in the identification of natural products that have been historically employed in the alleviation of pain. A large factor that has highlighted the importance of discovering novel compounds to treat pain has been in the fundamental understanding of the complex mechanisms of pain transmission in the nervous system. Nociceptive processing involves many receptor classes, enzymes and signaling pathways. The identification of novel classes of compounds from natural sources may lead to advancing the understanding of these underlying pharmacological mechanisms. With the potential of uncovering new compounds with idealistic pharmacological profiles (i.e., no side effects, no addictive potential), natural products still hold great promise for the future of drug discovery especially in the treatment of pain disorders and potentially drug addictions.

McGuigan, H. (1921). "Menthol and peppermint in acute catarrhal conditions of the respiratory tract." J Am Med Assoc* 76: 303-303.

No abstract available.

McKay, D. L. and J. B. Blumberg (2006). "A review of the bioactivity and potential health benefits of peppermint tea (Mentha piperita L.)." Phytother Res 20(8): 619-33.

Peppermint (Mentha piperita L.) is one of the most widely consumed single ingredient herbal teas, or tisanes. Peppermint tea, brewed from the plant leaves, and the essential oil of peppermint are used in traditional medicines. Evidence-based research regarding the bioactivity of this herb is reviewed. The phenolic constituents of the leaves include rosmarinic

acid and several flavonoids, primarily eriocitrin, luteolin and hesperidin. The main volatile components of the essential oil are menthol and menthone. In vitro, peppermint has significant antimicrobial and antiviral activities, strong antioxidant and antitumor actions, and some antiallergenic potential. Animal model studies demonstrate a relaxation effect on gastrointestinal (GI) tissue, analgesic and anesthetic effects in the central and peripheral nervous system, immunomodulating actions and chemopreventive potential. Human studies on the GI, respiratory tract and analgesic effects of peppermint oil and its constituents have been reported. Several clinical trials examining the effects of peppermint oil on irritable bowel syndrome (IBS) symptoms have been conducted. However, human studies of peppermint leaf are limited and clinical trials of peppermint tea are absent. Adverse reactions to peppermint tea have not been reported, although caution has been urged for peppermint oil therapy in patients with GI reflux, hiatal hernia or kidney stones.

Mimica-Dukic, N. and B. Bozin (2008). "Mentha L. Species (Lamiaceae) as promising sources of bioactive secondary metabolites." Curr Pharm Design 14(29): 3141-3150.

The use of mint species in traditional and conventional medicine is mostly due to the presence of two classes of secondary bimolecules: monoterpenoids in essential oils and different structural types of phenolic compounds. Essential oils are known to act as antimicrobial, antispasmodic, carminative, and antiviral agents. In addition, essential oils of several mint species have been recently qualified as natural antioxidants. However, since oil composition is highly variable, the pharmacological activity strongly depends on certain chemorace. On the contrary, composition of phenolic constituents is relatively stable within species. The most important phenolic compounds in Mentha species are flavonoids. Mints are characterized by the presence of specific lipophilic flavonoids. Phenolic compounds of mints are found to poses a wide range of pharmacological activity: antioxidant, antiulcer, cytoprotective, heptoprotective, cholagogue, chemopreventive, anti-inflammatory, antidiabetogenic etc. However, besides healing properties some mint species can exhibit an adverse effect on human health. Here we report on botany, chemistry and activity of Mentha species with special respect to their significance for the modern phytotherapy.

Nishino, T., Y. Tagaito, et al. (1997). "Nasal inhalation of l-menthol reduces respiratory discomfort associated with loaded breathing." Am J Respir Crit Care Med 156(1): 309-13.

To test the hypothesis that stimulation of cold receptors in the upper airway may alleviate the sensation of respiratory discomfort, we investigated the effects of nasal inhalation of l-menthol (a specific stimulant of cold receptors) on the respiratory sensation and ventilation during the loaded breathing in 11 normal subjects. Subjects were asked to rate their sensation of respiratory discomfort using a visual analog scale (VAS) while breathing on a device with a flow-resistive load (180 cm H2O/L/s) or with an elastic load (75.5 cm H2O/L). The effects of inhalation of l-menthol on ventilation and respiratory sensation were evaluated by comparing the steady-state values of ventilatory variables and VAS scores obtained before, during, and after l-menthol inhalation. In 8 of 11 subjects inhalation of strawberry-flavored air instead of l-menthol was performed during loaded breathing. Both during the flow-resistive loading and the elastic loading, inhalation of l-menthol caused a significant reduction in sensation of respiratory discomfort (flow-resistive loading: 62 +/- 14 [mean

+/- SD] VAS units before inhalation versus 36 +/- 16 during inhalation, $p < 0.01$; elastic loading: 68 +/- 13 before inhalation versus 55 +/- 17 during inhalation, $p < 0.01$) without a significant change in breathing pattern and ventilation. Comparison of the effects between the flow-resistive loading and the elastic loading also revealed that the reduction in VAS score was more during the flow-resistive loading than during the elastic loading ($p < 0.01$). Inhalation of strawberry-flavored air caused neither changes in VAS score nor changes in breathing pattern and ventilation, indicating that olfaction is not a contributing factor in the relief of respiratory discomfort. We concluded that stimulation of cold receptors in the upper airway with nasal inhalation of l-menthol reduces the sensation of respiratory discomfort associated with loaded breathing. This effect is more effective during the flow-resistive loading than during the elastic loading.

O'Mullane, N. M., P. Joyce, et al. (1982). "Adverse CNS effects of menthol-containing olbas oil." Lancet 1(8281): 1121.

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Parekh, D., M. A. Miller, et al. (2008). "Transdermal patch medication delivery systems and pediatric poisonings, 2002-2006." Clinical Pediatrics 47(7): 659-663.

Transdermal drug delivery systems are an increasingly popular method of medication delivery containing large quantities of medication and presenting new opportunities for toxicity. To provide a description of exposures to transdermal medications in a pediatric population, we studied exposures in individuals less than 12 years of age. This is a retrospective database study in which the Texas Poison Center Network database from 2002 to 2006 was reviewed. In all, 336 poison control center records of patch exposures over the 5-year period were identified. Of those, 110 cases involved children less than 12 years old. A majority of cases resulted in no significant clinical effects. One death resulted from opioid toxicity. Although a majority of patch exposures in children less than 12 years of age resulted in no significant clinical toxicity, practitioners and the public must be made aware of the available patch-based medications and their potential for toxicity in children.

Redolfi, S., M. Raux, et al. (2005). "Effects of upper airway anaesthesia on respiratory-related evoked potentials in humans." Eur Respir J 26(6): 1097-103.

Cortical potentials evoked by mid-inspiratory occlusion arise from numerous receptors, many of which are probably within the upper airway. Their precise nature is not known. The aim of the current study was to improve knowledge of this by studying the effects of topical upper airway anaesthesia on respiratory-related evoked potentials. Respiratory-related evoked potentials were described through the averaging of electroencephalogram (EEG) epochs following mid-inspiratory occlusions (C3-CZ; C4-CZ). A total of 21 healthy volunteers (13 male, aged 22-52 yrs) were studied during mouth breathing, before and after topical upper airway anaesthesia (lidocaine). Moreover, 15 subjects were studied during nose breathing with and without anaesthesia. Six subjects were studied whilst inhaling L-menthol. Typical potentials were present in all the subjects, their components featuring normal amplitudes and latencies. The route of breathing and upper airway anaesthesia did

not modify the EEG responses to inspiratory occlusions, qualitatively or quantitatively, during mouth or nose breathing. L-menthol had no effect. Upper airway receptors sensitive to topical anaesthesia are unlikely to contribute significantly to mid-inspiratory occlusion-evoked potentials. On the contrary, deeper receptors, such as joint and muscle receptors, could contribute dominantly to these potentials.

Riechelmann, H., C. Brommer, et al. (1997). "Response of human ciliated respiratory cells to a mixture of menthol, eucalyptus oil and pine needle oil." Arzneimittelforschung 47(9): 1035-9.

Nasal respiratory cells were harvested from 45 healthy individuals using a microcurette technique. Following harvest, cells were placed on microporous polycarbonate membranes and exposed for 30 min using a gas/liquid interface technique to a mixture of menthol, eucalyptus oil and pine needle oil (MEP), eucalyptus oil alone (ECO), and pine needle oil alone (PNO) at concentrations ranging between 0.2 and 11 g/m3. Ambient air served as control. Ciliary beat frequency (CBF) was assessed before and after exposure using video-interference-contrast microscopy. Control exposure to air (n = 10) did not alter CBF (7.1 +/- 0.9 Hz before and 7.0 +/- 0.9 Hz after exposure, -1.3% decrease), whereas a dose dependent decrease of CBF following exposure to MEP (max. decrease -22.6% at a concentration of 10 g/m3, $p < 0.01$), ECO (max. decrease -32.5% at a concentration of 7.5 g/m3, $p < 0.01$) and PNO (max. decrease -56.1% at a concentration of 9.4 g/m3, $p < 0.01$) was observed. The data show that essential oils in high concentrations can reduce in-vitro ciliary activity of human respiratory cells not protected by a mucus layer. These effects have to be verified by in vivo investigations.

Sant'Ambrogio, G., H. Tsubone, et al. (1995). "Sensory information from the upper airway: Role in the control of breathing." Resp Physiol 102(1): 1-16.

The functional integrity of extrathoracic airways critically depends on the proper orchestration of the activities of a set of patency-maintaining muscles. Recruitment and control of these muscles is regulated by laryngeal and trigeminal afferents that originate from pressure sensing endings. These sensors are particularly numerous among laryngeal receptors and, indeed, they constitute the main element in the respiration-modulated activity of the superior laryngeal nerve. Considering that the most compliant region of the upper airway, and thus more vulnerable to inspiratory collapse, lies cranially to the larynx, the laryngeal pressure-sensing endings seem to be ideally located for detecting collapsing forces and initiating reflex mechanisms for the preservation of patency. This process operates by activating upper airway dilating muscles and by decreasing inspiratory drive: both actions limit the effect of the collapsing forces. Cold reception is differently represented in various mammalian species within nasal and laryngeal segments. Cooling of the upper airway has an inhibitory influence on breathing, especially in newborns, and a depressive effect on upper airway dilating muscles. The latter response is presumably mediated through the inhibitory effect of cooling on laryngeal pressure endings. These responses could be harmful during occlusive episodes. Powerful defensive responses with distinct characteristics can be elicited through the stimulation of laryngeal and nasal irritant type receptors. Sneezing is elicited through the stimulation of trigeminal afferents, cough through the stimulation of laryngeal

vagal endings. Changes in osmolality and ionic composition of the mucosal surface liquid can lead to conspicuous alterations in receptor activity and related reflexes.

Silvers, W. S., R. Cohen, et al. (1993). "Comparative taste evaluation of aerosolized formulations of triamcinolone acetonide, flunisolide, and flunisolide with menthol." Clin Ther 15(6): 988-93.

The taste characteristics of aerosolized formulations of triamcinolone acetonide, flunisolide, and flunisolide with menthol flavoring were compared in 102 adult asthmatic patients. During a 2-hour test period, study participants evaluated the taste of each of the three inhaled corticosteroids, one at a time, in a randomly assigned sequence. The extent to which they liked the taste of each preparation and the taste intensity (strength of taste) of each product were rated on 100-point scales. Patients also characterized the predominant taste of each inhaled corticosteroid as "no taste," "salty," "sour," "sweet," or "bitter." Assessments were made immediately after inhalation and 2 minutes after inhalation. At both assessment times, subjects liked the taste of triamcinolone acetonide significantly more than the taste of flunisolide or flunisolide with menthol, and they liked the taste of flunisolide with menthol better than that of flunisolide without menthol. The taste intensity of triamcinolone acetonide was rated significantly less than that of the two flunisolide preparations at both evaluation times. There was no significant difference in the taste-intensity ratings for flunisolide with and without menthol. Triamcinolone acetonide was most frequently described as having no taste, whereas the taste of both flunisolide and flunisolide with menthol was most frequently described as bitter. Because of the possible adverse impact of an unpleasant taste on patient compliance with prescribed therapy, differences in the taste of inhaled corticosteroids should be an important consideration in selecting and recommending an aerosolized steroidal preparation for the control of asthma.

Sloan, A., S. C. De Cort, et al. (1993). "Prolongation of breath-hold time following treatment with an L-menthol lozenge in healthy man." J Physiol 473: 53P.

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Tamaoki, J., A. Chiyotani, et al. (1995). "Effect of menthol vapour on airway hyperresponsiveness in patients with mild asthma." Resp Med 89(7): 503-4.

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Tamaoki, J., A. Chiyotani, et al. (1996). "Menthol and aspirin-induced asthma - Reply." Resp Med* 90(4): 247-247.

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Watson, H. R., R. Hems, et al. (1978). "New compounds with the menthol cooling effect." J Society of Cosmet Chem Japan 29(4): 185-200.

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Brandwein-Gensler, M. and J. J. Hille (2003). "Behind the cover: The guthka story." Arch Otolaryngol 129(7): 699-700.

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Clark, P. I., P. S. Gardiner, et al. (2004). "Menthol cigarettes: setting the research agenda." Nicotine Tob Res 6 Suppl 1: S5-9.

No abstract available.

Delnevo, C. D. and U. E. Bauer (2009). "Monitoring the tobacco use epidemic III. The host: data sources and methodological challenges." Prev Med 48(1 SUPPL 1): S16-23.

This Host paper (III of V) reviews key surveillance and evaluation systems that monitor the characteristics, attitudes and behaviors of tobacco users that are crucial for tobacco control efforts. We summarize and expand on the recommendations from the Host Working Group of the National Tobacco Monitoring, Research and Evaluation Workshop. We also discuss research challenges and make additional recommendations for improving tobacco control surveillance and evaluation. We reviewed 10 major US surveys that collect data on tobacco use. A great deal of data is collected but gaps exist. Data collection on cigars, smokeless tobacco, brand, menthols, and PREPs is sparse and infrequent. Also, a number of factors, including, but not limited to, changes in US population composition, declines in survey response rates, and increases in cell phone use present research challenges that may impact the ongoing utility of these systems. Although the field of tobacco control research is an advanced area of public health, improvements in data systems are necessary to accurately evaluate progress and continue tobacco control gains. A coordinated surveillance and evaluation network would increase efficiency and improve the overall utility, quality and timeliness of the current data systems.

Henningfield, J. E. and M. V. Djordjevic (2004). "Menthol cigarettes: research needs and challenges." Nicotine Tob Res 6 Suppl 1: S11-6.

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Karter, M. J., T. L. Kissinger, et al. (1994). "Cigarette characteristics, smoker characteristics, and the relationship to cigarette fires." Fire Technol* 30(4): 400-431.

Data were collected from eight cities on a wide range of cigarette and smoker characteristics for a sample of smokers. Of these, 564 smokers had had fires and were identified through fire department response to those fires, while the other 1,611 smokers had not had fires and were identified through a telephone sample survey of the communities. The characteristics analyzed included those that had shown evidence of a relationship to the risk of a cigarette-initiated fire, either in laboratory studies or in previous statistical analyses of fire experience. The smoker characteristics analyzed were household income, education, age, gender, and race. The cigarette characteristics analyzed were filter, tobacco column length, filter length, circumference, density, amount of tobacco, menthol, citrate, porosity, and pack type. In addition, a variable was used to control for the smoker's city. After controlling for all smoker characteristics and city, logistic regression modeling showed four cigarette characteristics to be significant: filter, filter length, porosity, and type of pack. Filter, filter length, and porosity all affect air intake, which, therefore, appears to be an important physical element in the combustion process associated with risk. Analysis limited to filtered cigarettes only showed the same characteristics to be significant, plus tobacco column length. Extension of the analysis two-way interaction terms did not change any of the conclusions on which cigarette characteristics are important, but it did indicate that the role of pack type was different for men and women. Sensitivity analyses, shown in the appendix, supported the main conclusions that cigarette characteristics are significant after controlling for smoker characteristics and that the four specific cigarette characteristics-filter, filter length, porosity, and pack-are the ones that are significant. These analyses checked the impact of cluster sampling, sensitivity to missing data on smoker characteristics, and sensitivity to nonfire smoker cases with responses by people other than the smokers themselves. All this means that there are already cigarettes commercially available that exhibit a reduced propensity for ignition when one controls for smoker characteristics.

Keller, K. (1996). "Herbal medicinal products in Germany and Europe: Experiences with national and European assessment." Drug Inf J 30(4): 933-948.

The German Medicines Act (AMG) and the Council Directive 65/65 European Economic Community (EEC) apply fully to herbal medicinal products. This was confirmed by the European Court of Justice in 1992. A marketing authorization according to Article 4 of Council Directive 65/65 EEC granted by the competent authority is obligatory if herbal remedies are sold as finished medicinal products. The applicant must document quality, safety, and efficacy of its product. The term 'herbal remedies' includes medicinal products containing exclusively plant material or vegetable drug preparations as active ingredients. Homoeopathic preparations or isolated constituents such as Menthol or Digitoxin are not considered herbal remedies. Herbal drugs are included in the German Pharmacopoeia DAB '96 and in the European Pharmacopoeia. Specific aspects of quality control of herbal remedies are described in the EEC Note for Guidance 'Quality of Herbal Remedies' and, on a national level, in the 'Guidelines for the Testing of Drugs' following Article 26 AMG. The criteria for the evaluation of safety and efficacy apply to herbal remedies in the same way as they apply to other medicinal products with comparable indications. The complex

composition of herbal active ingredients, however, must be taken into account. Because herbal remedies can rely on long-term use and experience, bibliographic data can be used in the assessment according to Article 4 No. 8 a, ii of Council Directive 65/65 EEC. On a national level a definition of bibliographic data is set out in Article 22 AMG and in the 5th section of the 'Guidelines for the Testing of Drugs' following Art. 26 AMG. The review of old medicinal products on the German market has resulted in monographs on active ingredients of herbal origin providing a positive or a negative assessment of the safety and efficacy of these compounds. Herbal remedies with 'traditionally used' labeling do not comply with the European Union (EU) criteria. For this reason they are only acceptable on national markets and with strictly limited indications and special labeling.

Paine, J. B., 3rd (2008). "Esters of pyromellitic acid. Part II. Esters of chiral alcohols: para pyromellitate diesters as a novel class of resolving agents and use of pyromellitates as duplicands for chiral purification." J Org Chem 73(13): 4939-48.

Methods are presented for the preparation of pyromellitate esters of chiral terpene alcohols, including d- (3) or l-menthol (4), d-isomenthol (7), l-borneol (8), or d- (5) or l-isopinocampheol (6). Alcoholysis of PMDA in CH2Cl2/Et3N led to the formation of monoesters (e.g., 18) or diesters (11, 12), as needed, relying on the differential reactivity of the two anhydride groups. The easily isolated para diester (11) crystallized before the meta diester (12) from HOAc. Nicotine (1, 14) was efficiently resolved as 1:1 salts with the menthyl (11a, 11b) or bornyl (11f) para diesters, prototypes of what promises to be a large class of novel resolving agents. Recrystallization of para-di-d-menthyl pyromellitate (11a) greatly improved the chiral purity of the contained d-menthol (3), an example of purification by "duplication". An alternative synthesis of specific diesters took advantage of the easily separated benzyl diesters and their derived acid chlorides (19, 21), with the benzyl esters serving as temporary blocking groups removable by catalytic hydrogenolysis. Pyromellitate tetraesters (26) were prepared by base-catalyzed transesterification of the tetraethyl ester (25). Tri- l-menthyl pyromellitate (27b) was obtained by catalytic hydrogenolysis of benzyl tri-l-menthyl pyromellitate (31b), itself prepared from the alcoholysis of benzyl pyromellitate triacid chloride (30) with l-menthol (4).

Reid, J. R. (1993). "A history of mentholated cigarettes: This Spud's for you." Recent Advances in Tobacco Sciences 19: 71-84.

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Schmahl, D. P., E. Lichtenstein, et al. (1972). "Successful treatment of habitual smokers with warm, smoky air and rapid smoking." J Consult Clin Psychol 38(1): 105-11.

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Silver, W. L. (1992). "Neural and pharmacological basis for nasal irritation." Ann NY Acad Sci 641: 152-163.

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Taylor, R. (1963). "Chemical Stimulants to Respiration." Appl Ther 5: 1019-21 PASSIM.

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