EPIDEMIOLOGICAL EVIDENCE

ON RISK OF DISEASE

RELATING TO THE USE OF

MENTHOLATED CIGARETTES

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EXECUTIVE SUMMARY

Menthol itself has been widely used for many years and experimental studies provide no reason for concern that it is genotoxic or carcinogenic. It appears to be a substance of very low toxicity. However, there is evidence that it has acute effects on the mouth, nose and respiratory system that might possibly alter how smoke from cigarettes is inhaled.

The mentholated cigarette has assumed an important place in the US cigarette market over the last 50 years, and preference for mentholated cigarettes is very much greater in Blacks than Whites. Blacks have a higher risk of a number of smoking-related diseases, including lung cancer in men, despite smoking less heavily and tending to start smoking later in life. This has led some researchers to suggest that the excess risk in Blacks might be caused by menthol facilitating intake of tobacco smoke constituents. However, data from a number of studies provide no convincing evidence that mentholation increases puffing, inhalation or tobacco smoke uptake. Experimental data comparing mentholated and non-mentholated cigarettes shows comparable genotoxic effects and similar responses in the nose and respiratory tract following inhalation for 13 weeks.

Three relatively large and good quality epidemiological studies have compared the risk of lung cancer in smokers of mentholated and non-mentholated cigarettes. In all three studies, risk in women was somewhat lower in mentholated cigarette smokers than in non-mentholated cigarette smokers, and meta-analysis of the combined data showed that the reduction was statistically significant (RR 0.78, CI 0.63-0.98 for ever vs. never use; RR 0.70, CI 0.52-0.95 for long-term use vs. never use). One of the three studies reported a significant increased risk in men associated with use of mentholated rather than non-mentholated cigarettes, but the other two studies did not. Overall, combined estimates from the three studies showed an increase that was not statistically significant (RR 1.15, CI 0.93-1.43 for ever vs. never use; RR 1.23, CI 0.88-1.72 for long-term vs. never use). The overall evidence does not suggest that mentholation increases the risk of lung cancer to cigarette smokers, although future studies are needed to test for possible

effects of very long-term use. The evidence would seem to rule out the possibility that the increased risk of lung cancer in Black vs. White males could be explained by their much greater use of mentholated cigarettes.

Two of the same three studies that have reported results for lung cancer have also reported results for other cancers. One study found no relationship with mentholated cigarette use for a variety of cancer groupings. The other found no relationship for oropharyngeal cancer in either sex, no relationship for oesophageal cancer in males, but some increase in risk in females in an analysis that was open to objections for a number of reasons and did not fully clarify statistical significance. A study of pregnant women found no association of mentholated or non-mentholated cigarette smoking with preterm birth and associations with small-for-gestational-age birth that were somewhat stronger for non-mentholated than for mentholated cigarette smoking.

There are some weaknesses in the studies presenting data, discussed in detail in the report, and there is a notable absence of data relating use of mentholated cigarettes to common smoking-related diseases such as ischaemic heart disease, stroke or COPD. However, taken as a whole, the evidence is consistent with the addition of menthol to the tobacco having no effect on the toxicity or carcinogenicity of cigarettes.

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1. Introduction

This report reviews the evidence that the smoking of mentholated rather than non-mentholated cigarettes might have increased the risk of lung cancer and other smoking related diseases. The main objective of the report is to carry out a detailed assessment of the epidemiological evidence, lung cancer being considered in section 4 and other diseases being considered in section 5. To give greater insight into the possibility that mentholation may have had harmful effects, other relevant evidence is first summarized in sections 2 and 3.

Section 2 considers menthol itself, starting by describing its chemical properties, sources and uses, then summarizing evidence relating to its carcinogenicity in animals, genotoxicity and general toxicity and pharmacological effects, and finishing by referring to case-reports of adverse health effects.

Section 3 is concerned with mentholated cigarettes, describing how the market share of mentholated cigarettes has risen, how preference for mentholated brands differs between Blacks and Whites, as well as discussing how Blacks and Whites differ on other smoking characteristics and on risk of various smoking related diseases. Evidence regarding the possibility that mentholation might affect how cigarettes are smoked is also considered, while evidence relating to the relative carcinogenicity in animals, genotoxicity and general toxicity of mentholated vs. non-mentholated cigarettes is also summarized, as are data relating to pharmacological effects.

Finally, following the assessment of the epidemiological evidence in sections 4 and 5, section 6 reaches overall conclusions.

This report was prepared following (i) a MEDLINE search which identified 728 articles relating to menthol, (ii) study of the titles and abstracts of these articles to identify those relevant to the objectives of this report, (iii) obtaining copies of the relevant articles for detailed examination and (iv) where

appropriate, obtaining copies of additional articles cited by those originally identified.

2. Menthol

2.1 Chemical properties

Menthol ($C_{10}H_{19}OH$) is a monocyclic terpene alcohol which occurs as four pairs of optical isomers, (-)- and (+)- menthol, (-)- and (+)- neomenthol, (-)- and (+)- isomenthol and (-)- and (+)- neoisomenthol. (-)- menthol is the isomer that occurs most widely in nature and is the one assumed by the name menthol. It has a characteristic peppermint odour and exerts a cooling action when applied to skin and mucosal surfaces. The other isomers of menthol have a similar, but not identical, odour and do not have the same cooling action as (-)- menthol. The (-)- and (+)- isomers of menthol have identical physical properties apart from their specific optical effect on rotation of light. All the isomers have boiling points in the range 211.7-218.6^{o}C. A mixture of the (-)- and (+)- isomers of menthol is referred to as ($\pm$)- menthol. (-)- menthol is often referred to as l-menthol, while (-)+ menthol is often referred to as dl-menthol.[1]

Combustion of menthol has been found to produce compounds such as 3,4-benzpyrenes which are known carcinogens.[2-4] However, according to Richardson,[5] menthol does not give rise to any measurable amounts of 3,4-benzpyrenes when mentholated cigarettes are smoked.

2.2 Sources

l-menthol occurs naturally in over 100 essential oils.[6] It occurs in high concentrations in peppermint oil (*Mentha piperita*) and cornmint, or Japanese, mint oil (*Mentha arvensis*). Menthol is readily extracted from the plant by steam distillation. Due to the high price of *Mentha piperita*, menthol is mainly obtained from *Mentha arvensis*, which is grown commercially in Brazil, Paraguay, Japan and China.[1]

dl-menthol has not been reported to occur in nature but is prepared synthetically by hydrogenation of thymol followed by separation from its other isomers.[7]

2.3 Uses

Menthol and related cooling compounds are used in a wide range of products ranging from common cold medications and remedies for the treatment of digestive disorders to toothpastes, confectionery, soaps, detergents, creams, lotions, perfumes, pesticides, as well as in mentholated cigarettes. Peppermint oil is the world's third most important flavouring, exceeded only by vanilla and citrus flavours.[1]

2.4 Status

The Flavoring Extract Manufacturer's Association (FEMA) classifies menthol as GRAS (generally recognized as safe), while the US Food and Drug Administration (FDA) has approved menthol for food use. In 1968 the joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee of Food Additives published a monograph[8] giving an unconditional acceptable daily intake (ADI) of 0-0.2 mg/kg bw and a conditional ADI of 0.2-2 mg/kg bw. More recently a draft safety evaluation by FAO/WHO[9] allocated an ADI of 0-4 mg/kg bw.

2.5 Carcinogenicity in animals

The US National Cancer Institute[10] has concluded that (±)- menthol is not carcinogenic when given by the dietary route to either B6C3F1 mice at doses of 0, 2000 or 4000 mg/kg or Fischer 344 rats at doses of 0, 3750 or 7500 mg/kg. FAO/WHO[9] also refer to some other studies, none of which indicate that menthol is carcinogenic even at high doses. These include a study of female A/He mice given 2000 mg/kg bw menthol dissolved in tricaprylin by intraperitoneal injection, studies in which 0.5% and 1% menthol in the diet reduced mammary tumours in rats induced by 7,12-dimethylbenz[a]anthracene and an *in vitro* study in which concentrations of 0.1-2.5 mmol/L of menthol inhibited *ras*-mediated tumour growth in rat liver cells, with lovastatin as the positive control.

2.6 Genotoxicity

In their review, the WHO[9] concluded that "neither menthol nor its metabolites" were genotoxic *in vitro* or *in vivo*. They referenced 30 studies, 11 *in vitro* studies of (±)- menthol which were all negative, 11 *in vitro* studies of (-)- menthol of which 10 were negative and 1 equivocal, 3 *in vitro* studies of (+)- menthol of which 1 was positive and 2 were negative and 5 *in vivo* studies, 1 of (±)- menthol and 4 of (-)- menthol all of which were negative.

2.7 General toxicity

Although FAO/WHO, in 1976,[8] quoted an ADI as low as 0-0.2 mg/kg bw, Eccles[1] points out that this figure is not supported by any toxicological data and emphasizes that much larger doses have been taken by man without any ill effect. The higher figure of 0-4 mg/kg bw calculated in 2000 by FAO/WHO[9] was based on a no-effect level (NOEL) of 380 mg/kg bw per day in the long-term rat study referred to in section 2.5. That study did not in fact report any toxic effect even at the highest dose level tested. Eccles[1] concluded that "In general, menthol appears to be a substance of very low toxicity in acute studies, but more information is required to define a safe daily intake for chronic intake." The author's reservations about chronic intake appeared to relate to the smoking of mentholated cigarettes and the observation that US Blacks, who use mentholated cigarettes much more frequently than do US Whites, have increased risks of cancer of the oesophagus and lung (see section 3.3). The relevance of this observation will be considered later in this report.

2.8 Pharmacological effects

Eccles[1] has reviewed the pharmacological effects of menthol. These include:

Nasal decongestant activity Although menthol-containing inhalations, rubs and lozenges are often described as nasal decongestants, a number of studies have confirmed that menthol has no effect on nasal airway resistance, but causes a

marked increase in nasal sensation of airflow, believed to be due to stimulation of cold receptors served by the trigeminal nerve supply to the nose.

Respiratory reflexes Inhalation of menthol causes a reflex inhibition of respiration and inhibition of upper airway accessory respiratory muscle activity in conscious man, as does a cold air stimulus. This inhibition of respiration caused by cold-air stimulation of the nostrils in man may cause a brief period of apnea in newborn infants, and the same effect may be elicited by administration of menthol vapour directly to the nose of infants. Based on a large amount of clinical data on the use of menthol medication in infants suffering from acute respiratory tract infections, an international symposium in 1966 concluded that commonly used vaporub remedies were safe to use in infants but should not be directly applied to the nostrils.

Antitussive properties Menthol has been used for over 100 years as a treatment for cough, but there is little published literature to support antitussive efficacy. A recent randomized study[11] did report a highly significant reduction in cough, evoked by repeated challenges of inhalations of 33 μmol citric acid from an air driven dosimeter, in subjects inhaling 75% menthol in eucalyptus five minutes before challenge as compared to subjects inhaling one of two placebos (pine oil or air). Suggestions for the mechanisms by which menthol may act as an antitussive are speculative, but are based on established knowledge that menthol has already been shown to influence the activity of upper-airway sensory receptors and to modulate respiratory reflexes.

Mucus production and mucociliary clearance The literature is conflicting as to whether menthol may enhance or depress these important defence mechanisms against infection.

Pulmonary function Although some studies have shown that a mixture of aromatics (including menthol) improve pulmonary function, evidence relating to an effect of menthol alone appears to be very limited.

Oral cavity Cornmint oil and peppermint oil are widely used for flavouring toothpastes, chewing-gum and confectionery, the oils containing around 70% of (-)- menthol which is responsible for the pleasant cooling and refreshing taste of the oils. While menthol enhances cold sensations in the mouth, it can also enhance or attenuate warm sensations depending on the time period or pretreatment with menthol. The oral sensations are accompanied by a sensation of nasal cooling and a peppermint smell, as menthol vapour from the oral cavity reaches the nose.

Generally, although the evidence in some areas is not very clear, the data indicate that menthol has an acute effect on the mouth, nose and respiratory tract and certainly leaves open the possibility that menthol in cigarettes might affect puff volume, depth of inhalation and other aspects of how the cigarette is smoked. More recently, Garten and Falkner[12] have suggested that menthol induces unconscious breath holding which allows for greater transfer of inhaled tobacco smoke constituents into the pulmonary blood, and hence leads to a greater dependence on nicotine and a greater risk of tobacco attributable disease.

2.9 Case-reports of health effects

2.9.1 Asthma

Dos Santos *et al*[13] reported the case of a 40-year old woman with no history of asthma or allergy who presented dyspnoea, wheezing and nasal symptoms when exposed to mentholated products such as toothpaste and candies. The diagnosis was established by skin tests and bronchial challenge with menthol, and the symptoms never recurred once menthol was avoided. They referred to some other reported cases in the literature, but considered it to be a rare reaction as so few cases were documented in the literature.

On the other side of the coin, Tamaoki *et al*[14] described a randomized placebo-controlled study of nebulized menthol (10 mg, twice a day for four weeks) among nonsmoking chronic mild asthmatics in which exposure to menthol was associated with a significant reduction in wheezing, decrease in diurnal variation in peak expiratory flow rate and increase in the provocative concentration of methacholine required to cause a 20% fall in FEV_1. The study indicated, therefore, that menthol might be beneficial in the treatment of mild asthma.

2.9.2 Urticaria

Chronic urticaria with basophil leucopenia on challenge has been reported after contact with menthol in toothpaste, peppermint sweets and also mentholated cigarettes.[15] A case of generalized urticaria in a young woman resulting from a predilection for menthol from the same three sources has also been reported,[16] with strict avoidance of peppermint and all other sources of menthol leading to the effects disappearing promptly.

2.9.3 Idiopathic auricular fibrillation

Two cases arising from excessive peppermint sweet eating have been reported.[17]

2.9.4 Allergic cheilitis and dermatitis

Camarasa and Alomar[18] described a woman who acquired these symptoms from hypersensitivity to menthol in mentholated cigarettes. Patch testing revealed a strongly positive reaction to 1% menthol.

Wilkinson and Beck[19] reported two cases of allergic contact dermatitis associated with menthol in peppermint oil. They also refer to a number of other cases cited in the literature.

2.9.5 Purpura

A case of non-thrombocytopenic purpura from cigarettes containing menthol has been reported[20].

2.9.6 Inter-oral symptoms

Morton *et al*[21] reported 12 cases of contact sensitivity to menthol and peppermint oil in patients presenting with intra-oral symptoms in association with burning mouth syndrome, recurrent oral ulceration or a lichenoid reaction. Baer[22] also cites cases of oral symptoms associated with mint-flavoured gum or toothpaste.

2.9.7 Comment

These are only a few examples of rare health effects associated with menthol. Although there are more cases in the literature, the overall incidence is clearly very low.

2.10 Detection of lung cancer

According to Garten and Falkner[12] "It is very likely that smoking menthol masks the early warning signs of lung cancer, causing people to delay seeking medical attention until it is too late." However, no evidence is presented in support of what appears to be no more than speculation.

2.11 Summary

Menthol has been widely used for many years and there seems to be no reason for concern that it is carcinogenic or genotoxic. Case-reports of health effects seem relatively rare and it appears to be a substance of very low toxicity. With regard to possible health effects of mentholated cigarettes, the major interest of the material briefly reviewed in section 2 is the evidence that it may have acute effects on the mouth, nose and respiratory tract that might affect how cigarettes are smoked.

3. Mentholated cigarettes

3.1 Menthol in cigarettes

According to Hebert and Kabat,[23] about one third of the total of approximately 3500 tonnes of menthol produced worldwide is used in the tobacco industry. Full details of the nature and sources of the menthol used in cigarettes, and the level of inclusion, do not appear to be widely available, given the lack of information in the papers reviewed. However, an indication may be gained by the studies of Gaworski[6,24] who included 5000 ppm (w/w) synthetic ℓ-menthol, added to the tobacco during processing, in the experimental studies referred to below in section 3.5. In one of the two studies,[24] the test cigarette also included Brazilian menthol at 353 ppm (w/w). Miller *et al*[25] cite unpublished data indicating that 4 to 8 mg menthol corresponds to the range of menthol contained in popular commercial cigarettes.

3.2 Market share of mentholated cigarettes

The available literature on mentholated cigarettes and their possible health effects relates only to US populations, presumably because use there is much more widespread than in other countries.

Hebert and Kabat[26] note that, although mentholated cigarettes were introduced in the 1930s, they did not exceed 3% of the total market until 1949, when a slow but steady rise in market share began. The market share was 16% in 1963, rose to a peak of 29% in 1979, and then declined somewhat, to 25%, in 1994-1998.[12,27]

According to the US Surgeon-General[27] there does not appear to be a positive correlation between the presence of menthol and higher tar yields in cigarette brands. Of the 207 brands on the Federal Trade Commission list, 67% (51/76) of menthol brands had tar yields of less than 13 mg, as compared to 56% (73/131) of non-menthol brands. This does not, however, represent a direct comparison of the sales weighted average tar level of cigarettes smoked by users

of mentholated and non-mentholated cigarettes. In contrast, Richardson[5] states, without citing any reference as source, that mentholated cigarettes tend to be higher than non-mentholated cigarettes in tar and nicotine.

3.3 Relative use of mentholated cigarettes and relative cancer rates in US Blacks and Whites

Data from a number of studies, both national and regional in the US, are consistent in showing that preference for mentholated cigarettes is much stronger among Black than White smokers. For example, a national study in 1986 cited by the US Surgeon-General[27] found that, whereas 23.1% of White smokers smoked mentholated cigarettes, 75.5% of Black smokers did. Table 3.3.1 summarizes evidence from eight studies, which consistently show much higher mentholated cigarette use in Blacks than Whites.

The study by Sidney *et al*[28] of multiphasic examinees from the Kaiser Permanente Medical Care Program in California showed that the percentage of mentholated cigarette use was higher in women than in men in all age groups for Blacks and Whites and in most age groups for Asians. Interestingly, the proportion of smokers using mentholated cigarettes (presented graphically) was not obviously age dependent in Whites, but declined markedly with age in Blacks, from about 80% in 15-19 year olds to less than 30% in 70-79 year olds. The results are consistent with those of other studies in Table 3.3.1 which show a very high proportion of smokers using mentholated cigarettes in young Black females, e.g. 95% in a study of pregnant women in North Carolina[29] and 91% in women aged 18-30 in a study of four US states.[30]

Table 3.3.1 Percentage of smokers smoking mentholated cigarettes by race
Results from selected surveys

Year	Region	Age	Source	Race/gender	Mentholated cigarette smokers as % of all smokers
1979-86	California (Multiphasic examinees)	15-79	[28]	White males	18.1
				White females	27.1
				Asian males	35.7
				Asian females	47.9
				Black males	49.9
				Black females	55.5
				(Data are age-adjusted. In Blacks and Asians but not Whites mentholated use was much higher in younger subjects.)	
1985	USA 4 states	18-30	[30]	White males	24
				White females	34
				Black males	87
				Black females	91
1986	USA	17+	[27]	White	23.1
				Black	75.5
				Other	24.9
1986	USA 12 states	21-60	[31]	Black	73
1988	USA 10 sites	25-64	[32]	White non-Hispanic	22.5
				Black non-Hispanic	56.7
				Asian	38.7
				Hispanic	24.5
1995-99	North Carolina	Pregnant women	[29]	White females	26.3
				African-American females	94.7
1996	Florida	15-45	[33]	White	22.9
				Black	83.1
2000	USA	"Youth"	[34]	White	32.2
				African-American	73.6
				Asian-American	58.4
				Hispanic	51.3
				Hawaian/Pacific Islander	46.1

There are a number of other relevant differences in smoking habits between Whites and Blacks:

Prevalence of smoking The proportion of current smokers tends to be somewhat higher among Blacks than Whites. The 1989 US Surgeon-General's Report[27] presents prevalence estimates from National Health Interview Surveys over the period 1965-1987. On average prevalence is about 15% higher in relative terms and about 5% higher in absolute terms in Blacks. For example, prevalence was 36.5% in Whites and 41.4% in Blacks (Ratio 1.13, difference 4.9)

in 1970 and was 28.8% in Whites and 34.0% in Blacks (Ratio 1.18, difference 5.2) in 1987. According to Novotny *et al*[35] the difference in smoking prevalence between Blacks and Whites disappears if adjustment is made for occupation, education and other socioeconomic and demographic factors.

Amount smoked per smoker According to Richardson,[5] heavy smoking is much less common among African-American than among White smokers. Among evidence cited is:

(i) the average adult African-American smoker smokes 65% of the number of cigarettes smoked by the average White adult smoker[36];

(ii) the average number of cigarettes smoked per day by African-Americans is about seven less in men and about five less in women than the average smoked by Whites[37];

(iii) African-American men are three times less likely to be heavy smokers than Whites.[38]

According to the US Surgeon-General, whose 1998 report[39] contains extensive data on racial differences in smoking habits, the differences in the proportion of heavy smokers between racial groups is independent of educational attainment. Novotny *et al*[35] reach similar conclusions.

Age of starting to smoke Sterling and Weinkam,[36] based on data from the 1970 and 1979/80 National Health Interview Surveys, found that Black males consistently reported starting to smoke at an older age than did White males, by 0.5 years on average in 1970 and by 0.6 years on average in 1979/80. The difference was generally evident within occupational subgroups. Other evidence that African Americans tend to start smoking later in life is referred to by Hyland *et al*[32] and in the 1998 US Surgeon-General's report.[39]

Tar level According to Richardson,[5] studies have repeatedly shown that African Americans tend to smoke cigarettes that are higher in tar and nicotine.

Probability of quitting In an analysis based on data from the 1985 National Health Interview Survey, Novotny *et al*[35] found that Black smokers were substantially less likely to quit than Whites. (Odds ratio adjusted for a range of demographic and socioeconomic factors 0.7, 95% CI 0.6-0.9.) Whereas the proportion of ever smokers who were former smokers was 45% in Whites, it was only 30% in Blacks.

This finding was confirmed by the US Surgeon-General, whose 1998 report[39] summarized data from a number of National Health Interview Surveys and found that the quit rate was much lower in African-Americans than Whites, a difference that could not be explained by adjustment for educational attainment.

Royce *et al*[40] reported that, compared to Whites, African-Americans were more likely to smoke within 10 minutes of awakening (a behavioural indicator of nicotine dependence), to report a strong desire to quit smoking and to favour tobacco restrictions. They suggested that African-Americans were more nicotine dependent than Whites.

Cotinine levels The evidence is very consistent that Black smokers have higher cotinine levels than do White smokers.[30,41-44] In one large study[30] serum cotinine levels were found to average 210.2 ng/ml in White men, 244.8 ng/ml in Black men, 176.4 ng/ml in White women and 251.2 in Black women. After adjusting for age, education, gender, cigarettes/day, the nicotine content of the cigarette, years of smoking, inhalation frequency and ETS exposure, the difference in serum cotinine was estimated to be 83.3 ng/ml (SE 8.9 ng/ml). The higher cotinine level in Blacks was found to be significant when analysis was restricted to smokers of mentholated cigarettes (89.0 ng/ml, $p<0.0001$) or smokers of non-mentholated cigarettes (51.5 ng/ml, $p=0.0009$). The authors of the study suggested that "the difference in cotinine levels may be due to innate differences between the races in the metabolism or excretion of nicotine or cotinine." Other

studies[41,43,44] have confirmed that the difference in cotinine levels between Black and White smokers remains after adjusting for amount smoked and other smoking variables.

Table 3.3.2 summarizes differences between US Whites and Blacks in age-adjusted death rates for cancer of the respiratory system (which is almost all from cancer of the lung) over the period 1950-1995. Rates in Black and White women have remained similar, despite the marked rise over the period studied. However rates in Black and White men are very different, being about 50% higher in Blacks since 1980, though 20% lower in 1950.

TABLE 3.3.2 Age-adjusted[a] death rates for malignant diseases of the respiratory system by race and gender, United States, 1950-1995

	Males			Females		
Year	African-American	White	Ratio[b]	African-American	White	Ratio[b]
1950	16.9	21.6	0.78	4.1	4.6	0.89
1960	36.6	34.6	1.06	5.5	5.1	1.08
1970	60.8	49.9	1.22	10.9	10.1	1.08
1980	82.0	58.0	1.41	19.5	18.2	1.07
1985	87.7	58.7	1.49	22.8	22.7	1.00
1990	91.0	59.0	1.54	27.5	26.5	1.04
1995	80.5	53.7	1.50	27.8	27.9	1.00

[a] Age-adjusted to the 1940 US Standard Population
[b] African-American/White; calculated from race specific rates
Source : 1998 US Surgeon-General's Report[39]

The substantially higher lung cancer death rate of Black men compared to White men, despite their lower average cigarette consumption and later age of starting to smoke, has stimulated research to find an explanation. While there are a number of other potential candidate factors of importance, including genetics (e.g.[45]) and occupation,[36] a number of researchers, including Richardson[5] have considered the possibility that mentholated cigarettes may be part of the explanation. The very much higher mentholated cigarette use in Blacks, coupled with the known cooling effect of menthol, have led a number of researchers to consider the possibility that mentholation might have a "local anaesthetic effect" that would result in an increase in the volume of smoke inhaled, an increase in

smoke retention time in the lung and an increase in exposure to smoke components. The evidence relating mentholation to smoking characteristics is considered in the next section.

As noted in Table 3.3.3, which presents data for 1992-94 for a range of smoking related diseases, lung cancer in males is far from being the only cause of death with markedly different rates for Blacks and Whites. Blacks, in both sexes, have substantially higher rates of cancer of the oesophagus, stomach and larynx and of cerebrovascular disease, while much higher rates in Blacks are also seen for cancers of the lip, oral cavity and pharynx in men and for cervix cancer in women. Only for bronchitis/emphysema/COPD in both sexes and for bladder cancer in men are rates higher in Whites. For many of the diseases listed, Black/White differences in factors other than smoking (e.g. alcohol, diet, occupation, genetics) may have made a major contribution to the differences in disease rates noted.

TABLE 3.3.3 Age-adjusted[a] death rates for selected smoking-related causes of death by race and gender, United States, 1992-1994

	Males			Females		
Cause of death	African-American	White	Ratio[b]	African-American	White	Ratio[b]
Cancer						
Lip, oral cavity, pharynx	7.7	3.0	2.57	1.8	1.2	1.50
Oesophagus	11.4	4.4	2.59	3.0	0.9	3.33
Stomach	9.5	3.9	2.44	4.1	1.7	2.41
Pancreas	11.1	7.3	1.52	8.1	5.2	1.56
Larynx	4.6	1.7	2.71	0.8	0.4	2.00
Trachea, bronchus, lung	81.6	54.9	1.49	27.2	27.9	0.97
Cervix uteri	NA	NA	NA	5.7	2.2	2.59
Bladder	3.2	3.9	0.82	1.6	1.1	1.45
Kidney and other unspecified urinary organs	4.3	4.1	1.05	2.0	1.9	1.05
Cardiovascular diseases						
Coronary heart disease	138.3	132.5	1.04	85.0	62.9	1.35
Cerebrovascular disease	53.1	26.3	2.02	40.6	22.6	1.80
Respiratory diseases						
Bronchitis, emphysema and chronic airway obstruction, not elsewhere classified	22.3	26.6	0.84	8.2	16.0	0.51

[a] Age-adjusted to the 1940 US Standard Population
[b] African-American/White; calculated from race specific rates
Source : 1998 US Surgeon-General's Report[39]

3.4 Effect of mentholation on smoking characteristics

In 1984, Gardner *et al*[46] reported results of a study involving determining serum thiocyanate (SCN) concentrations from 130 young healthy persons and relating them to their smoking and physiologic characteristics. 70 were nonsmokers, 12 were smokers of mentholated cigarettes and 48 were smokers of non-mentholated cigarettes. Mean SCN (mg/ℓ) was 2.64 in nonsmokers and 8.09 in cigarette smokers and 7.36 in mentholated cigarette smokers. In a multiple regression analysis, 56% of the variance in SCN was explained by number of cigarettes used daily. Further terms included in the analysis, which were in turn gender, daily nicotine intake, marijuana use, menthol, daily tar intake and degree of inhalation, only increased the variance explained to 64%. In this model mentholation was associated with a reduction in SCN by 2.28 mg/ℓ but the statistical significance of this estimate is unclear. Mentholation did not appear as a significant predictor of SCN in analyses using an alternative statistical technique ("interaction analysis"). Mentholation was not mentioned as a contributor to SCN levels in the summary or discussion. The study was limited by failure to take diet into account, which may make an important contribution to SCN levels.

In 1993, Caskey *et al*[47] described the results of an experimental study involving 12 smokers of mentholated cigarettes (9 Blacks, 3 Whites) and 16 smokers of non-mentholated cigarettes (8 Blacks, 8 Whites). Each subject took part in two separate trials at a one week interval, one involving experimenter-supplied mentholated cigarettes (Salem king filter menthol soft pack, 1.2 mg nicotine, 17 mg tar, 17 mg CO) and one involving experimenter-supplied non-mentholated cigarettes (Marlboro king filter soft pack, 1.2 mg nicotine, 17 mg tar, 15 mg CO). In each experimental session baseline levels of CO, blood pressure and heart rate were determined and subjects then underwent a modified rapid smoking procedure using a controlled-dose smoke delivery system, subjects being asked to inhale 40 cc of cigarette smoke every 15 seconds for as long as they

could continue. Immediately after subjects said they wished to terminate their session, CO, blood pressure and heart rate were determined again.

The number of puffs taken before stopping, the main endpoint of the study, was significantly higher in Whites than Blacks. However it did not vary significantly according to cigarette preference (only tested in Blacks due to the small number of White mentholated smokers) or according to type of experimental cigarette smoked. The nearly identical means of 39.7 puffs for mentholated cigarettes and 40.5 for non-mentholated cigarettes conflicted with the study hypothesis that the cooling effect of menthol would allow more puffs to be taken from mentholated cigarettes.

No significant effects of cigarette preference or type of cigarette smoked were seen on pre- to post-smoking changes of CO or blood pressure. There was a marginally significant tendency for the rise in heart rate to be greater in Blacks who preferred non-mentholated cigarettes, but no significant effect of experimental cigarette.

In 1994, Jarvik *et al*[48] described the results of an experiment involving 20 regular smokers of at least 15 cigarettes per day. They consisted of 10 smokers of mentholated cigarettes (5 Blacks, 5 Whites) and 10 smokers of non-mentholated cigarettes (5 Blacks, 5 Whites). As in the previous study, each subject took part in two separate trials at an interval of one week (at least), one involving an experimenter-supplied mentholated cigarette (Marlboro menthol king size soft pack) and one an experimenter-supplied non-mentholated cigarette (Marlboro king size soft pack), both cigarettes having the same nicotine (1.2 mg), CO (15 mg) and tar (16 mg) levels. The order of smoking was balanced. In each session subjects first smoked one of their own cigarettes and then smoked, 30 minutes later, the experimental cigarette using a smoking apparatus designed to measure smoking topography and the amount of tar inhaled and retained in the lung. Table

3.4.1 summarizes differences noted in relation to the type of test cigarette smoked.

TABLE 3.4.1 Differences in smoking characteristics and intake of smoke components in relation to the test cigarette used - JARVIK 1994

Endpoint	Test cigarette mentholated vs. non-mentholated
Average puff volume	Smaller, $p<0.0001$
Total number of puffs	Smaller, $p<0.05$
Total puff volume	Smaller, $p<0.001$
Puff duration	NS
Mean puff flow	Smaller, $p<0.01$
Peak puff flow	NS
Inter-puff interval	NS
Inhaled volume	NS
Adjusted inhaled volume	NS
Lung retention time	NS
Butt length	NS
TPM inhaled	NS
% TPM retained	NS
COHb boost	NS ($p=0.053$)
CO boost	NS
COHb boost/total puff volume	Larger, $p<0.005$
CO boost/total puff volume	Larger, $p<0.001$

(NS = not significant)
Source : Jarvik *et al*[48]

No notable differences were seen in regard to whether the subject usually smoked mentholated or non-mentholated cigarettes.

The authors conclude in their abstract that

"Compared to regular cigarettes, mentholated cigarettes produced a significantly greater boost in carbon monoxide measured as both blood carboxyhaemoglobin 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."

However, their results, as presented, show otherwise - mean puff flow rates being decreased not increased and the COHb boost and CO boost not being significantly affected. They also state in their abstract that

"Mentholation of cigarettes may decrease volume of smoke inhaled but appears to increase exposure of smokers to toxic effects of carbon monoxide."

This too seems incorrect, since COHb and CO boost were not significantly increased. The significant increase is in relation to boost per puff volume, whereas boost itself would seem to be more relevant to toxic effects of CO.

In 1994, Miller *et al*[25] described a study involving 12 male African-American smokers of 15+ cigarettes per day, six primarily mentholated and six primarily non-mentholated cigarette smokers. Each subject took part in three separate trials, held at one week intervals, in which they inhaled a controlled dose of 1200 cc of smoke from a regular Marlboro cigarette (1.1 mg nicotine, 16 mg tar, 14 mg CO) injected with 0 mg, 4 mg or 8 mg menthol, 4 mg and 8 mg menthol corresponding to the range of menthol contained in popular commercial cigarettes. Pre- and post-experiment measures of exhaled CO, blood pressure, and pulse were collected at each session. The order in which the 12 subjects smoked the three cigarettes was random and balanced.

Puff volume, number of puffs and change in blood pressure and in heart rate pre- to post-smoking were all unrelated to the dose of menthol in the cigarettes or to whether the subjects were mentholated or non-mentholated cigarette smokers. However, significant differences in the change in CO pre- to post-smoking were seen between those who preferred mentholated cigarettes and those who preferred non-mentholated cigarettes (7.6 vs. 5.6 ppm, $p<0.05$) and in relation to the dose of menthol in the cigarettes, with the CO boost being higher for 8 mg menthol (8.1 ppm,) than for 4 mg menthol (6.1 ppm, $p<0.01$) or 0 mg menthol (5.6 ppm, $p<0.01$), 4 mg and 0 mg menthol not differing significantly.

In 1995, McCarthy *et al*[49] described the results of an experimental study involving 11 smokers of mentholated cigarettes (8 Blacks, 3 Whites) and 18 smokers of non-mentholated cigarettes (9 Blacks, 10 Whites). As in the Caskey *et al*[47] study, each subject took part in two separate trials at a one-week interval, again involving the same experimenter-supplied mentholated and non-mentholated cigarettes, with measurements made similar to before. Again, a rapid smoking procedure was used, with puffs taken every 15 seconds for as long as the subject could continue, but here the puff volume was chosen by the subject and not fixed.

Race and cigarette preference were unrelated to number of puffs or mean puff volume, but both number of puffs (18.9 vs. 23.0) and mean puff volume (59.6 vs. 67.2 cc) were significantly ($p<0.05$) lower when smoking the mentholated cigarette. Total puff volume was 1086 cc with mentholated and 1507 cc with non-mentholated cigarettes ($p<0.001$). No significant relationships with the experimental type of cigarette smoked were seen for expired air CO, blood pressure or heart rate.

The authors note that their results appear to contradict the theory that menthol is a local anaesthetic that may enable increased inhalation of cigarette smoke.

In 1996, Ahijevych *et al*[50] described a study involving 37 women reporting smoking up to 20 cigarettes/day. 18 smoked mentholated cigarettes (8 Blacks, 10 Whites) and 19 smoked non-mentholated cigarettes (10 Blacks, 9 White). Whereas the three previous studies referred to involved a crossover design with two experimental cigarettes, in this study each subject smoked one of her usual brand of cigarettes. Expired air CO, blood nicotine and cotinine were measured before smoking, and expired air CO and blood nicotine measured after smoking. Puffing topography measures were determined by a flow-meter

cigarette holder, with respiratory variables of inhalation and exhalation volume and duration measured by inductive plethysmography.

Analyses investigating possible effects of cigarette, race and their interaction were carried out. Table 3.4.2 summarizes differences noted comparing smokers of mentholated and non-mentholated cigarettes.

TABLE 3.4.2 Differences in sociodemographic variables, smoking characteristics and intake of smoke constituents in relation to the type of cigarette smoked - AHIJEVYCH 1996

Endpoint	Test cigarette mentholated vs. non-mentholated
Sociodemographic variables	NS
Smoking history variables	NS
Cotinine	NS (204 vs. 254 ng/ml)
Cotinine/cigarette	NS (15.3 vs. 18.1 ng/ml/cig)
CO boost	Smaller, p = 0.004 (unaffected by adjustment for brand CO)
Nicotine boost	NS (17.2 vs. 19.9 ng/ml)
Puffing and respiratory parameters	NS

(NS = not significant)
Source : Ahijevych *et al*[50]

The significantly lower CO boost with mentholated cigarettes and the non-significantly lower cotinine and lower nicotine boost are inconsistent with the "anticipated anesthetic effects of menthol cigarettes on smoke constituent exposure and topography."

In 1996, Clark *et al*[33] reported a study involving 65 Black and 96 White non-Hispanic adult established smokers. Subjects reported data on their smoking habits and details of the cigarettes they usually smoked (mentholated or not, length, tar level) were taken from a packet they provided for examination. They were given containers to collect the butts of all cigarettes smoked for a week and, at a second visit, had serum taken for cotinine analysis and CO in breath was measured after smoking one of their usual cigarettes. Serum cotinine levels were

found to be 84.5 ng/ml higher in mentholated cigarette smokers, after adjusting for race, cigarettes per day and the mean amount of each cigarette smoked ($p = 0.03$). Menthol was also associated with a significant ($p = 0.016$) increase in expired-air CO after adjustment for the same variables.

In 1999, Ahijevych and Parsley[51] described results of a study similar in design to that of Ahijevych *et al*[50] but larger, involving 49 female smokers of mentholated cigarettes (27 Blacks, 22 Whites) and 46 female smokers of non-mentholated cigarettes (21 Blacks, 25 Whites). Full results were not presented. Significant differences noted in relation to cigarette type were that mentholated cigarette smokers took larger puff volumes (45.8 vs. 37.8 ml, $p = 0.03$), had higher cotinine levels (239 vs. 189 ng/ml, $p = 0.02$), had higher cotinine levels per cigarette (17.8 vs. 13.1 ng/ml/cigarette, $p = 0.04$) and had a significantly shorter time to first cigarette (19.0 vs. 37.4 min, $p = 0.02$) as compared to non-mentholated cigarette smokers. The increase in puff volume associated with mentholated cigarettes appears to conflict with the results of a number of the previous studies considered which found either no association[50] or a decrease[48,49].

In 2002, Pickworth *et al*[52] described a study involving 18 mentholated cigarette smokers (17 Black, 1 White) and 18 non-mentholated cigarette smokers (3 Black, 15 White). Each subject participated in a single session during which three cigarettes were smoked 45 min apart in random order. The nicotine yields of the cigarettes smoked were 0.2 mg, 1.2 mg and 2.5 mg, the 1.2 mg cigarette being a commercial cigarette and the others research cigarettes. Subjects that ordinarily smoked mentholated cigarettes received mentholated cigarettes in the study, while non-mentholated smokers received non-mentholated cigarettes. Analyses separated out effects of nicotine yield and of mentholation. No significant effect of mentholation was seen on the increase in heart rate, blood pressure or CO resulting from smoking. Nor was any effect seen on number of puffs or on time to smoke the cigarettes. A number of changes were noted in relation to the

nicotine yield of the cigarette and the authors emphasize the importance of nicotine rather than mentholation on cardiovascular parameters.

The evidence cited above is based on a relatively small number of studies, many of which involve few subjects and some of which use an unusual protocol in which subjects take puffs every 15 seconds for as long as they can manage, which may not be too relevant to normal cigarette smoking. The results can be summarized as follows:

Number of puffs : Of six studies investigating this, four[25,47,50,52] found no effect of mentholation and two[48,49] report a reduced number in mentholated cigarette smokers.

Puff volume : Of five studies, two[25,50] found no effect, two[48,49] a decrease associated with mentholation and one[51] an increase.

Heart rate and blood pressure : All four studies[25,47,49,52] found no effect of mentholation.

CO : Of seven studies, two[25,33] found an increase associated with mentholation, one[50] found a decrease and four[47-49,52] found no effect, although one of these[48] appeared to claim an increase not shown in the analysis.

TPM : One study[48] found no effect.

SCN : One study[46] found some decrease with mentholation.

Cotinine : Two studies[33,51] reported an increase with mentholation, while another[50] found a non-significant decrease.

Taken as a whole, the data provide little clear support for the idea that mentholation may affect how a cigarette is smoked so as to increase uptake of toxic or carcinogenic smoke constituents.

3.5 Carcinogenicity in animals

FAO/WHO[9] cite a study by Gaworski *et al*[6] as evidence that "the presence of menthol in cigarettes did not enhance the incidence of lung cancer over that due to smoking unmentholated cigarettes." However, the study cited was only a short-term inhalation toxicity study in Fischer 344 rats, the 13-week period being far too short for any lung cancers to have occurred. The Gaworski study compared responses to an American-style, cellulose acetate-filtered, non-menthol reference cigarette with a similarly blended test cigarette containing 5000 ppm synthetic l-menthol tobacco, the rats being exposed, nose-only, for 1 hr/day, 5 days/wk at target mainstream smoke particulate concentrations of 200, 600 or 1200 mg/m^3. A control group were exposed to filtered air. Although histopathological changes, primarily associated with the epithelia of the respiratory tract, were noted in rats exposed to mainstream smoke from either cigarette, these changes were generally similar in the reference and menthol cigarette, they were not neoplastic, they were predominantly evident at the highest dose and they diminished significantly after a 6-week recovery period.

Similar conclusions were reached from further 13-week inhalation studies from the same group[24] in which the test cigarette, instead of differing from the reference cigarette only in having synthetic l-menthol added, differed in having 170 flavour ingredients added, including 353 ppm Brazilian Menthol, 5000 ppm synthetic l-menthol and 10 ppm l-menthone. Again, responses in the nose and lungs were similar in the test and reference cigarette, and largely reversible following the 6-week recovery period.

Although the results of the two studies by Gaworski *et al*[6,24] do not provide any concern regarding possible carcinogenic effects of addition of

menthol to cigarettes, it should be noted that, as far as this author is aware, no similar long-term (2 yr +) inhalation studies have been reported.

3.6 Genotoxicity

R J Reynolds have reported results from genotoxicity studies of cigarettes with added menthol. The first study[53] concerned mainstream smoke and compared three cigarettes, a reference cigarette (University of Kentucky 1R4F) which burns tobacco with no menthol flavour and two test cigarettes which heat tobacco, one with regular flavour and the other with menthol flavour. While mainstream smoke from the reference cigarette was mutagenic and/or cytotoxic in a number of the assays, mainstream smoke from both the test cigarettes was neither mutagenic nor cytotoxic in any of the assays used.

The second study[54,55] concerned sidestream smoke and compared five cigarettes, three as in the previous study, but also two ultra-low tar cigarettes which burn tobacco, one with regular flavour and one with menthol flavour. Again, the cigarettes which heat tobacco were neither mutagenic nor cytotoxic. The ultra-low-tar cigarettes were mutagenic and/or cytotoxic in a number of assays, but whenever positive results were found they were always found both for the cigarette with regular flavour and the cigarette with menthol flavour. Formal comparison of results for the two ultra-low tar brands were not carried out (though their responses were clearly broadly similar), attention being given mainly to the differences between the two main types of cigarette (i.e. heating or burning tobacco).

3.7 Pharmacological effects

Pritchard *et al*[56] investigated the central pharmacological effects of menthol in cigarettes in a study involving 12 subjects who usually smoked menthol cigarettes and 10 who usually smoked non-menthol cigarettes. Each subject smoked two cigarettes, one a “denicotinized” menthol cigarette, the other a “denicotinized” non-menthol cigarette, the level of nicotine (0.06 mg/cig) being

so low as to enable study of effects of menthol independent of nicotine. The order of smoking each cigarette was balanced and, for each cigarette, measurements of heart rate and EEG were made pre- and post-smoking. A total of 48 different endpoints indicative of central pharmacological effects were studied and for only one of these was there a significant difference between menthol and non-menthol cigarettes in the pre- to post-value, a difference attributed to chance by the authors. They concluded that "they found little evidence that menthol in cigarettes has central pharmacological effects."

3.8 Case-reports of health effects

The evidence summarized in section 2.9 described two reports of urticaria following exposure to menthol from various sources including cigarettes[15,16], one report of purpura menthol[20] and one of allergic cheilitis and dermatitis[18] from cigarettes containing menthol. The case of dermatitis was in a woman who had no other source of menthol, other sources of menthol not being referred to in the paper[57] citing the report on purpura. As far as is known to this author, there is no evidence that menthol in cigarettes causes responses that would not be caused by menthol alone or by cigarettes alone.

3.9 Summary

It is clear from the evidence summarized in section 3 that the mentholated cigarette has assumed an important place in the US cigarette market over the last 50 years, and that preference for mentholated cigarettes is very much greater in Blacks than Whites. Given that Blacks have a higher rate of a number of smoking-related diseases, despite smoking less heavily and tending to start smoking later in life and given that menthol has acute effects on the respiratory system (see section 2), a number of researchers (e.g.[5,23]) have suggested that mentholation may facilitate intake of tobacco smoke constituents, so increasing risk to the smoker. However, the evidence that mentholation in fact increases puffing, inhalation or tobacco smoke uptake is very far from convincing. Coupled with experimental data that suggest that the carcinogenicity and genotoxicity of

comparable mentholated and non-mentholated cigarettes is very similar, the combined evidence considered so far does not provide very strong support for menthol in cigarettes having any material effect on the risk of smoking-related disease.

However, it is of course necessary to look in detail at the more direct, epidemiological, data on the issue. This is considered in the following two sections.

4. Epidemiological evidence relating lung cancer to mentholated cigarettes

4.1 Introduction

There have been three epidemiological studies conducted in the USA which have provided evidence on the relative risk of lung cancer associated with smoking mentholated vs. non-mentholated cigarettes. These studies, one of prospective and two of case-control design, are described, and their findings summarized, in sections 4.2-4.4. Following section 4.5, in which the strengths and weaknesses of the studies are described in detail, meta-analyses of the combined results are presented in section 4.6 and conclusions summarized in section 4.7.

4.2 American Health Foundation multicentre case-control study – KABAT 1991

The first paper to report results relating use of mentholated cigarettes to risk of lung cancer was published by Kabat and Hebert in 1991[58]. It was based on data from the American Health Foundation multicentre hospital case-control study which had been ongoing for many years under the direction of the late Ernest Wynder. This involved patients with tobacco-related cancers and controls, hospitalized patients with conditions thought not to be associated with smoking, matched to the cases on age, sex, race, hospital and date of interview. The analyses described in the paper were restricted to current smokers of cigarettes (defined as subjects who had smoked within the year preceding diagnosis) interviewed between 1985 and 1990 in one of eight hospitals in four US cities (New York, Chicago, Philadelphia and Detroit). These included 588 male and 456 female histologically confirmed lung cancer cases and 914 male and 410 female controls.

All patients were interviewed in hospital using a standard questionnaire. This contained questions on the type of tobacco products used throughout life, brands of cigarettes smoked, cigarettes per day, use of filter and non-filter cigarettes, use of mentholated cigarettes, years of smoking each brand and age at initiation. Information on mentholation was obtained for each brand of cigarette

reported. For the purposes of analysis, subjects were classified into those who had never smoked a mentholated brand or had smoked one for less than 1 year, those who had smoked a mentholated brand for between 1 and 14 years and those who had smoked a mentholated brand for 15 years or more.

Statistical analysis, conducted by unconditional logistic regression, was used to estimate the risk of lung cancer associated with smoking mentholated cigarettes for 1-14 years or 15+ years relative to never having smoked mentholated cigarettes, with adjustment for age, race, education, cigarettes per day (of the current brand), inhalation, duration of smoking, body mass index and, where appropriate, also gender. Unadjusted relative risks could be derived from the distribution of cases and controls by menthol use, and relative risks for ever menthol use could also be derived by combining the results for 1-14 years use and 15+ years use based on the method of Fry and Lee [59].

The prevalence of menthol use among the controls, by race and sex, was shown to be quite similar to that reported in the Adult Use of Tobacco Survey[60] and in a survey reported by Sidney *et al.*[28] Use of mentholated cigarettes was higher in females (37.1%) than in males (26.7%) and was about twice as high in Blacks as in Whites in every age/sex group.

The estimated relative risks (RRs) and 95% confidence intervals (CIs) by menthol use are shown in Table 4.2.1. Without adjustment for potential confounding variables, use of mentholated cigarettes was associated with a reduced risk of lung cancer, not significantly in males (RR 0.92; CI 0.73-1.17) but significantly in females (RR 0.56; CI 0.42-0.75). With adjustment for the variables noted above, however, no significant association was seen in either sex (males 1.06; 0.82-1.37 females 0.78; 0.57-1.08). Nor was any association seen when results were considered by histological type. The results by histological type are only available for the sexes combined, and as adjusted relative risks.

TABLE 4.2.1 Risk of lung cancer by mentholated cigarette use among current smokers –American Health Foundation multicentre case control study - KABAT 1991

Histological type of lung cancer	Gender	No. of Cases	Adjusted[a]	Years of use of mentholated cigarettes: Never[b] RR	1-14 RR (CI)	15+ RR (CI)	Ever[c] RR (CI)
Any	Male	588	No	1.00	0.98 (0.72-1.33)	0.86 (0.63-1.18)	0.92 (0.73-1.17)
			Yes	1.00	1.14 (0.82-1.59)	0.98 (0.70-1.38)	1.06 (0.82-1.37)
	Female	456	No	1.00	0.56 (0.38-0.83)	0.56 (0.38-0.80)	0.56 (0.42-0.75)
			Yes	1.00	0.82 (0.52-1.28)	0.76 (0.53-1.16)	0.78 (0.57-1.08)
	Combined	1044	No	1.00	0.79 (0.62-1.02)	0.72 (0.56-0.91)	0.75 (0.63-0.91)
			Yes	1.00	1.02 (0.78-1.33)	0.88 (0.68-1.14)	0.94 (0.77-1.15)
Squamous cell carcinoma	Combined	268	Yes	1.00	1.17 (0.78-1.78)	0.92 (0.60-1.42)	1.04 (0.75-1.44)
Small cell carcinoma	Combined	131	Yes	1.00	0.80 (0.43-1.48)	0.86 (0.49-1.51)	0.83 (0.53-1.30)
Large cell carcinoma	Combined	106	Yes	1.00	1.99 (0.73-5.41)	0.84 (0.27-2.61)	1.28 (0.57-2.90)
Adenocarcinoma	Combined	400	Yes	1.00	0.98 (0.68-1.42)	0.95 (0.66-1.36)	0.96 (0.73-1.27)

[a] Yes = adjusted for age, race, education, cigarettes per day, inhalation, duration of smoking, body mass index. Combined gender analyses are also adjusted for gender.
[b] Or less than 1 year mentholated use.
[c] At least 1 year mentholated use.
RR relative risk
CI 95% confidence interval

The authors conclude that:

"Use of mentholated cigarettes was not associated with increased risk of lung cancer or of specific histological types of lung cancer in this study"

and note that

"If our results are confirmed by other researchers, the implication would be that use of mentholated cigarettes does not explain Black-White differences in lung cancer incidence or time trends."

4.3 Kaiser Permanente prospective study – SIDNEY 1995

The second paper to study use of mentholated cigarettes in relation to risk of lung cancer was published by Sidney *et al*. in 1995[61]. It was based on data from the Northern California Kaiser Permanente Medical Care Program in Oakland, California. The study population consisted of 5771 men and 5990 women aged 30 to 89 years who underwent a multiphasic health check-up between 1979 and 1985, who reported at that time that they were current cigarette smokers who had smoked for at least 20 years and who provided details of the mentholation status of the brand of cigarettes they usually smoked. Follow-up for lung cancer was determined up to the end of 1991 and a total of 318 incident cases were identified, 93 in mentholated cigarette users and 225 in non-mentholated cigarette users.

Of the 3654 users of mentholated cigarettes, 57% were women, 53% were aged under 50 and 43% were Black. These frequencies were all higher than seen in the 8107 users of non-mentholated cigarettes, where 48% were women, 46% were aged under 50 and 27% were Black. Education was not notably related to menthol use. As shown in Table 4.3.1, inhalation and amount of each cigarette smoked was similar in users of mentholated and non-mentholated cigarettes, but mentholated users smoked fewer cigarettes per day and had smoked for somewhat less long (no doubt due partly, at least, to their younger age). The cigarettes smoked by users of mentholated cigarettes were also of lower tar in males, but not in females.

TABLE 4.3.1 Comparison of mentholated and non-mentholated cigarette smokers – Kaiser Permanente prospective study - SIDNEY 1995

	Males		Females	
	Mentholated	Non-mentholated	Mentholated	Non-mentholated
Inhales all or most of the time	80.3%	82.4%	73.7%	73.7%
Inhales deeply	20.7%	22.7%	10.9%	12.1%
Smokes more than 3/4 of each cigarette	43.0%	44.2%	38.1%	38.6%
Tar >18 mg	18.9%	36.7%	19.2%	23.8%
Smoked for 40+ years	18.3%	23.2%	14.7%	19.2%
Smoked 40+ cigs/day	12.0%	16.3%	6.5%	8.9%
Mean tar, mg	15.0	16.1[a]	14.4	14.0[b]
Mean duration, years	30.1	31.3[a]	28.7	30.4[a]
Mean no. of cigs/day	20.7	23.3[a]	17.4	19.7[a]

[a] Difference noted as significant at $p<0.001$
[b] Difference noted as significant at $p<0.01$
Percentages presented have been recalculated where necessary to exclude those who did not respond.

Table 4.3.2 summarizes results relating to risk of lung cancer. In males, risks were somewhat higher in users than in non-users in every age group and after adjustment for age, the relative risk could be estimated as 1.40 (CI 1.01-1.94). This marginally statistically significant difference was also seen when adjustment was made for age, race and education as well as years of smoking and cigs/day (using a Cox proportional hazards model), the relative risk given being 1.45 (1.03-2.02). Duration of mentholated cigarette use also showed a significant ($p = 0.02$) trend with risk of lung cancer in men, with relative risks given as 1.10, 1.32 and 1.59 for, respectively, 1-9, 10-19 and 20+ years of cigarette use.

In females, however, risk of lung cancer was somewhat less in users than in non-users with the relative risk 0.71 (0.50-1.00) after adjustment for age and 0.75 (0.51-1.11) after additional adjustment for race, education, years of smoking and cigs/day. When data for males and females combined were considered, with additional adjustment for gender, there was no significant association of use of mentholated cigarettes with risk of lung cancer.

TABLE 4.3.2 Risk of lung cancer by mentholated cigarette use among current smokers for 20 years or more - Kaiser Permanente prospective study - SIDNEY 1995

					Duration of mentholated cigarette use (years)				
		No. of			0	1-9	10-19	20+	Any
Gender	Age	cases[a]		Adjusted	RR	RR (CI)	RR (CI)	RR (CI)	RR (CI)
Male	<50	6	(3)	No	1.0	-	-	-	2.2 (0.5-11.1)
	50-64	82	(24)	No	1.0	-	-	-	1.1 (0.7-1.8)
	65-74	60	(22)	No	1.0	-	-	-	1.7 (1.0-2.9)
	75+	20	(6)	No	1.0	-	-	-	1.7 (0.6-4.3)
	All	168	(55)	Age	1.00	-	-	-	1.40 (1.01-1.94)
	All	160	(51)[b]	Age, others[d]	1.00	-	-	-	1.45 (1.03-2.02)
	All	158	(57)[c]	Age, others[d]	1.00	1.10 (0.65-1.87)	1.32 (0.84-2.08)	1.59 (0.96-2.63)	-
Female	<50	11	(2)	No	1.0	-	-	-	0.3 (0.1-1.6)
	50-64	61	(19)	No	1.0	-	-	-	0.8 (0.5-1.4)
	65-74	50	(10)	No	1.0	-	-	-	0.6 (0.3-1.1)
	75+	28	(7)	No	1.0	-	-	-	0.9 (0.4-2.1)
	All	150	(38)	Age	1.00	-	-	-	0.71 (0.50-1.00)
	All	138	(34)[b]	Age, others[b]	1.00	-	-	-	0.75 (0.51-1.11)
	All	132	(42)[c]	Age, others[d]	1.00	0.72 (0.38-1.39)	1.01 (0.61-1.69)	0.70 (0.40-1.23)	-
Combined	<50	17	(5)	Gender	1.00	-	-	-	0.73 (0.26-2.04)
	50-64	143	(43)	Gender	1.00	-	-	-	0.95 (0.67-1.35)
	65-74	110	(32)	Gender	1.00	-	-	-	1.12 (0.74-1.69)
	75+	48	(13)	Gender	1.00	-	-	-	1.17 (0.62-2.21)
	All	318	(93)	Gender, age	1.00	-	-	-	1.02 (0.80-1.29)
	All	298	(85)[d]	Gender, age, others[d]	1.00	-	-	-	1.09 (0.85-1.41)
	All	290	(99)[c]	Gender, age, others[d]	1.00	0.93 (0.62-1.40)	1.17 (0.84-1.65)	1.10 (0.76-1.61)	-

[a] First number includes non-mentholated cigarette smokers, bracketed number is for mentholated cigarette smokers only
[b] There were fewer subjects in the analyses adjusted for age and other variables (see note d) than for those adjusted for age only, presumably because of missing data on the other variables
[c] The lesser total cases in this analysis than the previous one is presumably because of missing data on duration of mentholated cigarette use. However, it is unclear why there were more cases who smoked mentholated cigarettes
[d] Race, education, years of smoking and number of cigarettes per day

The authors noted that additional adjustment for aspects of smoking other than years of smoking and cigs/day did not substantially alter the estimate of relative risk for mentholated cigarette use.

The authors concluded that:

"This study suggests there is an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers."

4.4 Los Angeles County case-control study - CARPENTER 1999

Whereas the first two studies concerned current cigarette smokers, the final study also included former smokers in their analyses. This study, reported by Carpenter *et al.* in 1999[62], was of case-control design and was conducted in Los Angeles County in California. Cases were histologically confirmed and identified within seven months of diagnosis. Controls under age 65 were randomly selected from licensed drivers whilst those over age 65 were randomly selected from MediCare Beneficiaries. Controls were frequency matched to cases on age, sex and race. To qualify for the study cases and controls had to be resident in Los Angeles County, aged 40-84, be able to complete a questionnaire in English, be Caucasian (non-Hispanic) or African American and with no previous cancer (other than non-melanoma skin cancer). Subjects agreeing to participate were interviewed in person to obtain information on known and possible risk factors for lung cancer including smoking history, occupational exposures, ETS exposure and family history of lung cancer. Menthol smoking was classified based on response to the question "On average over your lifetime, out of every 100 cigarettes you smoked, how many were menthol?".

Of 859 cases and 3193 potentially eligible controls, 353 cases and 724 controls were available for interview and provided smoking information including menthol status. The analysis was restricted to the 337 cases (202 males and 135 females) and 478 controls (349 males and 129 females) who had ever smoked (as many as 100 cigarettes in their life). Analyses presented used unconditional logistic regression with adjustment for age, race, gender, total pack-years and years since quitting smoking. Other potential confounding variables (fruits, vegetables, occupational exposures, family history and ETS) had no appreciable influence on the association between mentholated cigarette smoking and lung cancer risk and were therefore not included in the regression models.

The prevalence of mentholated cigarette smoking in the controls was noted to be higher for African Americans (58%) than for Caucasians (40%).

Relative risks were presented by three aspects of mentholated cigarette smoking, pack-years of mentholated smoking (see Table 4.4.1), percentage of mentholated cigarettes smoked (see Table 4.4.2) and type of cigarette smoker (see Table 4.4.3). For all three aspects relative risks and confidence levels are either available or can be calculated (using the method of Fry and Lee[59] where appropriate) which are (a) unadjusted, (b) adjusted for the matching factors gender, age and race, or (c) adjusted for the matching factors as well as total pack-years and years since quitting smoking. No results are available for current and former smokers separately. Results by pack-years of mentholated smoking are available for males and females separately and for Caucasians and African-Americans separately.

TABLE 4.4.1 Risk of lung cancer by pack-years of mentholated cigarette use among ever smokers - Los Angeles County case-control study - CARPENTER 1999

Gender/ Race	No of cases	Adjusted	Pack-years of mentholated smoking 0 RR	1-15 RR (CI)	16-31 RR (CI)	32+ RR (CI)	Any RR (CI)
Male/ Both	202	No	1.00	0.63 (0.42-0.95)	1.40 (0.69-2.84)	2.60 (1.33-5.08)	0.92 (0.65-1.31)
		Age, race[a]	1.00	0.62 (0.41-0.93)	1.35 (0.67-2.73)	2.52 (1.29-4.92)	0.90 (0.64-1.28)
		Age, race, other[b]	1.00	0.87 (0.57-1.37)	1.21 (0.56-2.62)	1.48 (0.71-3.05)	1.00 (0.68-1.48)
Female/ Both	135	No	1.00	0.90 (0.52-1.57)	0.83 (0.36-1.96)	0.90 (0.38-2.15)	0.89 (0.55-1.44)
		Age, race[a]	1.00	0.87 (0.50-1.52)	0.68 (0.29-1.60)	0.72 (0.30-1.71)	0.80 (0.49-1.29)
		Age, race and others[b]	1.00	1.58 (0.77-3.22)	0.51 (0.19-1.34)	0.41 (0.15-1.11)	0.88 (0.50-1.57)
Both/ White[c]	181	No	1.00	0.64 (0.41-1.00)	1.35 (0.58-3.11)	1.80 (0.87-3.75)	0.86 (0.59-1.26)
		Age, gender[a]	1.00	0.68 (0.44-1.06)	1.41 (0.61-3.25)	1.78 (0.86-3.70)	0.90 (0.61-1.31)
		Age, gender and others[b]	1.00	1.01 (0.61-1.68)	1.01 (0.41-2.47)	1.06 (0.47-2.36)	1.02 (0.66-1.58)
Both/ Black[d]	156	No	1.00	0.71 (0.43-1.16)	0.91 (0.44-1.89)	1.56 (0.72-3.37)	0.85 (0.55-1.32)
		Age, gender[a]	1.00	0.66 (0.40-1.08)	0.77 (0.37-1.60)	1.46 (0.68-3.16)	0.79 (0.51-1.22)
		Age, gender and others[b]	1.00	0.96 (0.54-1.70)	0.69 (0.30-1.60)	0.90 (0.38-2.12)	0.89 (0.53-1.47)
Both/ Both	337	No	1.00	0.72 (0.52-1.00)	1.20 (0.70-2.06)	1.81 (1.07-3.07)	0.93 (0.70-1.23)
		Age, race and gender[a]	1.00	0.70 (0.51-0.97)	1.04 (0.61-1.79)	1.64 (0.97-2.77)	0.87 (0.66-1.15)
		Age, race, gender and others[b]	1.00	1.05 (0.72-1.54)	0.92 (0.50-1.68)	0.95 (0.53-1.70)[e]	1.00 (0.72-1.40)

[a] Width of estimated CI taken to be the same as the width of the unadjusted estimates, so may be slightly understated
[b] Other adjustment factors were total pack-years and years since quitting
[c] White defined as Caucasian
[d] Black defined as African-American
[e] RR (CI) are also available for 32-53 pack-years, 0.76 (0.37-1.59) and 53+ pack-years 1.38 (0.56-3.40)

TABLE 4.4.2 Risk of lung cancer by percentage of mentholated cigarettes smoked - Los Angeles County case-control study - CARPENTER 1999

Gender/ Race	No of cases	Adjusted	Percentage of mentholated smoking: 0 RR	1-19 RR (CI)	20-74 RR (CI)	75-100 RR (CI)	Any RR (CI)
Both/ Both[a]	337	No	1.00	0.87 (0.59-1.29)	0.84 (0.55-1.29)	1.09 (0.73-1.63)	0.93 (0.70-1.23)
		Age, race[b] and gender	1.00	0.94 (0.64-1.39)	0.73 (0.48-1.12)	0.94 (0.63-1.41)	0.87 (0.66-1.15)
		Age, race, gender and others[c]	1.00	1.11 (0.71-1.72)	0.90 (0.55-1.45)	1.02 (0.65-1.63)	1.01 (0.74-1.40)

[a] Caucasians and African/Americans
[b] Width of estimated CI taken to be the same as the width of the unadjusted estimates, so may be slightly too narrow
[c] Other adjustment factors were total pack-years and years since quitting

TABLE 4.4.3 Risk of lung cancer by cigarette smoker type - CARPENTER 1999

Gender/ Race	No of cases	Adjusted	Cigarette smoker type: Exclusive regular RR	Exclusive menthol RR (CI)	Mixed menthol/ regular RR (CI)	Any Menthol RR (CI)
Both/ Both[a]	337	No	1.00	1.17 (0.74-1.85)	0.86 (0.64-1.17)	0.93 (0.70-1.23)
		Age, race[b] and gender	1.00	1.10 (0.70-1.74)	0.83 (0.61-1.13)	0.89 (0.67-1.18)
		Age, race, gender and others[a]	1.00	1.04 (0.62-1.75)	1.01 (0.71-1.42)	1.02 (0.74-1.40)

[a] Caucasians and African/Americans
[b] Width of estimated CI taken to be the same as the width of the unadjusted estimates, so may be slightly too narrow
[c] Other adjustment factors were total pack-years and years since quitting

For all subjects, calculated relative risks comparing smokers who have ever and never used mentholated cigarettes are very close to 1.0, when adjustment is made for the matching factors and the smoking variables considered. Due to rounding of relative risks presented by level for the three aspects of mentholated cigarette smoking, these estimates are not quite the same in the three tables, being 1.00 (CI 0.72-1.40), 1.01 (0.74-1.40) and 1.02 (0.74-1.40) in Tables 4.4.1, 4.4.2 and 4.4.3, respectively. The results in Table 4.4.1 also show that the ever/never mentholated relative risk is quite close to 1 for men (1.00; 0.68-1.48), women (0.88; 0.50-1.57), Caucasians (1.02; 0.66-1.58) or African-Americans (0.89, 0.53-1.47). Nor is there any evidence of any variation in risk by proportion of mentholated cigarettes smoked (Table 4.4.2) or by cigarette smoker type (Table 4.4.3). After adjustment for the matching and smoking variables the relative risk

was 1.04 (0.62-1.75) for exclusive mentholated and 1.01 (0.71-1.42) for mixed menthol/regular (non-mentholated), as compared to exclusive regular.

The only apparent indication of any possible effect of mentholated cigarette smoking came in the results by pack-years of mentholation (Table 4.4.1). It is important to realise, in interpreting these results, that the relative risks which are unadjusted or which are adjusted only for the matching factors may be expected to show a tendency to rise with increasing pack-years of mentholated smoking, due to the greater likelihood of getting current and long-term smokers in the higher pack-years categories. When adjustment is also made for total pack-years and for years since quitting, this bias should be mainly removed, so that the results are more meaningful, though there remains the possibility of some residual confounding. After this adjustment there was no evidence of any variation in risk by pack-years of mentholation for the total population or for Caucasians or African-Americans separately. However, there was some evidence that risk increased with pack-years of mentholation in males (RRs 1.00, 0.87, 1.21 and 1.48 for 0, 1-15, 16-31 and 32+ pack-years, trend $p = 0.25$) and that risk decreased with pack-years of mentholation in females (RRs 1.00, 1.58, 0.51 and 0.41 for 0, 1-15, 16-31 and 32+ pack-years, trend $p = 0.04$), the decrease but not the increase being significant.

The authors conclude that “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.”

4.5 Strengths and weaknesses of the studies

Before summarizing the combined evidence from the three studies, it is important to consider their strengths and weaknesses.

Study design The studies covered the three most common types of design used in epidemiological research, the prospective study, the hospital case-control study and the population based case-control study. The prospective design, as used in SIDNEY 1995, has the advantage that data on exposure are collected before onset of lung cancer, so virtually ruling out the possibility of recall bias. However, SIDNEY 1995 did not follow changes of exposure during the follow-up period and the incidence of lung cancer was related to use of mentholation at one reported time point up to 12 years before. Case-control studies are quicker to conduct and can obtain large numbers of cases more readily, but suffer from the problem that exposure is determined after onset of disease which may have an effect on the answers given. It is unclear, however, why the accuracy of reporting of the relative use of mentholated and non-mentholated cigarettes should differ materially between lung cancer cases and controls. The use of hospital controls, as in KABAT 1991, has the advantage over the use of population controls, as in CARPENTER 1999, of making it easier to conduct interviews in a situation comparable to that used when interviewing the cases. However, ensuring that hospital controls are representative, in respect of the exposure of interest, of the population from which the cases arose (which is required if relative risk estimates are not to be biased) is difficult, especially when there is limited knowledge of the health effects the exposure may have. The issue of representativeness is considered further below.

Number of cases All three studies involved quite a reasonable number of lung cancer cases among the cigarette smokers considered in the analysis. The largest, 1044, was in KABAT 1991, with 337 in CARPENTER 1999 and 318 in SIDNEY 1995. Of these, respectively, 258, 151 and 93 were in men and women who had ever used mentholated cigarettes. The largest study was capable of

detecting about a 20% excess risk of lung cancer in mentholated cigarette smokers as significant at the 95% confidence level.

Adequacy of the cases There is abundant evidence that in-life diagnosis of lung cancer is unconfirmed by autopsy diagnosis in a moderate proportion (perhaps 10% or so) of cases[63]. None of the studies confirmed diagnosis by autopsy so it is likely some cases included were false positive. The cases in the KABAT 1991 and CARPENTER 1999 studies were histologically confirmed which would have greatly reduced the possibility of a false positive, but SIDNEY 1995 provided no data on the basis of diagnosis. Although there is evidence that knowledge of smoking habits may affect the likelihood that a lung cancer is detected in life[64,65], it seems implausible that knowledge of mentholation status would. In view of this, and in view of the moderate rate of misdiagnosis, it seems unlikely that inaccuracy of diagnosis will have had any material effect in these studies.

Representativeness In the SIDNEY 1995 prospective study, subjects had to attend for multiphasic health check-up and were noted to be somewhat more educated than the local population and underrepresentative of the extremes of wealth and poverty. If there is a differential risk of mentholated and non-mentholated cigarettes, this is unlikely to vary by education or income, so this is not an issue. Of somewhat more concern is the possible inadequacy of the controls used in the two case-control studies.

KABAT 1991 noted that their "controls were hospitalized patients with conditions thought not to be associated with smoking, including: cancers (of the colon, stomach, female breast, prostate, and skin, as well as leukemia, lymphoma, sarcomas, etc.); benign neoplastic diseases; and non-neoplastic conditions (such as musculoskeletal and connective tissue disorders, eye conditions, injuries, etc.). Sidney *et al*.[61] claim that "some of these conditions might have been associated with menthol use, obscuring an association with lung cancer." However, it seems

rather unlikely that a disease that is not affected by smoking non-mentholated cigarettes would be affected by smoking mentholated cigarettes. One could point out that risk of some of the cancers (stomach, breast, leukaemia) may, according to more recent evidence, be moderately associated with smoking. However, as they form only a proportion of the total controls and they may not be related to menthol use anyway, it is unlikely that their inclusion would have caused more than slight bias to the relative risk estimates.

Perhaps more dubious are the population controls used in CARPENTER 1999. These were derived from registers of licensed drivers aged under 65 and of MediCare Beneficiaries aged over 65. However, there does not seem to be any guarantee that cases aged under 65 could drive or that cases aged over 65 were on MediCare. It is possible that ability to drive or use of MediCare might be associated with use of mentholated cigarettes, so possibly causing bias. Also, some 25% of the potential controls asked to participate in this study refused to do so and refusers and non-refusers might differ in their choice of cigarette.

Reliability of the data collected All three studies are limited by possible inaccuracies in the reporting of smoking history and mentholation status. If these are random, this will tend to bias relative risk estimates towards 1.0 and reduce the power of the study to detect a true effect. However, it is not clear that errors will be random. For example, subjects may tend to think their past habits were more like their current habits than they actually were.

The source of the data on mentholation is not totally clear in the papers describing the results of the lung cancer studies. KABAT 1991 stated that questions were included on brands of cigarettes smoked and on use of mentholated cigarettes and also that information on mentholation was obtained for each brand of cigarette reported. However, no details were provided as to what happened if the data conflicted, e.g. the subject said they used mentholated cigarettes but the brand reported was not in fact mentholated, nor how often such conflicts arose.

SIDNEY 1995 also asked questions on the brand smoked and on whether the brand was mentholated, but did not report that they even obtained any information on which brands were mentholated, let alone that they checked one answer against the other. CARPENTER 1999 did not report asking about brand at all, only a question "On average over your lifetime, out of every 100 cigarettes you smoked, how many were menthol?" which would be rather difficult to answer. Neither of the two studies asking about brand smoked requested the subject to show a packet for confirmation, as is done in some studies.

The effect error in determining mentholation status would have had on the relative risk estimates is not totally clear. Inasmuch as mentholated cigarettes are, I believe, quite distinctive in taste, errors may not be too great.

Length of use of mentholated cigarettes All of the studies are inevitably limited by the lack of information on lifetime use of mentholated cigarettes. Mentholated cigarettes only reached an appreciable market share in the 1960s and 1970s so the studies cannot yet compare, for example, lung cancer risk in 70 year olds with 50 years smoking of mentholated cigarettes with that in 70 year olds with 50 years smoking of non-mentholated cigarettes. However, if there was a major difference in risk between the two types of cigarettes, one would expect it to emerge to some extent in the studies so far conducted.

Adjustment for potential confounding variables All three studies adjusted for age, race and, where appropriate, gender. KABAT 1991 and SIDNEY 1995, who considered current smokers, adjusted for cigs/day and duration of smoking, while CARPENTER 1999, who considered ever smokers, adjusted for pack-years and years since quit. KABAT 1991 also adjusted for education, inhalation and body mass index. The other two studies did not present results adjusted for other variables, but noted that additional adjustments had been tried, but made little difference. SIDNEY 1995 considered inhalation, tar level and amount of

cigarette smoked, while CARPENTER 1995 considered fruit and vegetable consumption, occupational exposures, family history of lung cancer and ETS.

It should be noted that none of the papers present results in a way that allows the reader to determine the effect adjustments for individual variables had on the relative risk estimates. Also, none of the papers discuss the appropriateness or otherwise of adjusting for smoking characteristics, such as amount smoked or inhalation which may be affected by the choice of brand smoked. There are two conflicting issues here. One is that one does want to guard against any potential bias arising if the sort of person who chooses mentholated cigarettes is a more (or less) "addicted" smoker than the sort of person who chooses non-mentholated cigarettes. The other is that if, say, switching to mentholated cigarettes results in an increase in daily consumption with no change in risk per cigarette, adjusting for amount smoked will lead to the impression that mentholation is risk free when it is not. Ideally, the comparison should be between switchers to mentholated cigarettes and non-switchers, adjusted for smoking characteristics before the switch, but such analyses have not been attempted.

4.6 Meta-analysis of results relating risk of lung cancer to use of mentholated cigarettes

Tables 4.6.1 and 4.6.2 summarize the results of meta-analyses relating the risk of lung cancer to use of mentholated cigarettes. Table 4.6.1 is based on data comparing ever vs. never use whereas Table 4.6.2 is based on long-term use vs. never use. All relative risks are adjusted for age, race, gender (where appropriate), various aspects of the smoking habit and, in some studies, additional variables. As is made clear in the tables, the exact comparisons, populations (current or ever smokers) and the adjustment factors vary somewhat between the studies.

TABLE 4.6.1 Risk of lung cancer by use of mentholated cigarettes – meta-analysis of results from three studies

Study	Comparison	Relative risk (95% CI) Men	Women	Combined
KABAT 1991	Ever/never used mentholated cigarettes (within current smokers)[a]	1.06 (0.82-1.37)	0.78 (0.57-1.08)	0.94 (0.77-1.15)
SIDNEY 1995	Used/did not use mentholated cigarettes (within current smokers for 20+ years)[b]	1.45 (1.03-2.02)	0.75 (0.51-1.11)	1.09 (0.85-1.41)
CARPENTER 1999	Ever/never used mentholated cigarettes (within ever smokers)[c]	1.00 (0.68-1.48)	0.88 (0.50-1.57)	1.00 (0.72-1.40)
Combined	Fixed-effects	1.15 (0.96-1.37) NS[d]	0.78 (0.63-0.98) $p<0.05$	1.00 (0.86-1.15) NS
	Random-effects	1.15 (0.93-1.43) NS	0.78 (0.63-0.98) $p<0.05$	1.00 (0.86-1.15) NS
	Heterogeneity χ^2 (2df)	2.70 NS	0.21 NS	0.81 NS

[a] Adjusted for age, race, education, cigarettes per day, inhalation, duration of smoking and body mass index. Sexes combined analysis adjusted also for gender.
[b] Adjusted for age, race, education, cigarettes per day and years of smoking. Sexes combined analysis adjusted also for gender.
[c] Adjusted for age, race, total pack-years and years since quitting. Sexes combined analysis adjusted also for gender.
[d] NS not significant ($p \geq 0.05$).

TABLE 4.6.2 Risk of lung cancer by long-term use of mentholated cigarettes – meta-analysis of results from three studies

Study	Comparison	Relative risk (95% CI) Men	Women	Combined
KABAT 1991	15+ vs. 0 yrs use of mentholated cigarettes (within current smokers)[a]	0.98 (0.70-1.38)	0.76 (0.53-1.16)	0.88 (0.68-1.14)
SIDNEY 1995	20+ vs. 0 yrs use of mentholated cigarettes (within current smokers for 20+ years)[b]	1.59 (0.96-2.63)	0.70 (0.40-1.23)	1.10 (0.76-1.61)
CARPENTER 1999	32+ vs. 0 pack-years of mentholated cigarettes (within ever smokers)[c]	1.48 (0.71-3.05)	0.41 (0.15-1.11)	0.95 (0.53-1.70)
Combined	Fixed-effects	1.18 (0.91-1.53) NS[d]	0.70 (0.52-0.95) $p<0.05$	0.95 (0.78-1.16) NS
	Random-effects	1.23 (0.88-1.72) NS	0.70 (0.52-0.95) $p<0.05$	0.95 (0.78-1.16) NS
	Heterogeneity χ^2 (2df)	2.87 NS	1.27 NS	0.92 NS

[a] Adjusted for age, race, education, cigarettes per day, inhalation, duration of smoking and body mass index. Sexes combined analysis adjusted also for gender.
[b] Adjusted for age, race, education, cigarettes per day and years of smoking. Sexes combined analysis adjusted also for gender.
[c] Adjusted for age, race, total pack-years and years since quitting. Sexes combined analysis adjusted also for gender.
[d] NS not significant ($p \geq 0.05$).

For men, there is slight but not significant heterogeneity between the study estimates, with SIDNEY 1995 giving the highest relative risk estimates. Random-effects meta-analysis shows a slight, but again non-significant, increase in risk associated with both ever use (RR 1.15; CI 0.93-1.43) or long-term use (RR 1.23; CI 0.88-1.72) of mentholated cigarettes.

For women, there is no evidence of heterogeneity between the study estimates, and all the estimates are below 1.00. Random-effects meta-analysis (which gives the same answer as fixed-effects meta-analysis as there is no heterogeneity) shows a significant ($p<0.05$) decrease in risk associated with both ever use (RR 0.78; CI 0.63-0.98) and long-term use (RR 0.70; CI 0.52-0.95) of mentholated cigarettes.

For the sexes combined, there was again no evidence of heterogeneity, with all study estimates quite close to 1. Random-effects (or fixed-effects) meta-analysis shows no association with ever use (RR 1.00; CI 0.86-1.15) or long-term use (RR 0.95; CI 0.78-1.16) of mentholated cigarettes.

Relative risks by histological type of lung cancer are only available for KABAT 1991. No association with use of mentholated cigarettes was seen for any of the four types considered (see Table 4.2.1).

4.7 Discussion

Although one of the three studies (SIDNEY 1995) has reported an increased risk of lung cancer in men associated with the smoking of mentholated cigarettes, this increase was only of marginal statistical significance and was not seen in women. However, the combined data show a non-significant increase in men and a marginally significant decrease in women associated with both ever use or long-term use of mentholated cigarettes. *A priori*, it seems implausible that mentholation should have differential effects in men and women and it is possible

that the result is a chance finding. Alternatively, it may be due to failure to control adequately for confounding or to biases present in the studies.

Although the three studies have some limitations, as noted earlier, they are relatively large and generally of a quality that is well above average for published epidemiological studies. Any concerns that exist are mainly with the reliability of the data collected on mentholation and with proper control of aspects of smoking (daily consumption and inhalation) that may both differ between people who choose to smoke mentholated cigarettes or non-mentholated cigarettes and be affected as a consequence of switching to mentholated cigarettes.

There is clearly a possibility that future studies, carried out when mentholated cigarettes have been smoked for longer durations, may show different results, but the evidence to date does not suggest that mentholation increases the risk of lung cancer to cigarette smokers. If there is an increase, it is likely to be quite modest and could not explain the higher risks in Blacks rather than White males in the US. For example, if (see national data in Table 3.3.1), 75.5% of Black cigarette smokers use mentholated cigarettes whereas only 23.1% of White cigarette smokers do, a relative risk of 1.15 for menthol use (meta-analysis data for males) would only imply that Black smokers would have a 7.6% higher lung cancer risk than Whites, much less than the 40% or 50% excess seen in males in recent years (see Tables 3.3.2 and 3.3.3). To explain fully the 50% higher risk in Black males, taking into account their lower cigarette consumption and later average age of starting, would require a relative risk for menthol of well over 2.

5. Epidemiological evidence relating other diseases to mentholated cigarettes

5.1 Introduction

There is relatively little epidemiological evidence relating to diseases other than lung cancer. Section 5.2 describes results relating to oesophageal cancer and oropharyngeal cancer from the same series of multicentre case-control studies conducted by the American Health Foundation for which results for lung cancer were described in section 4.2. Section 5.3 describes further results from the Kaiser Permanente Prospective Study already considered in section 4.3. Apart from for lung cancer, results are also available for various other forms of cancer. Finally, in section 5.4 results are summarized from a prospective study of pregnant women conducted in North Carolina. The data do not allow useful meta-analysis, the overall findings being discussed in section 5.5.

5.2 American Health Foundation multicentre case-control study – HEBERT 1989 and KABAT 1994

The multicentre hospital case-control study used to report results relating use of mentholated cigarettes to risk of lung cancer[58] (see section 4.2) has also been used to report results relating mentholated cigarette use to risk of oesophageal cancer and of oropharyngeal cancer. The analyses on oesophageal cancer, reported by Hebert and Kabat in 1989[23], were based on 209 male and 94 female cases and 301 male and 152 female controls. The analyses on oropharyngeal cancer, reported by Kabat and Hebert in 1994[66], were based on 194 male and 82 female cases and 845 male and 411 female controls. As for lung cancer, analyses were restricted to current smokers with interviews conducted in hospital, and controls were hospital patients with diseases unrelated to smoking. The details of the hospitals involved, matching variables, list of control diseases and period of enrolment of subjects in the study of oropharyngeal cancer[66] was identical to that in the study of lung cancer[58]. The study of oesophageal cancer[23], however, involved more hospitals (20 in 9 cities rather than 8 in 4 cities), matching criteria which only involved age and gender (and not race), control diseases which again were thought to be not related to tobacco products (but were

not specifically given) and covered a longer period (1969-1984 rather than 1985-1990).

The period of interview is relevant inasmuch as the paper on oropharyngeal cancer[66] notes that

"although larger numbers of subjects could have been collected before 1985, classification as to use of mentholated cigarettes was most detailed for the 1985-1990 period."

while the paper on oesophageal cancer[23] notes that

"Because the original study focused on the tar yield of cigarettes, no effort was made to identify all brands of menthol cigarettes. For about half (51%) of the brands no ambiguity exists, e.g. menthol or not-menthol. For the remaining brands, however, both menthol and non-menthol sub-brands exist. We have conducted two separate analyses: 1) including ambiguous brands, whose sales are largely from non-menthol sub-brands, in the non-menthol category and 2) excluding ambiguous brands entirely."

The main results for oesophageal cancer are shown in Table 5.2.1. Compared to never users of mentholated cigarettes, risk of oesophageal cancer in users tended to be somewhat lower in males and somewhat higher in females. After adjustment for race, education, religion, cigarettes per day, non-menthol smoking duration and alcohol consumption, the relative risks for 1-9 years use of mentholated cigarettes were 0.50 (0.23-1.07) in males and 1.50 (0.54-4.17) in females, while the relative risks for 10+ years use were 1.03 (0.39-6.89) in males and 2.30 (0.93-5.72) in females, none of these relative risks being statistically significant. In additional analyses, with adjustment for the same variables, risk per year menthol smoking duration was estimated to be 1.00 (0.95-1.05) in males and 1.05 (0.75-4.17) in females.

TABLE 5.2.1 Risk of oesophageal cancer by mentholated cigarette use among current smokers – American Health Foundation multicentre case-control study - HEBERT 1989

			Years of use of mentholated cigarettes				
	No. of	Adjustment	Never	1-9	10+	15+	Ever
Gender	cases	factors	RR	RR (CI)	RR (CI)	RR (CI)	RR (CI)
Male	216	No	1.00		0.80 (0.36-1.78)	1.18 (0.42-3.31)	0.71 (0.41-12.2)
		Yes[a]	1.00	0.50 (0.23-1.01)	1.03 (0.39-6.89)		
Female	96	No	1.00		2.03 (0.91-4.56)	2.83 (0.77-10.4)	2.05 (1.09-3.87)
		Yes[a]	1.00	1.50 (0.54-4.17)	2.30 (0.93-5.72)		

[a] Adjustment factors are race, education, religion, cigarettes per day, non-menthol smoking duration and alcohol consumption

The authors conclude that

"our results do not support the hypothesized relationship between menthol cigarette smoking and oesophageal cancer."

However, they regarded the issue of menthol cigarette smoking and oesophageal cancer as "not resolved" and recommended additional studies. This was partly because of limitations they perceived in their study. They noted that, because the study was conducted in teaching hospitals, the Blacks were likely to be unrepresentative, as evidenced indirectly by their unusually low reported menthol usage. They also noted that data on some potential confounders, in particular nutrition, were lacking and that the number of women in the study was quite small.

One should also draw attention to various unsatisfactory features of their analyses. These include:

(a) Failure to adjust for age in analysis. Although the cases and controls were age-matched, this matching would have been weakened by the restriction of the analysis to current cigarette smokers;

(b) Use of an unusual form of "two-stage" regression analysis, which may not give correct results;

(c) Adjustment for non-menthol smoking duration when it would seem more appropriate to adjust for overall smoking duration;

(d) Failing to make it clear how "ambiguous brands" had been dealt with in the analyses presented. As noted above, they stated at the start that they carried out analyses in two separate ways to deal with brands where ambiguity existed about whether they were mentholated or not, and later they stated that "inclusion or exclusion of ambiguous brands did not materially affect our results". However, only one set of results are presented and one does not know which it is; and

(e) Presenting unadjusted and adjusted analyses in a noncomparable format, in which, for the former, results were presented for the overlapping categories 10+ and 15+ years use of mentholated cigarettes, as well as for ever use, while, for the latter, results were presented for the non-overlapping categories 1-9 and 10+ years use with no results presented (or calculable) for ever use. It should be noted that the facts that the unadjusted relative risk associated with ever smoking mentholated cigarettes in females was statistically significant, and that the adjusted relative risk for 10+ years of mentholated use was greater than the unadjusted relative risk, seems to imply that an adjusted estimate for ever use would have been greater than the unadjusted estimate, and also statistically significant. However, the data are not presented in a way that allows such an adjusted estimate to be derived, and as their overall adjusted estimate for the increase in risk per year of mentholated cigarette smoking was not significant, this inference may not be reliable. [I note that this relative risk, 1.05, had confidence intervals presented of 0.75-4.17, which are wildly asymmetric on a logarithmic scale, and perhaps are a typographical error for 0.75-1.47, which are symmetric.]

In any event, the data regarding oesophageal cancer provide no evidence of any effect of mentholation in men and some rather dubious evidence of a possible increase in women.

The main results for oropharyngeal cancer are shown in Table 5.2.2. When all types of oropharyngeal cancer were considered together, ever users of mentholated cigarettes tended, in both sexes, to have a lower risk than did never users. After adjustment for age, race, education, filter use, cigarettes per day, body mass index, hospital and alcohol consumption, the relative risk was estimated as 0.74 (0.47-1.18) in males and as 0.85 (0.54-1.32) in females. Unadjusted estimates or estimates adjusted only for age showed somewhat lower relative risk estimates, as did estimates (not shown in Table 5.2.2) adjusted only for education, for cigs/day or for alcohol consumption. There was no evidence that risk was increased in long-term mentholated cigarette users. When results were separated by type of oropharyngeal cancer, no significant increases were seen, though relative risks for ever vs. never use were above 1.0 for pharynx cancer (males 1.7, 0.8-3.4; females 1.2, 0.4-3.7).

TABLE 5.2.2 Risk of oropharyngeal cancer by mentholated cigarette use among current smokers – American Health Foundation multicentre case-control study – KABAT 1994

Type of oropharyngeal cancer	Gender	No. of cases	Adjusted	Years of use of mentholated cigarettes			
				Never	1-14	15+	Ever
				RR (CI)	RR (CI)	RR (CI)	RR (CI)
Any	Male	194	No	1.0	0.57 (0.33-1.00)	0.77 (0.48-1.25)	0.68 (0.46-0.99)
			Age	1.0	0.6 (0.35-1.04)	0.8 (0.49-1.29)	0.70 (0.48-1.03)
			Age, others[a]	1.0	0.6 (0.3-1.1)	0.9 (0.5-1.6)	0.74 (0.47-1.18)
	Female	82	No	1.0	0.81 (0.42-1.57)	0.62 (0.30-1.27)	0.72 (0.42-1.21)
			Age	1.0	0.9 (0.47-1.73)	0.6 (0.29-1.23)	0.74 (0.44-1.25)
			Age, others[a]	1.0	1.0 (0.7-2.1)	0.7 (0.5-1.7)	0.85 (0.54-1.32)
Tongue	Male	44	Age, others[a]	1.0	-	-	0.4 (0.1-1.0)
	Female	27	Age, others[a]	1.0	-	-	1.3 (0.5-3.2)
Gum, floor of mouth, other	Male	83	Age, others[a]	1.0	-	-	0.6 (0.3-1.2)
	Female	34	Age, others[a]	1.0	-	-	0.5 (0.2-1.3)
Pharynx	Male	52	Age, others[a]	1.0	-	-	1.7 (0.8-3.4)
	Female	17	Age, others[a]	1.0	-	-	1.2 (0.4-3.7)

[a] Other adjustment variables are race, education, filter use, cigarettes per day, body mass index, hospital and alcohol consumption

Note: Data to one decimal place as given; data to two decimal places estimated from data provided

The authors note that

"the results of this analysis do not support the hypothesis that use of mentholated cigarettes is associated with oropharyngeal cancer overall, relative to smoking nonmentholated cigarettes."

They also pointed out several limitations in their study. These included the small number of exclusive users of mentholated cigarettes in their population, the small number of cases by subsite and the small number of Blacks in the study. A further limitation was that the analyses were not adjusted for duration of smoking, which might have differed systematically between the categories compared (with 0, 1-14 or 15+ years use of mentholated cigarettes). An analysis was presented in which risk was simultaneously related to years menthol, years non-menthol, cigs/day menthol and cigs/day non-menthol but this did not allow proper comparison of menthol and non-menthol use with adjustment for duration and daily consumption.

While the two papers provide little reason to believe that mentholated cigarette use affects risk of oesophageal or oropharyngeal cancer, the various weaknesses cited, particularly in the earlier paper based on less reliable data on mentholated cigarette use, do not allow great confidence in the conclusions reached.

5.3 Kaiser Permanente prospective study – FRIEDMAN 1998

The prospective study used to report results relating use of mentholated cigarettes to risk of lung cancer[61] (see section 4.3) has also been used to report results relating use to risk of other forms of cancer[67]. As before, analyses were restricted to men and women aged 30 to 89 years who, at multiphasic check-up between 1979 and 1985, reported that they were current cigarette smokers who had smoked for at least 20 years and who provided details of the mentholation status of the brand of cigarettes they usually smoked. The numbers of subjects,

5770 men and 5990 women, were also virtually as before. Here, however, follow-up for cancer incidence was until 1994, rather than 1991 as used for the lung cancer analyses.

Table 5.3.1 presents results comparing risk of various types of cancer in those smoking mentholated cigarettes at baseline with those smoking non-mentholated cigarettes. For all smoking-related cancers combined, mentholated cigarettes smokers had non-significantly lower risks, both in men (0.76; 0.52-1.11) and women (0.79; 0.53-1.18). No real indication of an effect was seen in either sex for any of the specific cancer types studied – upper aerodigestive, pancreas, renal adenocarcinoma, other urinary tract, uterine cervix or prostate. The authors noted that

"results were similar when current smokers of mentholated and plain [i.e. non-mentholated] were restricted, respectively, to persons who reported smoking mentholated cigarettes for at least 10 years and for less than six months."

TABLE 5.3.1 Risk of smoking-related cancers (other than the lung) by mentholated cigarette use among current smokers for 20 years or more – Kaiser Permanente prospective study – FRIEDMAN 1998

Site	Gender	Number of cases	Age adjusted RR (95% CI) for mentholated vs. non-mentholated use
Upper aerodigestive	Male	60	0.68 (0.36-1.28)
	Female	27	0.69 (0.30-1.67)
Pancreas	Male	34	0.60 (0.25-1.44)
	Female	26	0.76 (0.32-1.81)
Renal adenocarcinoma	Male	13	1.28 (0.39-4.15)
	Female	4	0.73 (0.08-7.00)
Other urinary tract	Male	57	0.83 (0.45-1.55)
	Female	28	0.71 (0.30-1.68)
Prostate	Male	Not given	1.15 (0.82-1.62)[a]
Uterine cervix	Female	34	1.06 (0.53-2.12)
All smoking-related (except lung)	Male	163	0.76 (0.52-1.11)
	Female	118	0.79 (0.53-1.18)

[a] Adjusted for age and race 1.12 (0.80-1.58)

The study is to some extent limited by the small number of cancers of specific types, particularly in mentholated cigarette users, and for reasons already discussed for lung cancer. Nevertheless, the data provide little support for an effect of mentholation on cancer risk.

5.4 North Carolina prospective study in pregnant women - SAVITZ 2001

Savitz *et al*[29] reported results of a prospective cohort study conducted in North Carolina in which 2418 pregnant women gave detailed information on smoking during pregnancy, including brand, number of cigarettes per day and changes during pregnancy. Analysis related the risk of preterm birth (<37 and <34 weeks gestation) and small-for-gestational-age (SGA) deliveries to tobacco use. Among the 472 Whites who smoked during pregnancy, 124 reported mentholated cigarette use (26%) while among the 207 African-Americans who smoked during pregnancy, 196 (95%) reported mentholated cigarette use.

Smoking was not related to preterm birth overall, regardless of race, mentholated/non-mentholated cigarette use or definition of preterm. However, a clear association and dose-response gradient was present for SGA. As is evident from the results, summarized in Table 5.4.1 below, the association was most clearly seen in White non-mentholated smokers and there was no indication that mentholated smokers had higher risks than non-mentholated smokers. Indeed, the results suggested that, if anything, the reverse was true, though comparison of mentholated and non-mentholated smokers is limited by the relatively small number of mentholated cigarette smokers in Whites and the very few non-mentholated cigarette smokers among African-Americans. In the discussion section of the paper, the authors[29] do not comment on the mentholated/non-mentholated difference, but do note that the great majority of studies on fetal growth provide "rather consistent evidence that African-American smokers experience less of an increased risk from smoking than Whites."

TABLE 5.4.1 Relationship of small-for-gestational-age births to type of cigarette smoked during pregnancy - SAVITZ 2001

			Relative risk (95% confidence interval)			
Subjects	Cigarettes	N*	Never smoked	1-9 cigs/day	10-19 cigs/day	20+ cigs/day
All	Any	75	1.0	1.4 (1.0-2.0)	1.8 (1.2-2.8)	2.4 (1.4-4.0)
	Menthol	30	1.0	1.1 (0.7-1.9)	1.8 (1.0-3.3)	1.6 (0.6-4.8)
Whites	Any	54	1.0	1.9 (1.2-3.0)	2.0 (1.2-3.3)	2.9 (1.6-5.2)
	Menthol	10	1.0	1.2 (0.4-3.2)	1.6 (0.6-4.1)	1.9 (0.5-7.2)
	Non-menthol	44	1.0	2.2 (1.3-3.6)	2.1 (1.2-3.7)	2.9. (1.4-5.8)
African-Americans	Any	21	1.0	1.0 (0.6-1.8)	2.3 (1.1-4.6)	Only 1 SGA
	Menthol	20	1.0	1.0 (0.6-1.8)	2.1 (1.0-4.5)	Only 1 SGA

*Number of SGA among cigarette smokers

The study, which is limited by the relatively small number of SGA cases and the failure to consider potential confounding variables, provides no indication of any specific adverse effect of mentholation of cigarettes on fetal growth.

5.5 Discussion

The evidence considered in this section is quite limited, consisting of data on oesophageal and on oropharyngeal cancer from a case-control study, data on various cancer types from a prospective study and data on preterm birth and SGA from a study in pregnant mothers. It is notable that there are no data whatsoever relating mentholated cigarettes to risk of such common smoking-related diseases as ischaemic heart disease, stroke or COPD.

For the diseases which are considered, the results provide little or no indication of an adverse effect of mentholation. The data from the SAVITZ 2001 study in pregnant women provide no suggestion of an increase in risk of preterm birth or SGA, the data from the FRIEDMAN 1998 prospective study give no support for any increase in risk of the various cancers studied and the data on oropharyngeal cancer from the KABAT 1994 case-control study also does not suggest risk of oropharyngeal cancer is increased in mentholated vs. non-mentholated smokers. In none of these studies were any significant effects seen and generally risk estimates seemed to be lower for mentholated than for non-mentholated cigarettes. The HEBERT 1989 case-control study also showed no

association of oesophageal cancer with use of mentholated cigarettes in males, but did indicate a possible increase in females. In view of the weaknesses of the study and the, at best, marginal statistical significance of the findings (which are poorly analysed and presented), the association in females does not provide at all convincing evidence of an effect. It should be noted that the authors did not regard their findings as supporting a relationship between use of mentholated cigarettes and risk of oesophageal cancer.

6. Summary of conclusions

Menthol itself has been widely used for many years and experimental studies provide no reason for concern that it is genotoxic or carcinogenic. It appears to be a substance of very low toxicity. However, there is evidence that it has acute effects on the mouth, nose and respiratory system that might possibly alter how smoke from cigarettes is inhaled.

The mentholated cigarette has assumed an important place in the US cigarette market over the last 50 years, and preference for mentholated cigarettes is very much greater in Blacks than Whites. Blacks have a higher risk of a number of smoking-related diseases, including lung cancer in men, despite smoking less heavily and tending to start smoking later in life. This has led some researchers to suggest that the excess risk in Blacks might be caused by menthol facilitating intake of tobacco smoke constituents. However, data from a number of studies provide no convincing evidence that mentholation increases puffing, inhalation or tobacco smoke uptake. Experimental data comparing mentholated and non-mentholated cigarettes shows comparable genotoxic effects and similar responses in the nose and respiratory tract following inhalation for 13 weeks.

Three relatively large and good quality epidemiological studies have compared the risk of lung cancer in smokers of mentholated and non-mentholated cigarettes. In all three studies, risk in women was somewhat lower in mentholated cigarette smokers, and meta-analysis of the combined data showed that the reduction was statistically significant (RR 0.78, CI 0.63-0.98 for ever vs. never use; RR 0.70, CI 0.52-0.95 for long-term use vs. never use). One of the three studies reported a significant increased risk in men associated with use of mentholated cigarettes, but the other two studies did not. Overall, combined estimates from the three studies showed an increase that was not statistically significant (RR 1.15, CI 0.93-1.43 for ever vs. never use; RR 1.23, CI 0.88-1.72 for long-term vs. never use). The overall evidence does not suggest that mentholation increases the risk of lung cancer to cigarette smokers, although

future studies are needed to test for possible effects of very long-term use. The evidence would seem to rule out the possibility that the increased risk of lung cancer in Black vs. White males could be explained by their much greater use of mentholated cigarettes.

Two of the same three studies that have reported results for lung cancer have also reported results for other cancers. One study found no relationship with mentholated cigarette use for a variety of cancer groupings. The other found no relationship for oropharyngeal cancer in either sex, no relationship for oesophageal cancer in males, but some increase in risk in females in an analysis that was open to objections for a number of reasons and did not fully clarify statistical significance. A study of pregnant women found no association of mentholated or non-mentholated cigarette smoking with preterm birth and associations with small-for-gestational-age birth that were somewhat stronger for non-mentholated than for mentholated cigarette smoking.

There are some weaknesses in the studies presenting data, discussed in detail in the report, and there is a notable absence of data relating use of mentholated cigarettes to common smoking-related diseases such as ischaemic heart disease, stroke or COPD. However, taken as a whole, the evidence is consistent with the addition of menthol to the tobacco having no effect on the toxicity or carcinogenicity of cigarettes.

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Note: In preparing this document, statements made have generally been based directly on the references cited. Exceptionally, in the case of some references,[2-4,8,10,15-17,20,38] reliance has been placed on the correctness of citations made in other documents.