

**NICOTINE AND TAR IN CIGARETTE  
TOBACCO: A LITERATURE REVIEW  
TO INFORM POLICY DEVELOPMENT**

**A report for the  
Ministry of Health**

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Prepared as a Ministry of Health  
contract for scientific services

by

Tony Blakely  
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January 1998

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## Glossary

Nicotine	The addictive substance in tobacco
Carbon Monoxide (CO)	A highly toxic gas found in tobacco smoke
Tar	A composite term for the particulate matter in tobacco smoke. Tar includes the majority of mutagenic and carcinogenic agents in tobacco smoke (IARC, 1986).
Nicotine yield	The nicotine measured in the smoke of a single cigarette using the Federal Trade Commission (FTC) smoking test.
Nicotine concentration	The concentration of nicotine found in the tobacco itself (ie, not in the smoke).
Nicotine content	The weight of nicotine in the tobacco itself (ie, not in the smoke) for any single cigarette.
Compensation, or compensatory smoking	Changes in smoking behaviours by smokers in an attempt to maintain a relatively constant intake of tobacco smoke constituents (mainly nicotine) as levels of constituents in the cigarette smoke change.
Level	In this report is used as a generic term for some measurement on nicotine (or other tobacco constituent), but not specified as the yield (as determined by the FTC smoking test), concentration or content.
Tar yield	The amount of tar measured by the FTC smoking test in the smoke of a single cigarette.
CO yield	The amount of CO measured by the FTC smoking test in the smoke of a single cigarette.
Tobacco-specific N-nitrosamines (TSNAs)	Carcinogenic substances in tobacco smoke that appear to have increased in the last couple of decades, and are not included in tar.
Federal Trade Commission (FTC) smoking test	The standard smoking test for determining cigarette yields.
Harm minimisation	Policy that aims to minimise the harm to health from tobacco, not by stopping people smoking, but by reducing both the number of cigarettes smoked and the harmful constituents in cigarettes.
Nicotine delivery device (NDD)	Any device that delivers nicotine to the bloodstream. NDDs include: cigarettes, patches, inhalers, aerosol inhalers, gum, and highly modified cigarettes that heat rather than burn tobacco. Alternative nicotine delivery devices (ANDD) exclude cigarettes.

## **EXECUTIVE SUMMARY**

### **Aims**

The aims of this report are to:

- ?? review the international scientific literature on the behavioural and health effects associated with varying the levels of nicotine and tar in tobacco
- ?? determine possible options for controlling nicotine and tar levels in tobacco, including advantages and disadvantages of each of these options.

### **Methods**

A literature review was conducted using Medline, and references obtained. Further references were then obtained on the basis of the primary references, and reports obtained from communication with experts in the field.

### **Results and conclusions**

Nicotine is the main addictive substance in tobacco. Tar includes many of the harmful constituents in tobacco, but not all of them. For example, tobacco-specific N-nitrosamines are highly carcinogenic and have been increasing in levels in recent decades, despite reductions in tar.

Epidemiological evidence suggests that low-yield cigarettes result in a lower incidence of lung cancer, probably a lower incidence of pulmonary disease, and possibly a lower incidence of cardiovascular disease. It is uncertain whether these results, which relate to cigarette yields from the 1950s to 1970s, can be extrapolated to current cigarette yields, although it seems plausible. However, the potential reduction in disease from low-yield cigarettes, compared to high-yield cigarettes, is, at best, small, especially in comparison to quitting smoking altogether.

Observational and experimental studies show that smokers learn to compensate for varying cigarette yields (e.g. by varying the frequency and volume of puffs, and by blocking ventilation holes in filters), mostly as a result of the need to maintain nicotine intake, although other factors may also come into play. For the range of cigarettes currently on the market in New Zealand (nicotine yields of 0.6 to 1.5 mg), it is likely that a smoker of a cigarette of less than 1.0 mg yield is taking in only marginally less nicotine than a smoker of a cigarette with a yield of greater than 1.0 mg. Because of the high correlation of nicotine and tar yields, the intake of tar is also likely to vary little across the range of commercially available cigarettes in New Zealand. Compensation becomes difficult with cigarettes below a nicotine yield of 0.6 mg, although the exact threshold (at which complete compensation is no longer possible) is uncertain.

The Federal Trade Commission (FTC) smoking test is inadequate to predict intakes of tar and nicotine for commonly available cigarettes. Work is underway to revise the FTC smoking test in the United States. For nicotine, the use of nicotine content and concentration is an alternative measurement method. However more research is required to determine whether nicotine content and/or concentration in cigarettes are superior predictors of nicotine intake. The yields currently printed on cigarette packets are misleading to smokers: a cigarette with a stated nicotine yield of 0.6 mg does not result in half the nicotine intake of a cigarette with a stated nicotine yield of 1.2 mg. A more useful labelling system would be categories, like 'very low' or 'low', based on ranges of yields (or some other test) that actually represented categories of cigarettes with discernible differences in intake.

There are four main policy options for controlling the levels of nicotine and tar in cigarettes:

?? do nothing

?? dramatically reduce nicotine levels to below the addictive threshold

?? moderately reduce the levels of both nicotine and tar

?? reduce tar levels, but maintain nicotine levels.

Each option has advantages and disadvantages, and the available research evidence is insufficient for the best policy option to be confidently stated. The basic policy options are currently the subject of intense debate in tobacco control forums, with no expert consensus yet apparent. The opinion of the authors is that a prudent path forward for New Zealand would be to gradually reduce nicotine and tar levels, so long as tar levels were decreased proportionately as much as, or more than, nicotine levels. That still leaves the option open for more dramatic reductions in nicotine levels, or further reductions in tar relative to nicotine levels, in the future should new research, or emerging expert opinion, point to this being a favourable policy option. Methods for implementing the policy options include regulation, voluntary agreements with the tobacco industry, or differential taxation. A ceiling for tar and nicotine levels seems the most likely mechanism.

Two further issues require simultaneous consideration when deciding among the four policy options. First, it needs to be considered whether current tobacco smokers should be encouraged to switch to alternative nicotine delivery devices with, putatively, less harmful effects on health. This would arise either purely out of health concerns, whereby the use of alternative nicotine delivery devices was deemed to be safer than cigarette use, or, if the above policy option to dramatically reduce nicotine levels in cigarettes was pursued, from pressure generated by smokers seeking alternative ways to maintain their nicotine intake. Currently, tobacco cigarettes are more readily available and cheaper than possibly safer alternative nicotine delivery devices. The second issue to consider simultaneously with the above four policy options is harmful tobacco smoke constituents not in the tar, the most prominent example being tobacco-specific N-nitrosamines. It seems unwise to purely focus on reducing tar in cigarettes if there is an associated increase in other harmful tobacco constituents, leading to no net health gain. The relationship between changes in tar and other harmful constituents of tobacco smoke requires further study.

## RECOMMENDATIONS

It is recommended that the Ministry of Health:

- ?? accept tobacco control policy needs to be a three-way co-ordinated approach involving (1) tobacco use prevention, (2) smoking cessation assistance, and (3) reduction of exposure to tobacco toxins for people who are unable or unwilling to completely abstain from tobacco (harm minimisation), either by product modification or by reducing the number of cigarettes per day smoked
- ?? note that the relative reduction in harm to health from product modification that reduces tar and nicotine yields is at best modest compared to tobacco use prevention and smoking cessation for the individual smoker, but may be substantial at the population level if a small reduction in risk is effected for all smokers
- ?? consider the following four policy options for controlling nicotine and tar levels:
  - ?? do nothing
  - ?? dramatically reduce nicotine levels to below the addictive threshold
  - ?? moderately reduce the levels of both nicotine and tar
  - ?? reduce tar levels, but maintain nicotine levels
- ?? consider the complementary role of alternative nicotine delivery devices with the above four policy options
- ?? consider changing the labelling requirements for tar and nicotine on cigarette packets, from the use of absolute levels, to categories of nicotine and tar with meaningful differences in intake
- ?? commission an independent monitoring programme of harmful tobacco smoke constituents other than tar and nicotine
- ?? remain informed on new research, and emergent expert opinion, on:
  - ?? policy options for the control of tar and nicotine levels
  - ?? modifications to the FTC smoking test
  - ?? the performance of nicotine content and/or nicotine concentration as a predictor of nicotine intake, as compared to the performance of nicotine yields.

We were unable to make a definitive and scientifically-based recommendation on the best policy option for controlling tar and nicotine levels in tobacco. However, our opinion is that it would seem prudent to pursue a policy of moderate reductions in tar and nicotine levels, with tar levels proportionately reducing by at least as much as, and preferably more than, nicotine levels. We believe that, taking all the available information into account, net tobacco-related harm will probably be decreased by pursuing this policy option, and that, most importantly, it is unlikely to result in a net increase in such harm. This prudent approach would still leave open the possibility of more dramatic reductions in nicotine levels, or in tar in relation to nicotine, in the future.

## INTRODUCTION

The Smoke-free Environments Act 1990, and its amendments, allow for the regulation of tobacco and tobacco smoke constituents. The Act allows for regulations that:

- ?? set limits for harmful constituents
- ?? enable bans on particularly harmful substances
- ?? require a regular and independent testing programme, paid for by the manufacturers.

To date, regulations have not been formulated under the Act in these areas. Regulation is, however, not the only method that could be used to implement controls on tar and nicotine in cigarette tobacco. Alternative possibilities include voluntary agreements with tobacco industry, and taxation.

Nicotine and tar are two tobacco constituents that are possible candidates for controls. This report aims to:

- ?? review the international scientific literature on the behavioural and health effects associated with varying the levels of nicotine and tar in tobacco
- ?? determine possible options for controlling nicotine and tar intake from tobacco, including advantages and disadvantages of each of these options.

This literature review focuses on tar and nicotine, but, where relevant, also considers other tobacco constituents, particularly carbon monoxide (CO).

### **Harm minimisation and tobacco control policy**

Tobacco control policy that focuses on the constituents of cigarette tobacco, or its smoke, aims to minimise the harm caused by tobacco consumption. This distinction is important. Traditionally, tobacco control has emphasised absolutist policies (Chapman, 1996). That is, policies that aim to stop people smoking completely on the premise that there is no safe level of tobacco consumption. Tobacco control policy that aims to reduce the number of cigarettes people smoke, or reduce the toxicity of the tobacco, is called “harm minimisation” in that it is based on an acceptance that, at least for the foreseeable future, some people will continue to smoke tobacco, and it is best to reduce the risk for these people. This report focuses on harm minimisation by modification of tobacco constituents.

In public health terms, there is a fine balance between the advantages and disadvantages of controlling constituents of tobacco and its smoke. The main advantage is that because tobacco consumption is so hazardous, and a significant proportion of the population are likely to continue to smoke tobacco, a small reduction in the health risk associated with smoking tobacco could have substantial benefit for the New Zealand population as a whole. Each year in New Zealand 4,500 deaths (17 percent of all deaths) are attributable to tobacco (Peto and Lopez, 1994), and even a proportionately small reduction in this number would be a substantial health gain. The major potential disadvantage of harm minimisation is that such a policy may be incorrectly perceived as implying that some tobacco products are

'safe'. The danger would be that some people could be more inclined to change the tobacco product they use, rather than quit, or could even be more inclined to take up smoking.

The balance between the advantages and disadvantages of policy that controls tobacco constituents will be revisited in more detail during the development of options later in this report.

## **Tobacco product modification**

Controlling the levels of tar and nicotine in tobacco can be seen, in more general terms, as but one example of a series of product modifications to tobacco following World War II. These modifications were driven by emerging health concerns for tobacco (US Department of Health and Human Services, 1996). The first was the introduction of filters, widely promoted by the tobacco industry as reducing the health risk from cigarettes. The second was the reduction in nicotine and tar yields of cigarettes; this report examines the evidence for continuing this reduction. Some argue that prototype cigarettes, like the Premier and Eclipse that heat rather than burn tobacco, represent the third wave of product modifications (Warner et al, 1997). There are also many other product modifications, such as reconstituted tobacco and ventilation holes<sup>1</sup>, that have led to reduced nicotine and tar yields. Commentators have been dismissive of tobacco product modifications, arguing that they have served more to protect market share for tobacco companies than causing gains for public health (Warner et al, 1997). The suggested lack of net gain to the public health from product modification is largely premised (1) on the knowledge that smokers are able to modify their smoking behaviour to maintain intake of tobacco smoke constituents, particularly nicotine (compensation), and (2) the possibility that the availability of 'safer' tobacco products will lead to more people smoking in the population, outweighing the health gains from 'safer' cigarettes for individuals.

The focus of this report is on tar and nicotine levels. Some consideration is given to how controls for tar and nicotine levels could engage with the developing area of alternative nicotine delivery devices. The impact of varying tar and nicotine levels on the health risks from passive smoking is not considered in this report.

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<sup>1</sup> It is uncertain whether New Zealand-manufactured cigarettes have ventilation holes. If so, they may be fine laser generated holes as opposed to visible holes. Information on ventilation holes in New Zealand-manufactured cigarettes would be useful.

## **METHODS**

The literature review was based on a literature search using Medline. Key search words were “nicotine”, “tar”, “tobacco chemistry”, “morbidity”, “mortality”, and “regulation”. Numerous search strategies were employed for the years 1987 to 1997. Further literature was selected on the basis of references cited in articles obtained through the Medline search. Reports were also obtained from experts in the field.

The report is broken down into five parts:

- ?? a description of tobacco constituents and methodological issues
- ?? a literature review of the health effects/benefits of varying the levels of tar and nicotine
- ?? a literature review of the relationship between nicotine and tar (and CO) yields, with particular emphasis on compensatory smoking
- ?? a consideration of what important questions remained unanswered
- ?? and a discussion of options for controlling tar and nicotine in cigarette tobacco.

## **PART 1: TOBACCO CONSTITUENTS AND METHODOLOGICAL ISSUES**

There are over 4,000 known constituents in cigarette tobacco or its smoke (US Department of Health and Human Services, 1989). Many of them are carcinogenic or toxic. The toxicological and pharmacological characteristics of three of the most important - nicotine, tar, and CO - are covered below. Others have been dealt with in detail elsewhere (IARC, 1986).

### **Nicotine**

Nicotine, a tertiary amine, is the major addictive substance in cigarette tobacco (US Department of Health and Human Services, 1988). Nicotine is given off by burning tobacco and carried into the respiratory tract on tar droplets and in the vapour phase. As a weak base, nicotine may exist in an ionised or a non-ionised form. The relative proportions of these two forms, determined by the pH of the smoke, affect where nicotine is most readily absorbed into the body. At the acidic pH of most cigarette smoke, absorption occurs predominantly in the lungs, but with the alkaline smoke produced by cigars and pipe tobacco, nicotine, being predominantly non-ionised, is absorbed mainly in the mouth. Absorption into the blood stream is rapid, and concentrations of nicotine in the blood rise rapidly during smoking. Nicotine is metabolised, mainly in the liver, and the two major metabolites are cotinine and nicotine-N'-oxide.

Nicotine is a powerful psychoactive agent that has a variety of central and peripheral nervous system effects, as well as effects on the cardiovascular, endocrine, gastrointestinal, and skeletal motor systems. Self administration of tobacco leads to physical nicotine dependence and psychological dependence on smoking behaviour, with withdrawal symptoms associated with smoking cessation. The action of nicotine on the brain occurs rapidly after smoking, and this is believed to provide optimal reinforcement for nicotine dependence.

Until recently, the tobacco industry had denied that nicotine in tobacco was addictive. However, recent disclosed internal communications within the tobacco industry indicate that, as long ago as the 1960s, the tobacco industry knew that nicotine was addictive, and that the industry acknowledged internally they were in the business of initiating and maintaining addiction. Excerpts from internal tobacco industry documents, cited in Kessler (1994) include:

*“Smoking is a habit of addiction”* (1962)

*“There is no doubt that nicotine plays a large part in the action of smoking for many smokers. It may be useful, therefore, to look at the tobacco industry as if for a large part its business is the administration of nicotine (in the clinical sense).”*

*“We are, then, in the business of selling nicotine, an addictive drug...”* (1963)

The direct contribution of nicotine to tobacco-associated diseases is unclear, as it is inhaled along with many other substances in tobacco smoke. The role of nicotine is to maintain the addiction and other substances in tobacco smoke, particularly tar and some of the gaseous components, are the main direct causes of disease. However, if tobacco did not include nicotine few people would continue smoking - nicotine is a necessary causal component for most of the health-related harm from tobacco smoking. This assumption underlines much of the thinking in this report.

## **Tar**

Tar is a composite term for the particulate matter that can be condensed from tobacco smoke. Tar includes the majority of mutagenic and carcinogenic agents in tobacco smoke (IARC, 1986). Tar probably contributes to the taste and aroma of cigarette smoke and, as such, probably has some influence on smokers' behaviour.

With nicotine, tar is the substance which, historically, has been measured in tobacco smoke for a long time. It is widely assumed to be the most health-damaging component of tobacco smoke.

## **Carbon monoxide**

Carbon monoxide (CO) is generated from incomplete combustion of carbon-containing substances and, as such, the amount of CO generated in smoking a cigarette is influenced by cigarette design and the puffing characteristics of the smoker (US Department of Health and Human Services, 1989).

CO combines with the haemoglobin in the blood to form carboxyhaemoglobin. This reduces the oxygen-carrying capacity of the blood. The precise nature of CO's contribution to tobacco-related disease is uncertain, but it is likely to make some contribution.

## **Measurement issues**

There are issues around how tobacco constituents should be measured.

### **Yields and the FTC smoking test**

The internationally accepted standard method for measurement of nicotine and tar in tobacco smoke is the Federal Trade Commission (FTC) smoking test, developed in 1965 (US Department of Health and Human Services, 1989). Prior to that, a range of measurement methodologies had been in place, and cigarette advertisements had been making conflicting claims for tar and nicotine levels. The FTC test uses a machine that takes one 35-ml puff for two seconds every minute, until a butt length of 23 mm, or a butt length of filter overwrap plus 3mm, is reached. The total amounts of tar and nicotine measured in the smoke are known as the tar and nicotine *yields*. These are different to, and not necessarily proportional to, the tar and nicotine contents of the cigarettes themselves. In

New Zealand, the nicotine and tar yields, expressed in mg ranges, are required to be printed on cigarette packets.

The main disadvantage of the FTC smoking test is that smokers do not smoke like smoking machines, and by modifying their smoking behaviours, they may extract considerably more tar and nicotine from cigarettes than is suggested by the yields. This is discussed in more detail in a subsequent section. However, it is pertinent to note here that the Massachusetts Department of Public Health has developed a modified version of the FTC test that takes one 45-ml puff for two seconds every 30 seconds, with 50 percent of ventilation holes covered. Nicotine and tar yields with this method, that supposedly more accurately reflects average smoking behaviour, are considerably greater than those for the FTC test. Results are available on the internet at <http://www.cancer.org/>.

Another commonly measured tobacco smoke constituent is carbon monoxide. CO yield tends to co-vary with tar and nicotine yields, but not always (Borland, 1983). Carbon monoxide is discussed occasionally in this report.

### **Nicotine content and concentration**

Tar, being predominantly a collection of combustion products, must be measured in the tobacco smoke. However, nicotine is present in the unburnt tobacco and is volatilised in the combustion process. Nicotine may be measured in the tobacco itself, although this is much less common than measurement of yields. When measured in the tobacco, nicotine is reported as *concentration*, or *content* (i.e. the absolute amount present in a cigarette). The concentration is usually expressed as percentage by weight, and it is important to know whether it is by dry weight or wet weight. The content is reported as mg per cigarette. There is no official or international standard method for determining nicotine content or concentration, although the Massachusetts Department of Public Health uses a published protocol (Federal Register, 1997). Neither the nicotine content nor the concentration is required to be printed on cigarette packets in New Zealand, nor is any tobacco company doing so voluntarily.

While there is abundant research on the relationship of nicotine (and tar) yields to smoking behaviour, biomarkers, and health effects (see sections later in this report), there is no equivalent body of research for nicotine content or concentration. Research that fulfils this gap would be useful, particularly if it evaluated the relative merits of nicotine yields as a predictor of nicotine intake, compared to nicotine content and concentration as predictors of nicotine intake. While not specifically addressing this issue, one small study of 15 United States brands of cigarettes found a minimal correlation of nicotine content with nicotine yield ( $r=0.10$ ), and an *inverse* correlation of nicotine concentration with nicotine yield (Benowitz et al, 1983). On the contrary, data from 16 New Zealand-manufactured cigarettes sampled in 1996 found a positive correlation ( $r=0.62$ ,  $p=0.01$ ) between the nicotine content and nicotine yield as reported for that brand variant to the Ministry of Health (previously unpublished results).

### **What tobacco constituents should be measured?**

Traditionally, tar and nicotine have been the two major tobacco constituents measured in tobacco smoke. It is possible to measure the thousands of known tobacco constituents

individually, but the commonly known health-damaging substances tend to vary with tar (Hoffmann and Hoffmann, 1997). Some gaseous phase constituents, like CO, and nitrate derivatives like tobacco-specific N-nitrosamines (TSNAs), may be exceptions to this generalisation. Nicotine is measured as it is the major addictive substance in tobacco, and has at least the potential to cause some health damage.

## **Compensatory smoking**

There is plenty of evidence that smokers modify the way they smoke cigarettes dependent on the nicotine and tar yields of cigarettes (IARC, 1986; Diding, 1987; US Department of Health and Human Services, 1996; US Department of Health and Human Services, 1988). As the yields of cigarettes fall (or increase), the smoker will modify the way they smoke the cigarette, in order to maintain their intake of tobacco constituents. Most of this compensation is due to the smoker maintaining a relatively constant intake of nicotine, although tar and other attributes of the cigarette may also partly influence how the cigarette is smoked. A rule of thumb is that smokers of modern cigarettes, with FTC nicotine yields of about 0.6 to 1.5 mg, smoke each cigarette in a manner that extracts about 1 mg of nicotine (Benowitz and Jacob, 1984a). There is, however, wide variation among individual smokers around this value of 1 mg of nicotine, and a residual tendency for intake to increase marginally with increasing yield.

The methods that smokers use, usually subconsciously, to compensate for variable yields of cigarettes include:

?? occluding ventilation holes

?? varying puff frequency, duration, volume, and intensity

?? varying the length of the portion of the cigarette that is smoked

?? varying the number of cigarettes smoked.

This report takes compensatory smoking as a widely accepted and well documented phenomenon, and does not produce evidence to prove that it actually occurs. Instead, the questions of importance are “how much compensation occurs in different situations?”, and “what tobacco constituents of tobacco are responsible for compensation, and what are their relative importance?”. These questions are considered in detail in Part 4 of this report (page 31), and help shape policy options for the control of tobacco constituents.

## **Previous tobacco/ tobacco smoke measurements in New Zealand, including nicotine concentration and content**

Tar and nicotine yields of cigarette brands are routinely reported to the Ministry of Health by the tobacco industry. Returns for 1996 indicate that the sales-weighted average yield for tar was 13.63 mg, and for nicotine was 1.17 mg (personal communication, Murray Laugesen, 1997). This compares to sales-weighted average yields of 12 mg for tar and 0.95 mg for nicotine in the United States in 1992 (Hoffmann and Hoffmann, 1994), and an average of 0.65 mg nicotine for Australia’s top selling (not sales-weighted) 30 brands of cigarettes in 1996 (Smoke-free Coalition, 8 June 1997).

Limited information only is available for trends in the nicotine and tar yields of New Zealand-manufactured cigarettes. Tobacco Statistics (Ministry of Health and the Cancer Society of New Zealand, 1996) includes data for 1980, 1988, 1990 and yearly thereafter for some brands. The trends suggest that tar yields may be increasing, and nicotine yields are relatively stable.

Nicotine content and concentration has been determined by ESR for 1996 and 1997 samples of New Zealand cigarette brands (Blakely et al, 1997). Published results for the 1996 sample have subsequently been found to be overestimates and a correction factor of about two thirds (0.68) needs to be applied to obtain the correct results (Blakely and Symons, 1997). This shows the average nicotine concentration to be about 2.0 percent (dry weight). This compares to United States and Canadian-manufactured cigarettes with a nicotine concentration of between 1.3 and 1.6 percent (Rickert, 1995; Benowitz et al, 1983). An important additional finding in the New Zealand cigarette measurements was that the nicotine content for 'mild' and 'regular' cigarettes only varied by about 10 percent, whereas nicotine yields varied by 25 to 50 percent. The implication is that cigarette manufacturers are more reliant on the design features of the cigarette to achieve a 'low' yield, rather than changing the nicotine content of the cigarette.

Using data from 16 New Zealand-manufactured cigarettes sampled in 1996, a positive correlation ( $r=0.62$ ,  $p=0.01$ ) was found between the nicotine content and nicotine yield as reported for that brand variant to the Ministry of Health (previously unpublished results). The range of nicotine yields was reasonable (0.6-1.5 mg). However, the variation in nicotine content was much less than the variation in nicotine yield, meaning that nicotine yields are not just a function of nicotine content, but also the design features of the cigarette.

## **The changing cigarette**

Since World War II there have been considerable changes to manufactured cigarettes. Most notable has been a progressive reduction in the tar and nicotine yields. In the United States the sales-weighted average FTC nicotine and tar yields have fallen from 38 mg tar and 2.7 mg nicotine per cigarette in 1954, to 12 mg and 0.95 mg, respectively in 1992. A similar fall also occurred in the United Kingdom over the same time period (Hoffmann and Hoffmann, 1997). This reduction was achieved more by alterations in the design features of the cigarette than through changes in the tobacco itself. (Djordjevic et al, 1995; Hoffmann and Hoffmann, 1997). Design features to reduce yield include:

- ?? incorporation of reconstituted tobacco in the retailed blend
- ?? selection of tobacco blends
- ?? incorporation of ribs and stems of the tobacco plant
- ?? introduction of filters
- ?? use of highly porous cigarette paper
- ?? expanded tobacco
- ?? tip ventilation.

In parallel with the reductions in tar and nicotine yields, there have been reduced yields of carbon monoxide, cyanide, volatile aldehydes, phenols, and polynuclear aromatic hydrocarbons (PAHs) (Hoffmann and Hoffmann, 1997). This generalised trend has been cited as justification for focusing control of smoke constituents mostly on tar and nicotine (Waller and Froggatt, 1996). However, an exception to this general downward trend is an increase in the yield of nitrates, and nitrate derivative products. This has been brought about by the use of tobacco plant ribs and stems, lower in nicotine, but higher in nitrates, than leaf, in the manufactured cigarette (US Department of Health and Human Services, 1989). This higher nitrate concentration enhances the combustion of the tobacco. More complete combustion decreases the carcinogenic polynuclear aromatic hydrocarbons (PAH), yet the increased nitrogen oxides increase carcinogenic tobacco-specific N-nitrosamines (TSNAs) (Hoffmann and Hoffmann, 1997).

It is important to note that the above evidence on the changing cigarette is mainly from North America - there is no guarantee that the same changes have occurred in New Zealand. Further research would be required to describe precisely the changes in changes in New Zealand.

The intake of nicotine is not only a function of the amount of nicotine in the smoke. The pH of the smoke is critical, such that the higher the pH the more nicotine is in the unionised form and therefore more readily absorbed, particularly in the upper respiratory tract. The pH of the smoke of most blended cigarettes (as are those in New Zealand) does not exceed about 6.2 (IARC, 1986). It has recently been shown that ammonia has been added to manufactured cigarettes to increase the pH, thereby increasing the relative uptake of nicotine (Kessler, 1994). This is done by using reconstituted tobacco (tobacco that is processed into a homogenous product and used as part of the final blend for the manufactured cigarettes) as a vehicle for ammonia. Thus, while the absolute nicotine levels of nicotine, in either the tobacco itself or mainstream smoke, may be reduced, alterations to the chemistry of the cigarette can maintain the actual nicotine uptake of the smoker, even in the absence of compensatory smoking behaviour. This point is important. It means that even if the nicotine level (be it yield, content or concentration) is lowered in tobacco, mechanisms other than just compensation can maintain nicotine intake. Knowledge of potentiation of nicotine intake by ammonia has only recently become available outside the tobacco industry; and it may be that there are other chemical interactions that can be used to maintain or potentiate nicotine intake.

### **Public perception of low-yield cigarettes**

As far as we are aware, there has been no research in New Zealand on the public perception of low-yield cigarettes. This may partly be due to the relative lack of low-yield cigarettes on the New Zealand market compared to countries like the United States. However, in the United States, where tobacco companies have in the past attempted to market low-yield cigarettes as 'safer', and currently imply relative safety by stressing mildness or low-yields, there has been research into public perceptions (Warner and Slade, 1992; Cohen, 1996). A 1993 Gallup survey in the United States showed that 56 percent of

smokers believed that cigarette advertising using terms like ‘low-tar’, ‘low-nicotine’, and ‘lower yield’ were trying to communicate that the brand was safer, healthier, or less harmful (cited in Cohen, 1996). An ominous potential outcome of this is that smokers may choose to smoke a lower yield cigarette rather than quit, and this may be exploited by the tobacco companies. Cohen (1996) cites evidence from tobacco industry documents that addresses this:

*“We have evidence of virtually no quitting among smokers of those brands (ultra-low brands), and there are indications that the advent of ultra low-tar cigarettes has actually retained some potential quitters in the cigarette market by offering them a viable alternative.”*

Cohen (1996) surveyed 1005 United States adults, of whom 325 had smoked in the past two to three years. Seventy nine percent of the smokers did not know the tar yield of their usual cigarette, and, of those that claimed to know the tar yield of what they smoked, the correlation between their beliefs and the actual tar yield of their cigarettes was poor. Most smokers did not know whether tar yields of five or 15 mg were considered to be high, low or normal. Smokers of cigarettes with an actual tar yield of one to five mg (i.e., low-tar) were more likely to be aware of the yield.

## **PART 2: HEALTH EFFECTS OF VARYING THE LEVELS OF TAR AND NICOTINE IN CIGARETTE TOBACCO**

There has been some research into the changes in health risk associated with varying tar and nicotine levels in cigarettes. The outcomes are disease-specific mortality and morbidity. Most research has been observational (cross-sectional, cohort and case-control studies), but a few experimental studies have been undertaken. There are substantial, difficult-to-avoid biases and methodological issues associated with the epidemiological research on the health effects of varying nicotine and tar. These biases and issues will be discussed in the following sections that present that research.

The epidemiological research on the health effects of varying tar and nicotine is presented under three headings: pulmonary function and disease, cardiovascular disease (mostly coronary heart disease), and lung cancer. Tables summarising the methods and results of studies on the association of tar and nicotine yields (and occasionally CO yield) with pulmonary function and disease, cardiovascular disease, and lung cancer are included in Appendix 1 as Table 4, Table 5, and Table 6 respectively. These tables are summarised further, presenting a single indication of the direction and magnitude of each study's results and a one sentence summary, and included in the following sections.

### **Pulmonary function and disease**

Results for studies on the association of nicotine and tar yields with pulmonary function and disease are presented briefly in Table 1, and in more detail in Table 4 in Appendix 1 (page 57).

When a study investigates an association of pulmonary function and disease with either tar or nicotine yield, but not both, it is likely that a similar association exists for the other yield. This is because tar yield and nicotine yield tend to be highly correlated. However, this makes it difficult to disentangle the separate contributions of tar and nicotine, but the weight of evidence suggests that tar is more likely to be damaging to the lungs than nicotine.

**Table 1: Brief summary of results for studies on the association of tar and nicotine in cigarettes with pulmonary function and disease<sup>1</sup>**

Author	Evidence <sup>2</sup>	Brief summary of results <sup>3</sup>
Hawthorne and Fry 1978	+ / null	Three cross-sectional studies, subsequently followed-up as cohorts, of which only one study found a decrease in the prevalence of <i>shortness of breath</i> and <i>wheeze</i> with lower tar cigarettes, but no difference for bronchitis, phlegm, angina myocardial infarction, and mortality.
Higgenbottam et al 1980	+	A cross-sectional study that found a lower prevalence of <i>phlegm</i> production with lower tar yield, but no association for FEV <sub>1</sub> .
Schenker et al 1982	+	A cross-sectional study that found a lower prevalence of <i>chronic cough</i> , and possibly <i>chronic phlegm production</i> , with lower tar yield, but no association for wheeze and dyspnoea.
Petitti and Friedman 1985	null	A cohort study that found no association of hospitalisations for respiratory disease with tar yield.
Sparrow et al 1983	null	A cohort study that found no association of FEV <sub>1</sub> or FVC with tar yield.
Brown et al 1991	+	A cross-sectional study that found a lower prevalence of <i>chronic cough</i> and <i>chronic phlegm</i> with lower tar yield for women only.
Krzyanowski et al 1991	+	A series of cross-sectional health surveys that found a lower prevalence of <i>wheeze</i> for both lower tar and nicotine yield, a possibly lower prevalence of cough, phlegm and dyspnoea, and no association with FEV <sub>1</sub> .
Withey et al 1992	null	A randomised controlled trial that found no association of cough, phlegm and PEF <sub>R</sub> with tar and nicotine yields.
Tang et al 1995	+ / null	A large prospective study, combining four separate cohorts, that found a statistically non-significant lower mortality due to chronic obstructive respiratory disease with lower tar yield.

<sup>1</sup> A more detailed summary of each paper is included in Appendix 1 (Table 4, page 57).

<sup>2</sup> ++, strong evidence for decreased harm to health from lower yield; +, moderate evidence; null, null finding; -, moderate evidence for increased harm to health from lower yield; --, strong evidence.

<sup>3</sup> Statistical significance is assumed to be at the five percent level.

The two observational studies with tar and nicotine yields approximately equal to those of current cigarettes (Krzyanowski et al 1991, Brown et al 1991) provide some evidence that associations of tar and nicotine with pulmonary symptoms and disease may extend to the nicotine and tar yields of current cigarettes.

A major concern with almost all the studies in Table 1 is that the results are prone to possible confounding, which potentially could shift measures of effect in either direction (ie, causing underestimates or overestimates of the magnitude of the actual effect). For example, it may be that people who were less likely to get (or report) pulmonary symptoms and disease were more likely to smoke low-yield cigarettes. If this were the case then it would create the impression that low-yield cigarettes were protective. However, the confounding could also act in the reverse direction, hiding, or even reversing, any true positive association. For example, this would occur if people already with pulmonary symptoms or disease were more likely to swap to low-yield cigarettes than were those without such symptoms or disease.

Properly conducted randomised control trials remove the possibility of confounding. The one randomised control study shown in Table 1 (Withey et al, 1992) found no difference for cough, phlegm and PEFR (peak expiratory flow rate - a measure of lung function) between randomised groups, each smoking a different type of cigarette (in terms of tar and nicotine yields), at the end of the 24 week trial. However, this study has two important limitations. First, the differences between the groups in tar and nicotine yields were not great. Second, the pulmonary symptoms and disease attributable to smoking are often due to long-standing and cumulative damage from tobacco. It may be that the trial period was insufficiently long for any difference between groups to be observed.

Exposure misclassification bias also potentially affects all the studies shown in Table 1. This would tend to bias any 'true' effect toward the null (i.e. cause an underestimate of any true effect). The misclassification bias is operating in three ways. First, and most importantly, smokers do not smoke cigarettes like FTC smoking machines. (This is, arguably, more a mismeasurement or misspecification of exposure bias than a misclassification bias). As discussed above, smokers can easily adjust (compensate) their smoking habits to increase their intake of nicotine and tar from lower yield cigarettes. This in turn means that there is really only a small difference in exposures between yield categories. Second, there is likely to be imprecision in the FTC smoking test, and a large degree of variation of actual yields can be expected about those measured. Third, many of the studies use only the most recent yields for estimating exposures, and do not adjust for changes in yields over the smoking histories of the subjects.

**Key points from studies on the association of tar and nicotine in cigarettes with pulmonary function and disease**

- ?? There is probably an effect of tar and nicotine yields on pulmonary function and disease, although the observed effect is small.
- ?? When observed, the association of lower tar and nicotine yields with less pulmonary dysfunction and disease was often stronger for smokers of fewer cigarettes per day (e.g. Higgenbottam et al 1980, Krzyzanowski et al 1991).
- ?? The true effect may be somewhat larger if misclassification bias is significant. Residual confounding could be acting in either direction.
- ?? Only two of the studies (Kryzanowski et al 1991, Brown et al 1991) examined the effect of cigarettes with tar and nicotine yields that would be comparable with currently available cigarettes.
- ?? All studies found that the number of cigarettes smoked per day was a much stronger predictor of respiratory symptoms and disease than tar or nicotine yields.

## Cardiovascular disease

Most of the studies focus on coronary heart disease, rather than the more general category of cardiovascular disease. Summarised results for the studies that have addressed the associations of nicotine, tar, and CO yields with cardiovascular disease are shown in Table 2, and in more detail in Table 5 on page 61. It is important to remember that smoking per se (ie, smoker versus non-smoker), and the number of cigarettes smoked per day, are strong proven risk factors for cardiovascular disease. What the studies reviewed here seek to answer is whether there is any additional effect from tar or nicotine yields on cardiovascular disease.

**Table 2: Brief summary of results of studies on the association of tar and nicotine in cigarettes with cardiovascular disease<sup>1</sup>**

Author	Evidence <sup>2</sup>	Brief summary of results <sup>3</sup>
Hammond et al 1976	++	A large cohort that found a lower coronary heart disease mortality rate for lower nicotine and tar yield cigarettes.
Higenbottam et al 1982	+ / null	A cohort study that found a statistically non-significant lower coronary heart disease mortality with lower tar.
Borland et al 1983	- / null	A cohort study that found a statistically non-significant <i>higher</i> coronary heart disease mortality with lower CO yields.
Kaufman et al 1983	null	A case-control study that found no association of myocardial infarction with nicotine or tar yield.
Petitti and Friedman 1985	+ / null	A cohort study that found a statistically non-significant lower incidence of cardiovascular disease with tar yield.
Palmer et al 1989	null	A case-control study that found no association of myocardial infarction with nicotine or CO yield.
Negri et al 1993	null	A case-control study that found no association of myocardial infarction with nicotine or CO yield.
Parish et al 1995	+	A case-control study that found a lower incidence of myocardial infarction with lower tar.
Tang et al 1995	+	A large prospective study, combining four separate cohorts, that found a lower coronary heart disease mortality with lower tar yield.

<sup>1</sup> A more detailed table summarising these studies is in Appendix 1 (Table 5, page 61).

<sup>2</sup> ++, strong evidence for decreased harm to health from lower yield; +, moderate evidence; null, null finding; -, moderate evidence for increased harm to health from lower yield; --, strong evidence.

<sup>3</sup> Statistical significance is assumed to be at the five percent level.

As previously mentioned, when a study reports an association for either tar or nicotine yield, but not both, it is likely that a similar association exists for the other yield because of the strong correlation between tar and nicotine yields. However, CO yields do not necessarily correlate with those for nicotine or tar (Borland et al, 1983). Two studies (Borland et al 1983, Kaufman et al 1983) using CO yields found no significant association with coronary heart disease overall, although Borland et al (1983) reported a protective association

between increasing CO yields and coronary heart disease among smokers reporting that they inhaled (versus smokers that do not inhale the tobacco smoke).

Of the remaining studies, a large case-control study (Parish et al 1995), three cohort studies (Petitti and Friedman 1985, Higgenbottam et al 1982; Hammond et al 1976), and a large prospective study of four separate cohorts (Tang et al 1995) found significant associations between yield and cardiovascular disease. In the case-control study an odds ratio of 1.17 (95% CI 1.03-1.33) for non-fatal myocardial infarction in 60 to 79 year olds was observed for medium-tar (? 10 mg) smokers compared to low-tar smokers (<10 mg). The cohort study of Petitti and Friedman (1985) observed a relative risk of 1.15 (95% CI 1.03-1.29) per five mg increase in tar yield for any cardiovascular disease (including coronary heart disease). The Whitehall study (Higgenbottam et al 1982) found an effect of tar yield among smokers of 1-9 cigarettes per day, but less so for smokers of 10-19 and 20+ cigarettes per day. The last cohort study, Hammond et al (1976), is important because of its large size - over 400,000 smokers followed for 12 years. For smokers of cigarettes that were about twice as high in both nicotine and tar yield, the relative risk of mortality from coronary heart disease was 1.16 ( $p < 0.001$ ).

Also important is a large prospective study combining four separate cohorts to give a total of 56,255 men, followed up for an average of 13 years (Tang et al 1995). The relative risk for coronary heart disease mortality per 15 mg decrease in tar was 0.77 (95% CI 0.61-0.97), the reciprocal relative risk for a 15 mg increase being 1.30.

Of those studies that observed an effect (Borland et al 1983, Higgenbottam et al 1982, Parish et al 1995, Petitti and Friedman 1985, and Tang et al 1995), only Parish et al report findings for tar yields that are consistent with current tar yields of manufactured cigarettes.

As with studies of pulmonary symptoms and disease, the studies of cardiovascular disease have limitations in terms of their potential for confounding and exposure misclassification bias.

#### **Key points from studies on the association of tar and nicotine in cigarettes with cardiovascular disease**

- ?? There is possibly an effect of tar and nicotine yields on cardiovascular disease, mostly coronary heart disease, although the observed effect is small (relative risks in the order of 1.0 to 1.2 for five to ten mg increases in tar yield).
- ?? The true effect may be somewhat larger if misclassification bias is significant. Residual confounding could be acting in either direction.
- ?? Only one of the studies (Parish et al 1995) examined the effect of cigarettes with tar and nicotine yields that would be comparable with currently available cigarettes.
- ?? All studies found that the number of cigarettes smoked per day was a much stronger predictor of cardiovascular disease than tar or nicotine yields.

## Lung cancer

Smoking is known to cause lung cancer, and causes the vast majority of lung cancer. This section reviews studies that seek to answer whether the risk of lung cancer changes with alterations in tar or nicotine yields.

Summarised results for the studies addressing the association of lung cancer with tar yields, and, in one study (Borland et al 1983), CO yields, are shown in Table 3 below, and in more detail in Table 6 on page 64.

**Table 3: Brief summary of results for studies on the association of tar and nicotine in cigarettes with lung cancer<sup>1</sup>**

Author	Evidence <sup>2</sup>	Brief summary of results <sup>3</sup>
Hammond et al 1976	++	A cohort study that found a lower lung cancer mortality with lower nicotine yield.
Higenbottam et al 1982	+ / null	A cohort study that possibly found a lower lung cancer incidence with lower nicotine yield.
Vutuc and Kunze 1982	+	A case-control study of females that found a lower incidence of lung cancer with lower tar yield.
Borland et al 1983	+ / null	A cohort study that found a statistically non-significant lower lung cancer mortality with lower CO yield.
Vutuc and Kunze 1983	+	A case-control study of males that found a lower incidence of lung cancer with lower tar yield.
Lubin et al 1984	+ / null	A case-control study that found a possible lower incidence of lung cancer with lower tar yield.
Petitti and Friedman 1985	+ / null	A cohort study that found a statistically non-significant lower incidence of lung cancer with lower tar yield.
Zang and Wynder 1992	++	A case-control study that found a lower incidence of lung cancer with lower tar yield.
Benhamou et al 1994	+ / null	A case-control study that found a possible lower lung cancer incidence with lower nicotine yield.
Tang et al 1995	+ / null	A large prospective study, combining four separate cohorts, that found a statically non-significant lower lung cancer mortality with lower tar yield.

<sup>1</sup> A more detailed summary of each paper is included in Appendix 1 (Table 6, page 64).

<sup>2</sup> ++, strong evidence for decreased harm to health from lower yield; +, moderate evidence; null, null finding; -, moderate evidence for increased harm to health from lower yield; --, strong evidence.

<sup>3</sup> Statistical significance is assumed to be at the five percent level.

The general trend is for increasing tar yields to be associated with increasing risk of lung cancer. Only one study found a protective association between increasing tar yield and lung cancer (Petitti and Friedman, 1985), but that was not statistically significant. Several studies (Zang and Wynder, 1992; Hammond et al, 1976; Tang et al, 1995) estimate the effect at about a 15 to 20 percent reduction in the risk of lung cancer for a 10 mg reduction in tar yield. This concurs with a 1985 consensus paper that stated:

“Prospective epidemiological studies of lung cancer show, on average, an approximate 20% reduction in risk associated with lower-tar (or filter) cigarettes

compared with higher tar (or plain) - a difference that is very much what would be expected from intake studies.” (Participants of the Fourth Scarborough Conference on Preventive Medicine, 1985)

All of the studies in Table 3 include subjects that were smoking cigarettes with considerably higher levels of tar yield than are found for current cigarettes. Therefore, it is uncertain whether the results are directly applicable to currently manufactured cigarettes.

Again, there are potential problems with confounding and exposure misclassification bias. It is uncertain what effect confounding would have, but exposure misclassification bias should make any effect of changes in yield more difficult to detect.

It may be that any effect of lowering tar yields of cigarettes on reducing lung cancer is not uniform for different types of lung cancer. In particular the incidence of adenocarcinoma of the lung, a previously uncommon type of lung cancer compared to squamous cell carcinoma, has been reported to be increasing among smokers (Hoffman and Hoffman, 1994). It is biologically plausible that this may be explained by both compensatory smoking (ie, deeper inhalation of smoke) that causes toxins to reach peripheral lung tissue (where the adenocarcinomas are more likely to occur), and the increase in tobacco-specific N-nitrosamines in tobacco smoke in recent decades (IARC, 1986; Wynder and Muscat, 1995).

**Key points from studies on the association of tar and nicotine in cigarettes with lung cancer**

- ?? There is almost definitely an effect of tar and nicotine yields on lung cancer, with a reduction of lung cancer incidence with reducing tar and nicotine yields. The apparent effect is a 15 to 20 percent reduction in the risk of lung cancer for a 10 mg reduction in tar yield.
- ?? The true effect may be somewhat larger if misclassification bias is significant. Residual confounding could be acting in either direction.
- ?? None of the available studies examine cigarettes with yields comparable to current cigarettes.
- ?? All studies found that the number of cigarettes smoked per day was a much stronger predictor of lung cancer than tar or nicotine yields.

## Summary of health effects of varying nicotine and tar yields

The magnitude of the observed reductions in risk for the health events considered in the previous three sections is not directly proportional to the decrease in tar (or nicotine) yield. That is, a large reduction in yield is associated with a lesser reduction in risk of disease. There are several possible reasons for this. First, and most important, is the ability of smokers to compensate for reduced tar and nicotine yields, so that their actual exposures to tar (and nicotine) reduce proportionately less than would be indicated by a comparison of yields. Some commentators have surmised that, for lung cancer at least, the observed decrease in risk for lung cancer with decreased tar yields is consistent with the actual decrease in exposure, taking into account the degree of compensation in intake by smokers for decreasing yields (Participants of the Fourth Scarborough Conference on Preventive Medicine, 1985). Tang et al (1995) likewise concluded:

“About a quarter of deaths from lung cancer, coronary heart disease, and possibly other smoking related diseases could be avoided by switching from higher tar cigarettes (30 mg/cigarette) to lower tar ones (15 mg/cigarette). This is consistent with studies of compensatory smoking; switching to cigarettes of half the tar yield reduces the intake by about a quarter rather than a half.”

A second consideration is that concentrations of the health-damaging constituents in tobacco smoke may not change in direct proportion to the tar and nicotine yield. For example, gaseous phase smoke constituents, such as CO, may be partly responsible for the increased risk of coronary heart disease from smoking tobacco.

Confounding needs to be considered as a possible explanation for the observed association of tar and nicotine yields with health effects. As mentioned above, it may be that smokers who (for, say, reasons of socio-economic circumstances or lifestyle) were less likely to develop disease chose to smoke low-yield cigarettes. Or, conversely, smokers with early stage disease may be more likely to switch to smoking low-yield cigarettes. These possible confounding factors might be explored by investigating proxy variables like socio-demographic differences between smokers of low and high-yield cigarettes, although this assumes a correlation between the socio-demographic variables and the postulated true confounding factors. All the studies presented in the preceding sections control for some or many of the following: cigarettes per day, years smoking, sex, age, socio-economic factors, area of residence, and other health states. In some of the studies statistically significant results remained after controlling for these confounders. Another consideration arguing against confounding explaining the observed associations is that it seems more likely that those at risk of disease, and who are unable to give up smoking, would be likely to change to lower yield cigarettes (i.e. possible confounding in the opposite direction to the observed effect). This would diminish any observed association of yield with disease.

The final bias to consider is misclassification of the exposure. This is almost definitely present in all the studies in the previous sections, and will reduce the magnitude of any observed association.

A 1981 report to the U.S. Surgeon General concluded that there was an association between yield and cancer, possibly for pulmonary disease, and that there was no clearly demonstrable association with cardiovascular disease. A recent National Cancer Institute Expert Committee in the United States has concluded similarly that yields have an effect on cancer, possibly pulmonary disease, but not for cardiovascular disease (US Department of Health and Human Services, 1996). This committee, however, did not include the two latest studies reviewed in this report on coronary heart disease - Parish et al (1995) and Tang et al (1995). Both of these studies found an association between lower coronary heart disease incidence or mortality and lower tar yield. In light of this recent research evidence, we have elected to state that tar yield is *possibly* associated with coronary heart disease.

**Summary key points for all epidemiological studies on the health effects of varying levels of tar and nicotine**

- ?? Lower tar and nicotine yield cigarettes do lower the risk of lung cancer
- ?? Lower tar and nicotine yield cigarettes probably lower the risk of pulmonary symptoms and disease
- ?? Lower tar and nicotine yield cigarettes possibly lower the risk of coronary heart disease
- ?? Confounding is unlikely to explain the associations of increasing tar and nicotine yields with increasing risks of diseases, and exposure misclassification bias is likely to cause the associations to be underestimated.

## **PART 3: THE RELATIONSHIP BETWEEN YIELD AND INTAKE: COMPENSATORY SMOKING**

As briefly discussed earlier in this report, in order to maintain their usual intakes of tobacco smoke constituents, smokers modify their smoking behaviour in response to changing yields of nicotine (and possibly tar) in cigarettes. This report considers the phenomenon of compensatory smoking to be well-established, and moves beyond this to review studies with the objectives of determining: a) the extent of compensation in different scenarios, and b) what tobacco constituents are most responsible for compensation.

Studies are reviewed under four headings:

- ?? observational studies of compensatory smoking
- ?? experimental studies of compensatory smoking, using cigarettes with varying yields, but relatively constant tar to nicotine ratios
- ?? experimental studies of compensatory smoking using cigarettes with varying tar to nicotine ratios
- ?? other studies.

All studies considered measured yields as the exposure, and biomarkers or smoking behaviour as outcomes. These associations were then interpreted as relationships between cigarette yields and actual intake of tobacco constituents. Commonly used biomarkers were:

- ?? serum or urinary nicotine or cotinine as biomarkers for nicotine
- ?? expired CO or carboxyhaemoglobin as biomarkers of CO.

There is no directly equivalent biomarker for tar intake. Proxies sometimes used include urine mutagenicity, and serum thiocyanate. Alternatively, estimates of tar intake are calculated on the basis of their relativity to intakes of other tobacco smoke constituents with biomarkers (Stephen et al, 1989).

### **Observational studies of compensatory smoking**

In a study of 272 people, Benowitz et al (1983) found that the nicotine yield of cigarettes smoked did not correlate with serum cotinine. The range of FTC nicotine yields for currently-smoked cigarettes was 0.05 mg to 2.0 mg, the majority being between 0.3 mg and 1.5 mg. Serum cotinine concentration was statistically significantly ( $p < 0.01$ ) correlated with the number of cigarettes per day smoked ( $r = 0.40$ , for afternoon serum samples,  $r = 0.45$  for morning samples following eight hours abstinence). However, the correlation between nicotine yield and serum cotinine concentration was not statistically significant ( $r = 0.15$  and  $0.06$ , respectively). The correlation of perhaps most interest, the partial correlation of serum cotinine with nicotine yield, controlling for number of cigarettes per day, was not reported. However, the results presented suggest it would have been small. That supposition is supported by the finding that adding nicotine yield to a multiple regression analysis of sex, age, and number of cigarettes per day on serum cotinine improved the variance accounted for by only 2.8 and 5.0 percent, respectively, for afternoon and morning samples.

Using metabolic clearance data to estimate the total daily intake of nicotine, Benowitz and Jacob (1984a) again found that nicotine yield did not correlate with nicotine intake. That is, compensatory smoking completely overcame variation in cigarette yields, such that a similar amount of nicotine was obtained from each cigarette smoked, regardless of the yield. The study involved 22 smokers of more than a pack per day, smoking their selected cigarettes with an average nicotine yield per cigarette of  $1.24 \pm 0.27$  mg (range 0.87 to 1.80 mg). The correlation coefficient ( $r$ ) for the association between nicotine intake and number of cigarettes smoked per day was 0.59 ( $p < 0.01$ ), but was -0.12 ( $p > 0.05$ ) for the correlation of nicotine intake *per cigarette* and nicotine yield. The average nicotine intake per cigarette was 1.04 mg, but with wide variability ( $sd = 0.36$  mg, range 0.37-1.56).

In a further study of 248 smokers (Benowitz et al, 1986a), 137 of whom were subjects in the previous study (Benowitz et al, 1983), found that nicotine intake was reduced only for those smoking cigarettes with a nicotine yield less than 0.20 mg. The mean serum cotinine for the 18 people smoking cigarettes of less than 0.20 mg yield was 189 ng/ml compared to 305, 303 and 329 ng/ml for smokers of cigarettes with yields of 0.21-0.60, 0.61-1.00, and >1.01 mg nicotine ( $p < 0.05$  for the low-yield group compared with other yields). Thus, this research suggests a threshold nicotine yield around 0.20 mg, below which smokers have difficulty maintaining their nicotine intake through compensation. [Note: no retailed manufactured cigarettes in New Zealand during 1996 had a nicotine yield below 0.6 mg (Ministry of Health 1997)].

In contrast to the studies of Benowitz and his colleagues, Bryd et al (1995) found a strong positive association between nicotine yield and daily nicotine uptake. Thirty three smokers were recruited, mainly from employees of RJ Reynolds in North Carolina. The smokers were divided into four groups with mean nicotine yields for their preferred cigarettes of 0.14, 0.49, 0.67, and 1.13 mg. Twenty four hour urine samples during *ad libitum* smoking determined the nicotine uptake per cigarette as 0.23, 0.56, 0.60 and 1.19 mg, respectively, for each of the four groups. Thus, the nicotine uptake per cigarette was approximately equivalent to the stated yield. The authors suggested that the reason they found a strong linear relationship between yield and uptake, in contrast to other studies, was the use of accurate methods for determining nicotine intake, a large range of nicotine yields over which to make comparisons (although this also applies to Benowitz et al, 1986a), and that they were studying smokers in their natural environment. The possible bias from using RJ Reynold employees must also be considered. Another speculative possibility for explaining the difference that occurs to us is that it may be possible that the smokers in the study of Byrd et al were smoking cigarettes in which the yield and either nicotine concentration or content were correlated. This would be in contrast to subjects in the research of Benowitz and colleagues, where the nicotine concentration and content of cigarettes was not correlated with yield (Benowitz et al, 1983). This is an important possible explanation, and requires more research.

A study of 298 mainly Hispanic smokers found poor correlations between nicotine yield and salivary cotinine, and between CO yield and expired CO ( $r = 0.12$  and  $0.03$ , respectively) (Coultas et al, 1993). The range of yields did not appear to be wide (tar yields were between 10 and 20 mg for about 80-90% of the sample), compromising the ability to

find any association. The number of cigarettes per day was a superior predictor of both salivary cotinine and expired CO ( $r=0.52$  and  $0.51$ , respectively;  $p=0.001$  for both). Multiple linear regression models including cigarettes per day, and time since last cigarette found no independent effect for FTC yields in predicting either salivary cotinine or expired CO. Likewise, FTC tar yields did not independently predict the number of cigarettes smoked per day.

A recent study in the United Kingdom (Parish et al, 1995) did find an association of both tar and nicotine yields with serum cotinine. The results come from a large case-control study, and involved 2,324 control subjects who were also smokers. Twenty six percent of the smokers were low-tar smokers ( $<10$  mg tar yield, , mean nicotine yield  $0.75$  mg). The remaining middle-tar smokers (mostly  $12-15$  mg tar yields, mean nicotine yield  $1.18$  mg) had serum cotinine levels 19 percent higher than low-tar smokers ( $p<0.0001$ ), although this was less than the 50 percent expected difference on the basis of nicotine yields, indicating compensation in smoking behaviour. As with other studies, the number of cigarettes was strongly associated with serum cotinine, being a linear relationship up to 15 cigarettes per day, then flattening off. The authors suggest that the flattening off means that heavier smokers extract less nicotine per cigarette.

A study of 77 regular smokers found no association of nicotine yield with the uptake of nicotine (Andersson et al 1997). The smokers were divided into three groups with average nicotine yields of  $0.70$ ,  $1.05$  and  $1.34$  mg, and average tar yields of  $6.4$ ,  $11.0$  and  $16.0$  mg, respectively. The average number of cigarettes consumed per day did not significantly differ between groups. There were no statistically significant differences in salivary cotinine or total nicotine equivalents excreted between the three groups, although the salivary cotinine was highest in the high-yield smoking group. There was no adjustment for age and duration of smoking.

Sutton et al (1982) reported evidence from a cross-sectional survey that lower tar yield was a significant predictor of higher plasma nicotine concentration, after controlling for the nicotine yield of cigarettes. This suggests that lowering the tar yield alone can lead to compensatory smoking behaviour, in the same manner as lowering the nicotine yield. The study must be interpreted with caution as it included only 52 smokers, and the high correlation of nicotine and tar yields make the conclusions based on statistical path analysis somewhat tenuous. However, it does offer some support for an independent effect of tar on smoking behaviour.

Lynch and Benowitz (87) traced 203 out of 813 subjects of smoking research that had taken place between three and six years before. One hundred and nine people had not changed the nicotine yield of the cigarette they smoked ( $0.83$  mg average nicotine yield: controls), 62 had decreased the yield ( $1.09$  to  $0.68$  mg: “decreasers”), and 32 had increased the yield ( $0.42$  to  $0.85$  mg: “increasers”). The publication does not state the average tar yields for the three groups, but it is reasonable to assume that tar yields changed in proportion to nicotine yields. Average numbers of cigarettes smoked per day fell for all three groups, particularly the decreasers. Decreasers had a reduction in serum cotinine and expired CO, but this was due to smoking fewer cigarettes per day rather than decreased

nicotine and CO consumption per cigarette. Increases had higher serum cotinine and expired CO due to increased nicotine and CO intake per cigarette.

Stephen et al (1989) found an average compensation for nicotine yield of 76 percent in three observational studies they reviewed, after adjusting for the number of cigarettes smoked per day and using serum nicotine as the biomarker. That is, the observed difference in serum nicotine between smokers of varying yield cigarettes was 76 percent less than the difference that would have been expected if serum nicotine levels had changed in direct proportion to nicotine yield. A higher average compensation of 82 percent was found for the studies reviewed of CO intake compared to CO yield. The estimated compensation for tar intake was similar.

### **Key points from observational studies of compensatory smoking**

- ?? Most observational studies show only a small, if any, reduction in nicotine, tar, and CO intake with reducing yields in the natural setting.
- ?? Some researchers have estimated that for most commonly retailed cigarettes, smokers extract about 1.0 mg of nicotine per cigarette, regardless of the FTC nicotine yield.
- ?? Tar, nicotine, and, usually, CO yields in commonly available cigarettes are highly correlated, making difficult the determination of independent effects for each yield.
- ?? A threshold probably exists for FTC nicotine yields below which full compensation is difficult. The exact threshold is uncertain, but is probably less than 1.0 mg and probably greater than 0.1 mg. A best estimate from the available literature is about 0.2 to 0.6 mg.

### **Experimental studies of compensatory smoking using cigarettes with varying yields, but relatively constant tar to nicotine ratios**

In an early study, Russell et al (1973) demonstrated behavioural compensation for differing yields, and an interesting pattern of COHb levels across cigarettes with different yields. The study was of 10 smokers exposed to three different cigarettes: low-yield (0.3 mg nicotine, 4 mg tar), their usual cigarette (average nicotine 1.34 mg, average tar not stated), and a high nicotine yield cigarette (3.2 mg nicotine, 38 mg tar). Over the five-hour experimental period the number of cigarettes smoked and the weight of tobacco consumed, was highest for the low-yield cigarette, and lowest for the high-yield cigarette. This led Russell et al to speculate that the least harmful cigarette may be one high in nicotine, but low in tar and CO. (The research on this hypothesis is reviewed on page 38 of this report).

Benowitz and Jacob (1984b) found that smokers with experimentally imposed low-yield cigarettes maintained their nicotine intake by a combination of increasing the number of cigarettes smoked, and compensation of their smoking behaviour. Eleven regular smokers were changed from their regular cigarette (average nicotine yield 1.0 mg, average tar yield 16.3 mg) to a high-yield cigarette (1.2 mg nicotine, 16 mg tar) and a low-yield cigarette (0.4

and 4.9 mg). The study had a balanced cross-over design, with four days smoking each of the three cigarettes before measurements were taken. Smokers were not blind to what they were smoking. Nicotine uptake was estimated on the basis of blood and urinary concentrations of nicotine in combination with metabolic clearance data for nicotine. The average estimated nicotine intake per day for the subjects' usual cigarette was 35 mg, but for each of the two experimental cigarettes was 26 mg. Thus this research indicates that smokers were able to fully compensate their nicotine intake when switched to an experimental low-yield cigarette compared to an experimental high-yield cigarette, mostly due to compensatory smoking behaviour for each individual cigarette, but also partly by varying the number of cigarettes. What it also shows is that smokers in this particular study reduced their nicotine intake when moving from their regular cigarette to an experimental cigarette that was higher in nicotine yield. Presumably, there are factors other than tar and nicotine (e.g. taste, pleasantness) that modulate nicotine intake.

In an extension to the above study, Benowitz et al (1986a) found that smokers could no longer fully compensate their nicotine intake with ultralow cigarettes (0.1 mg nicotine and 0.8 mg tar) compared to low-yield (0.4 and 4.9 mg) and high-yield (1.2 and 16 mg). For high and low-yield brands there were no differences in nicotine, CO, or tar (as measured by mutagenicity of urine) intake. However, exposure to nicotine, tar, and CO for the ultra-low-yield cigarette compared to the high-yield cigarette was reduced by 56, 49 and 36 percent respectively. The finding of reduced exposures for only ultra-low cigarettes agrees with West et al (1984) and Gori and Lynch (1983). Research by Robinson et al (1992) also found that ultralow-nicotine yield cigarettes (0.06 mg nicotine yield) resulted in a much decreased average post-cigarette rise in serum nicotine (3.6 ng/ml), compared to a standard low-yield cigarette (0.6 mg nicotine yield, 26.4 ng/ml serum nicotine rise) among five volunteer smokers from R.J. Reynolds Tobacco Company.

In a study of 11 subjects the difference between pre- and post-cigarette serum nicotine levels was correlated with nicotine yield ( $r=0.52$ ,  $p<0.05$ ; Herning et al, 1983). The specially manufactured experimental cigarettes were 2.5 mg higher or 0.4 mg lower in nicotine yield than the smokers' normal cigarettes (mean nicotine yield for normal cigarettes 'about' 1.0 mg). The correlation coefficient improved to 0.93 when individual differences in smoking behaviour were accounted for (interpuff interval, number of puffs, puff volume, puff duration, inhaled volume, and duration of inhalation). The authors concluded that about 25 percent of the variation in the difference between pre and post-cigarette nicotine levels was due to the nicotine yield of the cigarette, but 50-60 percent was due to differences in smoking behaviour.

A United States study using commercially available cigarettes demonstrated that compensation for decreasing nicotine yield is substantial, but not complete, down to at least nicotine yields of 0.1 mg (Zacny and Stitzer 1988). Ten smokers were included in a randomised cross-over study with five types of cigarette: the subjects' usual cigarette (mean nicotine yield 1.0 mg, tar 16 mg, 15 mg CO), and four experimental cigarettes with decreasing nicotine yields (1.1, 0.7, 0.4, and 0.1 mg), and proportionately decreasing tar (16, 10, 5 and 1 mg, respectively) and CO yields (14, 11, 5 and 2 mg, respectively). The percentage reductions in serum cotinine for the three lower-yield experimental cigarettes

versus the highest yield experimental cigarette were 15, 27.3 and 41.5 percent, respectively. Thus, for each of the three lower-yield experimental cigarettes, the smokers managed to compensate for about 55 percent of the expected decline in nicotine intake predicted by the FTC nicotine yield. There was no difference in expired CO associated with the different cigarettes, except for the lowest yield cigarette which was associated with lower expired CO levels.

Stephen et al (1989) reviewed 17 published studies to derive combined estimates of compensatory smoking behaviour. The average compensations for nicotine intake (62 percent) and CO intake (69 percent) for experimental studies were somewhat less than for observational studies (76 and 82 percent respectively). This demonstrates how smoke intake is found to vary, on average, more with yield in experimental studies than in observational studies.

The experimental studies discussed above have all examined the short-term compensation of smokers in response to lowering levels of tar and nicotine in an experimental setting. An important question is whether the compensation for low-yield cigarettes in an experimental setting is maintained, increased, or decreased over the long-term. Some of the earliest evidence on this comes from a study by Russell et al (1982) that found that compensation is maintained at the same level over time. In this study, nicotine uptake and estimated tar uptake for lower-yield cigarettes remained less than with their previous cigarettes over time. The study was of twelve subjects who switched from their usual cigarettes (mean nicotine yield 1.3 mg, tar 17.4 mg, and CO 17.0 mg) to low-yield cigarettes (nicotine 0.7 mg, tar 10.9, and CO 12.9), that is a 47, 37, and 24 percent reduction in nicotine, tar, and CO yields respectively. From the beginning to the end of the 10 week follow-up, the serum nicotine, serum cotinine and estimated tar intakes remained consistently less (30%, 30%, and 15%) than before changing to the low-yield cigarette. That equates to a compensation of 36 percent for reduced nicotine yield. Carboxyhaemoglobin and serum thiocyanate levels did not alter after changing to the low-yield cigarette. Also of interest was that, straight after the change, smokers did not rate the low-yield cigarettes much less satisfying than their usual cigarette, and, by the end of the 10 weeks, satisfaction ratings were the same as those initially for their usual cigarettes. Finally, Russell et al hypothesised that the reason reduced serum nicotine and cotinine levels, and reduced estimated tar intakes, are found in experimental studies, but not in cross-sectional population studies of low-tar smokers, is that only smokers who are able to fully compensate will continue to smoke low-yield cigarettes in the natural setting. In contrast, all smokers in experimental studies are required to change.

Frost et al (1995) provided evidence from a large randomised controlled trial (not blinded) that compensation is maintained in the long-term, but is not complete. Four hundred and thirty four British civil servants who tolerated a 10 percent lead-in reduction in yield were randomly allocated to control, fast reduction (one step change), or slow reduction (change over several months) groups. Initial average nicotine, tar and CO yields for the subjects' cigarettes were 1.37, 15.5, and 15.7 mg, respectively. Follow-up was for three months. Compared to the pre-randomisation data (i.e. after the 10 percent reduction), the fast reduction group had a reduction in nicotine yield of 40 percent, which was associated with an 11 percent (95% CI 6-16%) reduction in nicotine intake. They also had a reduction in

CO yield of 45 percent that was associated with a 19 percent (14-24%) reduction in CO intake. Results were similar, although slightly lower, for both yields and intakes, in the slow reduction group. Overall, people in the reduction groups compensated for 79 percent of the reduction in nicotine yield, 62 percent of tar yield reduction, and 65 percent of CO yield reduction. Data from the fast reduction group suggested that intakes remained stable over the three month follow-up period. The authors concluded:

“There is no doubt that the best advice to smokers is to give up smoking altogether. The effect of switching to low-tar cigarettes is small in comparison with giving up altogether, and much less than would be expected from a comparison of published tar yields. While our results indicate that switching to low-tar cigarettes is likely to confer some health benefit in respect of at least some diseases associated with smoking, the effect will be modest compared with not smoking at all. If smokers cannot give up smoking then switching to cigarettes with a lower tar yield would be better than making no change at all.”

Guyatt et al (1989) also studied the long-term effects of reducing the nicotine and tar yield of cigarettes smoked, and found that the reduced intake of nicotine, CO, and tar was maintained over nine months. Twenty eight smokers were enrolled and assessed for baseline parameters during five visits at monthly intervals, while continuing to smoke their usual cigarette (average nicotine yield 1.36 mg, tar 15.1 mg, and CO 15.2). They were then asked to change to another brand of cigarette with a nicotine yield at least 30 percent less than their usual brand, resulting in average yields for the new cigarettes of 0.91, 9.3, and 9.6 mg respectively. Both serum cotinine and carboxyhaemoglobin dropped by 18 percent, meaning that the fall was only about 40 percent of that predicted by FTC yields, or that compensation was about 60 percent. At six weekly visits for a further nine months serum cotinine and carboxyhaemoglobin remained unchanged.

**Key points from experimental studies of compensatory smoking using cigarettes with varying yields, but relatively constant tar to nicotine ratios**

- ?? Most experimental studies show a small, but significant, reduction in nicotine, tar, and CO intake with reducing cigarette yields. The degree of compensation varies between studies, but on average is about 50 to 70 percent.
- ?? The degree of compensation varies between studies, but on average is about 50 to 70 percent.
- ?? One experimental study (Benowitz et al 1986) found no reduction in nicotine intake with a reduction in nicotine yield 1.2 to 0.4 mg, and some reduction in nicotine intake when the nicotine yield was reduced from 0.4 to 0.1 mg, suggesting a threshold.
- ?? Long-term follow-up of experimental studies find that reduced nicotine intakes with reduced nicotine yields persist.

## **Experimental studies of compensatory smoking using cigarettes with varying tar to nicotine ratios**

In 1973, Russell et al proposed that the least harmful cigarette may be one that is low in tar and CO, but high in nicotine. This is premised on the assumption that the major determinant of smoking behaviour is nicotine, and the major risk to health was represented by tar and CO. Therefore, maintaining the nicotine yield in a low-tar cigarette may reduce exposure to the harmful constituents more effectively than a cigarette low in both nicotine and tar. The experimental studies can be divided into those addressing maintained-nicotine cigarettes in which the tar is reduced, but nicotine maintained at common retail levels, and other studies addressing various changes to the tar:nicotine ratio.

### **Maintained nicotine cigarettes with a reduced tar to nicotine ratio**

Armitage et al (1988) compared the tar and CO intake between three cigarettes: a maintained-nicotine cigarette (nicotine yield 1.4 mg, tar 11.2 mg, CO 9.9 mg, tar:nicotine ratio 8.0), a middle-tar (1.7 mg, 16.9 mg, 15.1 mg, ratio 9.9), and a low-tar cigarette (0.8 mg, 9.1 mg, 8.5 mg, ratio 11.4). They found that the CO intake did differ between the three cigarettes, being 30 percent lower for the maintained-nicotine cigarette compared to the middle-tar cigarette. The CO intake for the low-tar cigarette was intermediary. Estimated tar intake was 25 percent lower for the maintained-nicotine cigarette compared to the middle-tar cigarette. However, data was incomplete for the low-tar cigarettes, and the authors could only state that the estimated tar intake for the low-tar cigarette was probably closer to the maintained cigarette than the middle-tar cigarette. A weakness in the study design is that the range of yields between the three cigarettes is not great, and, moreover, the tar:nicotine ratios differ for the low-tar and middle-tar cigarette making interpretation of the results for the maintained-nicotine cigarette difficult.

Stepney (1981) found that a maintained nicotine cigarette did not reduce estimated tar intake any further than a moderately low-yield cigarette (i.e. tar and nicotine yield both reduced). Nineteen middle-tar smokers (mean nicotine yield 1.55 mg, tar 19 mg, CO 18 mg) were exposed in a crossover design experiment to their usual cigarette, a control cigarette (0.7 mg, 11 mg, and 13 mg), and a maintained cigarette (1.1 mg, 10 mg, 12 mg). The rise in expired CO after a cigarette was greatest for the usual cigarette, lowest for the maintained nicotine cigarette, and intermediate for the control cigarette. Cotinine excretion was similar for the usual and maintained cigarette, and less (approximately 20-25%) for the control cigarette. Estimated exposure to tar was similar for all three cigarettes, although a little higher for the usual cigarette. Stepney concludes that the results appear to suggest that smokers compensate more for reduction in tar than a reduction in nicotine. He argues that this may be explained by the tar and nicotine yields of commercially available cigarettes being so highly correlated that smokers in the short term use the sensory impact of tar to moderate the intake of nicotine.

In a study of smokers perception of cigarettes, a maintained cigarette (1.4 mg nicotine yield, 10 mg tar) tended to be perceived (mouth impact, throat impact, chest effect, roughness) more like a middle-yield cigarette (1.7 mg and 17 mg) than a low-yield cigarette (0.8 mg and 8.8 mg) (Kochlar and Warburton 1990). However, on overall satisfaction the maintained cigarette was midway between the other two.

### **Other studies of varying the tar to nicotine ratio**

Hasenfratz et al (1993) provided further evidence that tar (or some correlate thereof, such as flavouring) modifies smoking behaviour in addition to any effect of nicotine. Twelve females smoked three different commercially available cigarettes: usual (mean nicotine yield 0.81 mg, tar 10.1 mg, CO 9.6 mg), an ultra-low-yield (“ultralight”) cigarette (0.22 mg, 1.83 mg, 3.3 mg), and a moderate tar, ultra-low-nicotine cigarette (“Next”; 0.08 mg, 9.3 mg, 9.9 mg). There was a large amount of compensatory smoking for the ultralight cigarette, as shown by nicotine uptake to nicotine yield and CO intake to CO yield ratios, but not for the “Next” brand. The lack of compensation compared to the usual cigarette for the “Next” brand, despite having an extremely low-nicotine yield, was interpreted by the authors as evidence that gustatory and olfactory sensations, which are supposed to be more dependent on tar than nicotine, play a bigger role in governing compensation behaviour than previously believed. The implication of this research is that maintained-nicotine cigarettes will reap reductions in estimated tar intake that are less than that predicted by the reduction in tar yields.

Pritchard et al (1996) provided supporting evidence for regulation of compensation by the tar yield. They showed little compensation for variable nicotine yields in cigarettes with the same tar yield. Thirty two subjects, all smokers of one ‘light’ brand (nicotine yield 0.71 mg, tar 8.6 mg), smoked five different experimental cigarettes in double blind sessions. The nicotine yields were 0.08, 0.17, 0.37, 0.48 and 0.74 mg, and the tar yields 8.5, 9.1 9.8, 9.8 and 10.4 mg respectively. The association of blood nicotine rise after smoking each cigarette was near linear, with the regression line intersecting with the origin, suggesting little if any compensation for varying nicotine yield. Pritchard et al (1996) also showed that satisfaction with the experimental cigarettes decreased with decreasing nicotine yield.

There is conflicting evidence on whether tar yield affects compensation behaviour. A Chinese study found no difference in serum nicotine levels between two cigarettes that differed in tar yield, but were the same in nicotine yields (Wang 1987). The two experimental cigarettes both had a nicotine yield of 1.0 mg, and tar yields of 29 and 19 mg. The research, involving 45 smokers, was a double blinded and randomised cross-over study. After smoking each brand for two days, there was no difference in serum nicotine levels. The author concluded that:

“... as long as the nicotine yield is constant, the tar yield may have little effect on the amount of smoke taken from each cigarette.”

In an early study of behavioural effects only (Herning et al 1981), smoking behaviour was found to change when smoking cigarettes of variable nicotine yield, but similar tar yield. Twenty four smokers were exposed to each of three experimental cigarettes with nicotine yields of 0.4, 1.2, and 2.5 mg, but a tar yield of 31.8, 24.5 and 29.6 mg respectively. Smoking behaviour varied little between the 1.2 and 2.5 mg nicotine yield cigarettes, but was significantly different for the 0.4 mg yield cigarette. Most notable was the puff volume that was about a third higher than for the two other cigarettes.

### **Key points from intervention studies of compensatory smoking using cigarettes with varying tar to nicotine ratios**

?? The available evidence suggests that maintained-nicotine cigarettes do maintain the nicotine intake of the smoker, and reduce the CO intake relative to equivalent low-yield cigarettes (low in all of CO, tar and nicotine). However, there appears to be little, if any, reduction in tar intake from maintained nicotine cigarettes relative to equivalent low-yield cigarettes.

?? There is conflicting evidence for and against tar yields having an effect on regulating smoking behaviour independent of nicotine yields. The weight of evidence supports some independent effect of tar.

### **Miscellaneous**

None of the above studies assesses the effect of imposing changes in the number of cigarettes smoked on uptake of nicotine, tar, and CO, as opposed to changing yields. Benowitz et al (1986b) showed, as would be expected, that when smokers were required to drop their daily intake from an average of 37 cigarettes per day to 5 per day, intake per cigarette increased. The increase was about three-fold, meaning that cutting down the number of cigarettes by, in this case, an average of 86 percent resulted in only a 50 percent reduction in intake of tobacco toxins.

Russell (1989) provides a useful review of studies seeking to answer whether nicotine is the major determinant of smoke intake, given the difficulty disentangling highly correlated nicotine and tar yields for commercially available cigarettes. He concludes that nicotine is the major determinant. He also addresses the issue of a nicotine yield threshold below which it is difficult to fully compensate, and estimates it to be about 0.6 mg.

Waller and Froggatt (1996) have argued that the decrease in age-specific lung cancer mortality rates in Britain is not fully explained by decreases in tobacco consumption alone, and that the reduction in tar yields is a likely to have been important cause of decreasing lung cancer rates. However, a cohort study of British doctors found opposing evidence of both an increase in the relative risk of death for smokers compared to non-smokers, and an increase in the absolute risk of lung cancer death among smokers, for the period 1971-1991 compared to 1951-71 (Doll et al 1994). The finding in this latter study may have been related more, though, to the study population and the maturation of the tobacco epidemic, than to tobacco constituents (Peto et al 1994, Prescott et al 1997).

Russell (1989) proposed an alternate explanation to that of Waller and Froggatt (1996) for the decrease in national lung cancer rates since World War II. He cites evidence that smokers down regulate nicotine consumption more so than up regulate (the latter being what we have termed compensation in this report). That is, a smoker will not progressively

increase nicotine uptake with increasing nicotine yield, but will only smoke enough tobacco to maintain a “ceiling” level of nicotine. Extending this argument back in time, he argues that it is reasonable to assume the intake of tar post-World War II was no different from what it would be with current cigarettes, as previously cigarettes with high nicotine yield would have been under-smoked. Russell then draws on evidence that tar in currently available cigarettes is less carcinogenic than tar in cigarettes previously produced, and hypothesises that the observed reduction of lung cancer incidence is not due to a decrease over time in the quantity of tar inhaled, but due to decreasing carcinogenic potency of tar over time that has accompanied falling tar yields.

Finally, Rickert (1983) has shown that under experimental smoking machine conditions, approximating the more intensive smoking (as would be the case in compensatory smoking), the ratio of tar to nicotine yields was increased compared to that predicted by the standard FTC smoking machine parameters. The implication is that compensatory smoking increases the actual *inhaled* tar to nicotine ratio compared to that derived from using FTC yields.

### **Synthesis of the research on the relationship between yield and intake, and the epidemiological research**

This part of report has two objectives: a) to determine the extent of compensation in smoking behaviour in different scenarios, and b) to determine what tobacco constituents are most responsible for compensation. The answers are not definitive, but it seems safe to conclude this part of the report with the following points.

#### **Summary of studies on the relationship between intake and yield**

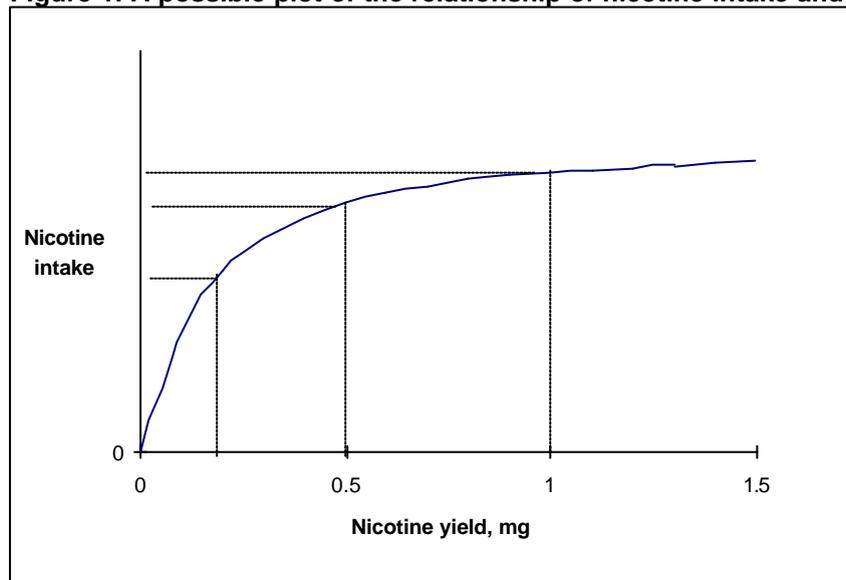
- ?? In the natural setting, most studies find that smokers almost fully compensate for varying nicotine yields in the range of approximately 0.6 to 1.5 mg, obtaining on average about 1 mg of nicotine per cigarette smoked, regardless of nicotine yield
- ?? Most experimental studies find that smokers can compensate for varying nicotine yields, but that the compensation is not complete, being about 50 to 70 percent.
- ?? Below nicotine yields of about 0.6 mg, compensation becomes increasingly difficult and nicotine intake falls more rapidly.
- ?? Tar intake varies roughly in proportion to nicotine intake, although may be modified by variation in the tar to nicotine ratio.
- ?? There is some evidence for a lower tar intake from a cigarette with low-tar, medium nicotine (maintained nicotine cigarette), compared to a low-tar, low-nicotine cigarette. However the difference in tar intake between these two types of cigarette appears to be relatively small.
- ?? Nicotine is probably the biggest determinant of compensatory smoking behaviour. Tar, taste, and other cigarette attributes probably also have a role, but less so than nicotine.

?

There is an inconsistency between observational and experimental studies of the relationship of nicotine yield to nicotine intake. Observational studies suggest smokers almost fully compensate for varying nicotine yields in the range of approximately 0.6 to 1.5 mg, obtaining on average about 1 mg of nicotine per cigarette smoked regardless of nicotine yield. Experimental studies also find that smokers can compensate for varying nicotine yields, but that the compensation is not as complete as that measured in observational studies, being about 50 to 70 percent. The most plausible explanation for this discrepancy is that only smokers who are able to fully (or near fully) compensate for lower yields will change to lower yield cigarettes in the natural setting.

While being a gross simplification of the relationship between nicotine intake and nicotine yield, it is helpful to consider Figure 1. This is a graphical relationship of the possible relationship of nicotine intake with nicotine yield. The important points to note are, first, that it is assumed that a zero nicotine yield cigarette will have zero nicotine uptake, meaning that compensation must become incomplete at some stage! In Figure 1 this is represented by the steeper slope for cigarettes with a yield less than about 0.5 mg in nicotine yield.

**Figure 1: A possible plot of the relationship of nicotine intake and nicotine yield**



Second, the research evidence presented previously in this section on the average relationship between yield and intake would suggest that the curve shifts to the left for observational studies, and to the right for experimental studies.

Third, the shape of the curve may be different for the following two scenarios:

- ?? research where there is *no*, or little, correlation between nicotine yield and nicotine content among the cigarettes smoked by study participants (i.e. the nicotine yield of the cigarettes is more determined by design features, rather than the actual nicotine in the tobacco)
- ?? research where there *is* a correlation between nicotine yield and nicotine content among the cigarettes smoked by study participants.

More research is required on the possible effect of nicotine content and concentration on nicotine intake, and indeed it is surprising that it has not already been done. The implication is that if a cigarette low in both nicotine yield and content is more likely to result in less nicotine intake than a cigarette that is low in only nicotine yield, but not content, then nicotine content may have a role in health messages on cigarette packets.

Given, then, that observational studies show little, if any, variation in nicotine, tar and CO intake across yield categories for common retailed cigarettes, then why do epidemiological studies find a small, but evident, reduction in lung cancer, and possibly coronary heart disease, associated with lower nicotine and tar yields? Five possible explanations occur to us:

- ?? there is in fact a small reduction in nicotine, tar and CO intake with reducing yields, and it is sufficient to explain the reduction in disease
- ?? there is self-selection in the natural setting, such that those less likely to develop disease tend to smoke low-yield cigarettes (actually confounding in epidemiological terms rather than a selection bias)
- ?? intake measures in research (usually, tar, nicotine, and CO) do not represent the constituents in tobacco smoke that are actually responsible for health damage, and these substances do vary in intake across nicotine and tar yields
- ?? intake measures in research do not represent the relative carcinogenicity or toxicity of constituents in tobacco smoke, and their carcinogenicity or toxicity does vary across nicotine and tar yields
- ?? the outcomes in the epidemiological studies (e.g. lung cancer) are due to cigarettes that predate the cigarettes examined in recent research on the association between yield and intake. While much recent research shows little association of yield with intake in the natural setting, it may be that this was not the case historically for cigarettes that were responsible for the disease outcomes in the epidemiological studies. (This seems an unlikely explanation as some of the epidemiological studies are recent, and some of the behavioural and biomarker studies are relatively old.)

These five explanations are not mutually exclusive, and all may be partially correct. Nor is it possible to confidently determine the relative roles of each explanation, although it seems likely the first explanation is likely to be at least part of the total explanation. This lack of certainty makes it very difficult to propose policy options on tar and nicotine levels for the future - the subject of the Part 6 of this report.

## **PART 4: WHAT IMPORTANT QUESTIONS REMAIN UNANSWERED?**

Despite the abundant international research, some important questions remain unanswered. Four stand out as requiring comment here. First, what is the best predictor of nicotine uptake: yield, or concentration and content? We are aware of no research on this. Nicotine content and concentration may also explain some of the variable findings in the research presented in the previous sections. For example, it may be that studies of cigarettes with similar yields, but different nicotine content or concentration, will find different intake results. A cynic may argue that because there is relatively little variation in nicotine content and concentration between cigarettes (compared to some variation in yields), and that there is relatively little variation in nicotine intake, therefore nicotine content and concentration are superior predictors of intake than yield. However, it would be necessary for research testing this hypothesis to include cigarettes with a greater range of nicotine content and concentration than those currently available.

The next unanswered question is whether a smoking test that better approximates how smokers smoke than does the current FTC trade test will better predict nicotine, tar and CO uptake, and, eventually, the health effects of smoking tobacco. Work is in progress in Massachusetts, United States, on using a modified smoking test, with modified nicotine and tar yields recently published on the internet (<http://www.cancer.org/>). (The association of the modified smoking test yield results with intake remains to be investigated.) However, any modified smoking-test method will have definite limitations: on what type of smoking behaviour should such a modified test be based - that of a low, medium, or high-yield smoker? This is important. The Massachusetts testing method simulates the behaviour of the average smoker of, presumably, average yield cigarettes. This may more accurately predict the intake of tar and nicotine for the average smoker of average yield cigarettes, but not necessarily the intake of smokers of low-yield cigarettes who have different smoking behaviour again. A possible solution to this is to have different testing parameters for different types of cigarettes, but this becomes complicated. Additionally, changes to the standard FTC smoking test will not allow comparisons of smoke yields over time. While alterations to the testing parameters of the smoking test may be useful in certain situations, our view is that it will not be a panacea for deficiencies identified in the current FTC smoking test.

The third, and probably most important, unanswered question is whether lower nicotine levels (measured as yield, content or concentration) in cigarettes reduce the chance of an experimental smoker becoming addicted. This is a critical deficit in our knowledge. There are two possible reasons to reduce tobacco smoke yields: a) to reduce exposure to health damaging substances, and b) to stop people becoming addicted in the first place. Much research has already been reviewed in this report on the former, but there has been no research on the latter (Benowitz and Henningfield, 1994a). Benowitz and Henningfield (1994b) summarise:

“An important, if not the most important, component of a policy to reduce tobacco use in the population is to prevent the development of nicotine addiction in young people. Young people do not start smoking because they are addicted, but rather because of psychosocial and environmental influences, particularly peer influences, psychological factors, and advertising. Young people generally underestimate the addictiveness of nicotine, and most of them at first intend to smoke only for a few years. However, once they begin to smoke, many become addicted to nicotine, and this addiction sustains the self-injurious behaviour into adulthood. The result of nicotine addiction is a 40 percent probability of premature death from illness caused by tobacco. It is difficult to prevent adolescents from experimenting with cigarettes. However, by regulating the availability of nicotine in tobacco products, it may be possible to prevent the transition from experimental to occasional smoking to addiction.”

While there is ample evidence demonstrating that experienced smokers can compensate for variations in nicotine yield, maintaining the necessary nicotine intake to support their addiction, it seems reasonable to assume that an inexperienced and non-addicted smoker will be receiving nicotine doses more in proportion to the stated nicotine yield. Therefore, reducing the nicotine yield *may* mean that inexperienced smokers are more likely to pass through a phase of experimental smoking without becoming addicted. It would be ethically very difficult to conduct research examining this possibility (Benowitz and Henningfield, 1994a). However, if a moderate reduction in the nicotine levels in cigarette tobacco prevented even a small percentage of experimental smokers becoming lifelong smokers, the health gains to the population would be substantial and significant. The importance of this possibility, although being theoretical and lacking in evidence, cannot be overstated.

Fourth, it is now known that nicotine intake can be modified by the addition of ammonia to tobacco. There are likely to be other chemical additives and manipulations that can further potentiate nicotine intake over and above the effect of yield, content, concentration, and compensatory behaviour. Any control of nicotine intake via control of tobacco constituents will require knowledge of all means of potentiating nicotine intake.

## **PART 5: OPTIONS FOR CONTROLLING TAR AND NICOTINE IN CIGARETTE TOBACCO**

This section begins with a review of what policy options other countries and jurisdictions have pursued in the past. Then, four policy options for controlling tar and nicotine levels are presented, with a discussion of their advantages and disadvantages. Because of deficits in research identified above, and the lack of research on the proposed nicotine yields for some options (i.e. an option to reduce nicotine yields to zero), much of the discussion of options steps necessarily beyond evidence into opinion. Finally, nicotine and tar yields in current labelling on New Zealand cigarette packets is considered.

### **Approaches of other countries**

#### **Product modification programme in the UK**

For more than 20 years there has been a coherent 'product modification programme' for cigarettes in the United Kingdom (Waller and Froggatt, 1996). In 1993, the sales-weighted average yield for tar was 11 mg, and for nicotine about 0.9 mg. The 'product modification programme' was driven by the Independent Scientific Committee on Smoking and Health (ISCSH), an advisory body to Ministers and the tobacco industries, established in 1973 and disbanded in 1991. Voluntary agreements between government and the tobacco industry were reached in 1973, 1977, 1980 and 1984, including targets for nicotine and tar yields. (It must, however, be noted that a tax on tar was also used (Gray, 1996)). A programme of incremental steps involved implementing filters, using more porous paper, and so on. Waller and Froggatt (1996) argue that the programme has been successful in causing a reduction in lung cancer rates among smokers. The incremental nature of the programme was seen as important to keep smokers on side. For example, the tar and nicotine yields of cigarettes were gradually reduced so that brand loyal smokers were slowly adjusted to lower levels. Waller and Froggatt (1996) argue that meeting the targets of reducing nicotine and tar yields was met more by gradual reduction of yields of loyal smokers' brands than by consumer-driven switching to lower-yield brands. This latter point is, in our view, extremely important. The United Kingdom have achieved reductions in the sales-weighted average yields, not by consumer driven choice following educational campaigns informing smokers about yields as in the United States, but by just gradually reducing yields across all brands, with little consumer awareness or impact. This has, therefore, probably also reduced the likelihood of smokers turning to low-yield cigarettes as a 'healthy' option, rather than quitting. Put another way, it may be that the UK approach is less likely to result in smokers changing to low-yield cigarettes rather than quitting, compared to the US approach. In health promotion terms, the UK approach is more one of health protection at the population level, or supportive environments, and the US approach is more one of health education at the individual level, or building personal skills (World Health Organisation et al, 1986).

The United Kingdom is now subject to the European Union's regulations on tar and nicotine, but is well on the way to meeting targets for 1997. Finally, it is worth noting that Waller and Froggatt (1996) state that the assumed reduced chance of inexperienced

smokers becoming addicted is a prime motivator for incremental and gradual reductions in the nicotine yield.

### **Consumer choice and marketing in the United States**

Cigarette manufacturers in the United States have led the world in trying to make cigarettes 'safe', and tobacco companies have in the past attempted to market low-yield cigarettes as 'safer' (Warner and Slade, 1992). In recent decades, tobacco companies have not been allowed to advertise with explicit claims concerning cigarette safety - but many advertisements still imply relative safety by stressing mildness or low-yields (Cohen, 1996). As of 1997, the average nicotine yield for United States-manufactured cigarettes was less than 0.9 mg, and the average tar was about 12 mg.

### **Voluntary agreement in Australia**

A voluntary agreement between industry and government in Australia permits no cigarette produced since 1988 to have a tar yield greater than 14 mg (Gray 1996). This followed previous voluntary agreements in 1982 and 1986 establishing 18 and 16 mg upper limits, respectively. As of 1996, 85 percent of cigarettes produced less than 12 mg tar, and a third produced less than 6 mg tar. However, it may be that the reduction in tar yields in Australia has been less a result of the voluntary agreements than a result of excise tax on tobacco, levied by weight (Winstanley et al, 1995). Between 1975 and 1992 the weight of tobacco in each cigarette has fallen, resulting in a corresponding reduction in yield.

### **The European Union**

The European Union has mandated an upper limit of 12 mg tar by 1997, replacing the current upper limit of 15 mg (Gray 1996).

## **Options for controlling nicotine and tar**

So as not to preclude the use of alternative measures to the standard FTC smoking test yields, tar and nicotine measures under the following options should be interpreted as potentially substitutable by a revised yield measure, or nicotine content and concentration in the case of nicotine.

### **Option 1: Do not pursue harm minimisation policy for tobacco**

There is considerable unease in the tobacco control community about allowing a policy focus on reducing the harm from tobacco (reducing the number of cigarette per day excepted), as opposed to policy that aims to stop, or prevent, people smoking (Chapman, 1996). However, there appears to be a growing emphasis on harm minimisation via controls on tobacco constituents (Warner et al, 1997). A recent United Nations-sponsored roundtable on the reduction of tobacco smoking by alternative nicotine delivery systems concluded that:

“Although tobacco prevention efforts are critical to long-range public health efforts, in the intermediate term it is necessary, and possible, to reduce death and disease among existing smokers through cessation efforts. All present forms of tobacco consumption are associated with adverse health effects and should be strongly discouraged. However, it is now evident that the risk of death and disease is related to the amount and nature of tobacco exposure.”

“The foregoing observations lead to the conclusion that existing cigarette smokers would benefit from support in their efforts to achieve smoking cessation. Furthermore, it is increasingly recognized that for health problems, such as illegal drug dependence or malaria, it is important for prevention and treatment efforts to occur in a simultaneous and coordinated fashion. Thus to maximise the achievement of reduced tobacco-caused death and disease in existing and in future generations, it is important to adopt a triadic approach of co-ordinated (1) tobacco use prevention, (2) cigarette smoking cessation, and (3) reduction of exposure to tobacco toxins in people who are unable or unwilling to completely abstain from tobacco.” (UN System Focal Point on Tobacco or Health, 1997)

This ‘triadic approach’ confirms a role for harm minimisation in a total tobacco control strategy, and seems a sensible starting point for developing tobacco control policy. It may be useful though to break the third component of the triad into two sub-components: reduction in the number of cigarettes per day smoked, and control of tobacco constituents or product modification. How much resource should be allocated to the latter sub-component is difficult to determine. Moreover, what specific harm minimisation strategies should comprise the third component of the triad is debatable. The remaining options proposed in this report consider possible harm minimisation strategies for tobacco constituents.

### **Option 2: Reduce nicotine levels in manufactured cigarettes to below the addictive threshold**

This is a bold and ambitious option. It focuses more on preventing nicotine addiction than reducing tobacco harm. It was first proposed in detail by Benowitz and Henningfield in 1994 (Benowitz and Henningfield, 1994b), and has been the subject of considerable debate since then. Benowitz and Henningfield presented their option in the context of the FDA’s 1994 announcement of their intention to consider regulating nicotine. Using assumptions derived from available research, they calculated that cigarettes would need a nicotine *content* of less than 0.4 to 0.5 mg to prevent addiction being maintained. That is a content 20 to 30 times lower than commonly retailed cigarettes today. They proposed that it be phased in over 10 to 15 years to allow already addicted smokers time to adjust and withdraw slowly. This strategy would, of course, require regular measurements of nicotine content and concentration in addition to nicotine yields. Benowitz and Henningfield do issue caveats that, in the absence of supporting research, the option is theoretically justified only. They also acknowledge that to prevent short to medium-term harm to current smokers, current tar yields would also have to be lowered to prevent an increase in tar intake due to compensation. Emphasising the long-term and population-based focus of Benowitz and Henningfields’ option, they state that there may conceivably be increased health harm from cigarettes in the first 10 to 15 years due to compensatory increase in tar intake, but that in the long-term the individual smokers will benefit if they stop smoking following compulsory withdrawal, and future generations will benefit enormously.

Other commentators, while acknowledging the huge potential of this ‘brave-new-world’ solution to tobacco control, were quick to point out disadvantages of the option. Hughes (1994) pointed out that low-yield cigarettes may be more likely to induce adolescent

smoking as they are less harsh. Benowitz and Henningfield (1994a) rebutted this by pointing out that few adolescents smoke 'mild' cigarettes. Hughes also challenged the derivation of assumptions for the 0.4 to 0.5 mg nicotine content threshold, stating that, as it was based on self selected smokers of five or less cigarettes per day, the assumptions may not apply to other smokers. Finally, Hughes points out that the policy may cause cigarettes to be perceived as safe, increasing experimentation.

Foulds and Ghodse (1995) argued that the subjection of the total population of smokers to compulsory withdrawal would be likely to create a black market in nicotine, or alternative nicotine delivery devices. Instead they advocate the alternative approach of reducing tar levels while maintaining nicotine levels, such that smokers end up with virtually smokeless cigarettes, or they switch to nicotine inhalers (or some other delivery device).

Building on from the work of Benowitz and Henningfield (1994b), and review of Foulds and Ghodse (1995), there is an extension to the basic idea proposed by Benowitz and Henningfield (1994b) that warrants consideration. That is to make alternative nicotine delivery systems readily available to addicted smokers so they can migrate from tobacco to purely nicotine delivery systems, ranging from patches to lollipops (Warner et al, 1997). The tobacco industry is also piloting devices that heat tobacco rather than burn it (e.g. the Eclipse and Premier 'cigarettes'), putatively resulting in large reductions of toxins inhaled by the smoker. Some argue that the advent of the Eclipse and Premier cigarette is simply the third wave of design modifications to cigarettes driven by health concerns (the previous two being filters, then low-yield cigarettes), and that it will likewise not result in the substantial reductions in harm to health claimed by the tobacco industry, and serve only to maintain market share for tobacco companies.

Alternative nicotine delivery devices, generally, are currently the subject of much debate within tobacco control forums. For example, a workshop titled "Alternative Nicotine Delivery Systems: Harm Reduction and Public Health" was held in Toronto during March of 1997, with debate centred around five questions:

- ?? should nicotine levels in cigarettes be minimised or maximised?
- ?? should long-term use of alternative nicotine delivery systems be actively encouraged in those who appear unable to quit?
- ?? should tobacco products and non-tobacco products containing nicotine be regulated separately or together?
- ?? how freely should alternative nicotine delivery devices be available to the public (e.g. prescription only, or over-the-counter), and from whom (tobacco companies, pharmaceutical companies, or other)?
- ?? should nicotine replacement therapies be subsidised?

The answers to these questions were far from obvious, and respected experts in tobacco control presented opposing answers to each question. An additional point is that nicotine delivery devices are more expensive than cigarettes, and less readily available. This creates a seeming paradox whereby people addicted to nicotine are ostensibly 'forced' to smoke cigarettes, rather than to use 'safer' nicotine delivery systems. Warner et al (1997) have proposed a middle road whereby the least hazardous nicotine delivery devices are made

available to the public. While a review of nicotine delivery systems is beyond the scope of this report, it is important to recognise that such devices could be an important component/complement of any strategy to control nicotine and/or tar levels.<sup>2</sup> Debate is also likely to continue in tobacco control circles. We recommend that the Ministry of Health keep a watching brief on developments with nicotine delivery systems, until such time as some form of consensus as to the role of alternative nicotine delivery devices in tobacco control emerges.

Returning to the crux of Option 2, to reduce nicotine levels in manufactured cigarettes to below the addictive threshold, the foregoing discussion can be developed into a list of advantages and disadvantages. The advantages for Option 2 are:

- ?? a potential for huge health gains by stopping people taking up smoking, and causing people to stop smoking, rather than attempting to make cigarettes marginally less hazardous
- ?? it tackles the breadth of tobacco control in one policy option

The disadvantages are numerous, including:

- ?? achieving political, industry, and public support to implement this option is unlikely to be easy, particularly since it lacks supporting experimental or epidemiologic evidence<sup>3</sup>
- ?? the current ethos of individual rights and freedoms are unlikely to be conducive to withdrawal of the 'right' to smoke tobacco with 'sufficient' levels of nicotine
- ?? black markets in cigarettes may be established, causing crime to be associated with tobacco in much the same way as it is with other addictive drugs (and cannabis)
- ?? smokers may not quit nicotine, but move to alternative nicotine delivery devices. This is probably 'safer', but not ideal
- ?? to have a substantial chance of effect, many countries would have to embark on the policy concurrently
- ?? even though the reduction is primarily of nicotine, not tar, the emerging cigarette may be perceived as safer, increasing use
- ?? a low-yield cigarette may be more attractive to some inexperienced smokers, discounting the potential advantage of being less addictive to the inexperienced smoker
- ?? without simultaneous and proportional reductions in tar, the short to medium-term effect for addicted smokers may be that they are exposed to more harmful tobacco constituents than currently
- ?? enforcement costs to government are likely to be high
- ?? the tobacco industry may find ways around the policy by increasing the bioavailability even further for the nicotine in the cigarette, thus preventing reduction of intake below the addictive threshold. The addition of ammonia to tobacco to increase nicotine intake is one current example.

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<sup>2</sup> A useful, and current, starting point for the interested reader is the article in the Journal of the American Medical Association by Warner et al (1997).

<sup>3</sup> This disadvantage applies to the other options presented in this report in varying degrees, but is probably most prominent for this option.

### **Option 3: Moderate reductions in both nicotine and tar**

This option approximates the gradualism and incrementalism of the UK modification programme. As such, it still aims to lower the addictiveness of cigarettes, but also aims to reduce the harm caused by manufactured cigarettes. Both are unproven, but theoretically likely, outcomes of lowering nicotine and tar further in New Zealand. The reason the possible harm minimisation is an unproven option is that the epidemiological evidence for health effects relates almost exclusively to historically higher nicotine and tar levels. For a health gain to accrue from further reductions requires extrapolating down the dose-response curve. If there were to be reduced harm, it would be considerably less than would be associated with stopping smoking altogether.

The method of implementation could be either a voluntary agreement with the tobacco industry, regulations under the Smoke-free Environments Act 1990, or by a tax on tar and/or nicotine.

A risk of this option is that the availability of low-yield cigarettes may substantially reduce rates of smoking cessation. It appears that this may have happened, in the United States at least, due to the perception by smokers of low-yield cigarettes as a 'safe' option (Giovino et al, 1996). This has led some commentators to speculate that the movement to low-yield cigarettes in recent decades *may* have increased the aggregate societal burden from tobacco, compared to a scenario where low-yield cigarettes had not been promoted, directly or indirectly, as 'safer' (Warner et al, 1997). This might be applicable to the United States where tobacco companies have attempted to promote low-yield cigarettes as safer to the consumer. Such a danger may, however, be averted with stringent marketing controls on the tobacco industry, and an across-the-board policy that slowly reduces nicotine and tar levels in cigarettes with little apparent effect to the consumer, as discussed on page 46 of this report.

One emerging concern with focusing on just tar and nicotine is that harmful constituents not included by the umbrella category of tar may be missed. Tar includes the majority of mutagenic and carcinogenic agents in tobacco smoke (IARC, 1986), and, historically at least, the commonly known health-damaging substances have tended to vary with tar (Hoffmann and Hoffmann, 1997). However, other tobacco constituents, like CO and tobacco-specific N-nitrosamines (TSNAs), may be exceptions to this rule. Therefore, it is possible that, by focusing exclusively on tar, some of the most harmful tobacco constituents will be overlooked. There is some evidence for this possibility with the observation of a relative increase in adenocarcinoma of the lung, putatively due to increasing TSNAs in cigarette tobacco (Wynder and Muscat, 1995). Further and future possible exceptions to the rule cannot be discounted if, in order to meet imposed tar and nicotine levels, the tobacco industry is forced to change the design of cigarettes and levels of harmful constituents not included in tar rise concurrently. Guarding against this possibility cannot be assured as some harmful tobacco smoke constituents may not yet have even been identified. With that caveat in mind, it seems prudent that periodic monitoring of known harmful constituents, other than tar, should be carried out, as part of Option 3, to keep abreast of trends. A recent report from the US Department of Health and Human Services (1996) recommends that the standard FTC smoking protocol should not be extended to include

other harmful substances *that are published simultaneously with tar, nicotine and CO yields*, in order to avoid confusing smokers. However, that does not preclude monitoring for other harmful constituents to keep regulatory and policy organisations informed, without printing the results on packets of cigarettes.

The advantages of Option 3 are:

- ?? it is probably achievable in New Zealand
- ?? it could bring New Zealand yields in line with United States, Australian and European Union levels
- ?? it may reduce the number of experimental smokers becoming addicted smokers
- ?? it may reduce the harm from tobacco for already addicted smokers
- ?? while benefits to public health are not guaranteed, it seems unlikely that the net effect would be deleterious to public health, so long as tar yields are proportionately reduced as much as, or more than, reductions in nicotine. (A caveat here is the possibility of rises in the levels of harmful tobacco constituents not included in tar.)

The disadvantages of this approach are:

- ?? lowering the yields of cigarette tobacco may be perceived by some as making smoking safe, and any benefits incurred from this option may be negated if this causes more people to take up smoking, or to continue smoking
- ?? because of possible compensatory smoking behaviours, further gradual reductions in tar and nicotine levels are not guaranteed to result in substantial health gains
- ?? if tar is the most harmful component in tobacco smoke, reducing tar and nicotine together may not be as effective in reducing harm from smoking tobacco as reducing tar only and maintaining nicotine at current levels
- ?? reductions in tar may not result in reductions of all harmful tobacco constituents, known or unknown. A current example is nitrate derivatives, such as TSNAs.

#### **Option 4: Reductions in tar, but maintain nicotine**

The argument to support this option is that smokers tend to smoke in such a way as to maintain a certain nicotine intake. Therefore, harm may be minimised by maintaining nicotine yield at a constant level and reducing tar yield relative to this. Many of the issues for Option 4 have already been discussed in relation to the above options. Option 4, like Option 3, could be introduced in an incremental and gradual manner. The complementary monitoring of harmful constituents other than tar seems appropriate in combination with Option 4 in the same way as with Option 3.

Compared to Option 3, the main advantage is that the reduced harm to already addicted smokers may be somewhat greater. The research evidence suggests that the extra decrease in, say, intake of tar from smoking a maintained nicotine cigarette is not much greater than that for a cigarette reduced in both nicotine and tar. Therefore, the reduction to harm for Option 4 compared to Option 3 for the *already addicted* smoker, who will not cease smoking, is likely to be modest only.

The main disadvantage compared to Option 3 is that there would be no reduction in nicotine levels, and therefore no chance of reducing the number of experimental smokers that

become addicted smokers. However, in the absence of research evidence, whether reducing nicotine would actually reduce the chances of addiction occurring remains theoretical.

If a gradual and incremental approach to controlling tar and nicotine levels is favoured, the choice seems to be between Option 3 and Option 4. The main decision point therein is whether the potential further decreased harm to already addicted smokers by Option 4 compared to Option 3 would outweigh the potential (and theoretical) increased chance of experimental smokers becoming addicted. Unfortunately, there is not enough research evidence to make a scientifically informed decision regarding this trade-off. It may be best to pursue a combination of Option 3 and Option 4.

### Summary

Given incomplete (and often conflicting) research evidence, and a lack of consensus among experts in the field, it is not possible for us to make an emphatic or definitive scientifically-based recommendation to the Ministry of Health on which option for controlling nicotine and tar is the best option. Instead, we recommend that the Ministry of Health:

?? consider each of the options detailed above

?? consider the complementary roles of:

?? alternative nicotine delivery devices

?? monitoring harmful tobacco constituents other than tar

?? maintain a watching brief on international developments, particularly new research and any emerging expert consensus.

It is also prudent to note that there are opportunity costs from pursuing Options 2, 3 and 4. It may be that resources that would have to be dedicated to implementing one of these options could be used more effectively and efficiently elsewhere in tobacco control (e.g. smoking cessation programmes), or in public health generally

While not being able to make a definite scientific recommendation, the Ministry of Health may be interested in our opinion having regard for the information we have been able to access during the preparation of this report. We believe that priority should be assigned to a policy that combines Options 3 and 4. The aim would be to, achieve an incremental and gradual reduction in tar and nicotine levels to at least those of North America, Europe and Australia, and at the same time gradually reduce the tar to nicotine ratio. This could be brought about by regulations under the Smoke-free Environments Act 1990, a voluntary agreement with the tobacco industry, or taxation. In the absence of any modification to the FTC smoking test, or the complementary use of nicotine content and concentration, a ceiling limit for the nicotine and tar yield could be set. The European Union ceiling limit of 12 mg of tar seems a sensible target, and could be achieved in, say, five years. Regarding nicotine, a yield of 1.0 mg could be set as a ceiling, as per the 'global cigarette' (Gray, 1996), but this could see a rise in the tar to nicotine ratio. The current ratio of tar to nicotine for New Zealand cigarettes, using the sales-weighted average yields for 1996, is 11.64 (see page 18 of this report). If 12.0 and 1.0 mg of tar and nicotine, respectively, were set as the yield limits, then the ratio of the *ceiling limits* would be 12. It may be more prudent, therefore, to set the limit for nicotine at 1.1 mg, making a tar to nicotine ratio (using the ceiling limits) of

10.9. The adoption of an incremental and gradual combination of policy Options 3 and 4 in New Zealand would not preclude moving to Option 1 if, at some stage in the future, this latter option became the most favourable.

### **Options for measuring tobacco constituents and labelling cigarettes**

Alternative measurement tests need to be considered for tar and nicotine. However, more research would be required on either modified smoking tests, or the use of nicotine content and concentration, before either option could seriously be considered as possible substitutes for the current FTC smoking test. No recommendation can be made to change the current system until that research is available. Regarding the use of nicotine content and concentration, research is urgently needed to determine whether these measures more accurately predict nicotine intake than does nicotine yield. As such, this would be relatively simple research. However, there is little variation in nicotine content and concentration in currently available manufactured cigarettes to allow a robust investigation.

Dependent on future research, likely options for measuring tobacco constituents are:

?? status quo (i.e. retain FTC smoking yield test)

?? change to new standard smoking test

?? change to, or add, nicotine content and concentration to current nicotine yield measurements.

In the meantime, changes could be made to the current labelling of cigarette packets using the FTC smoking test yield results. The FTC smoking yields clearly do not have a direct linear relationship with intake. A possible relationship of nicotine yield and intake was shown in Figure 1 (page 42). (The same caveats expressed on page 42 of this report regarding the figure also apply here.) With regard to the current labelling of cigarette packets, the consumer is under the impression that a halving of yield should be accompanied by a halving of intake (Cohen, 1996). This is clearly false. Using Figure 1, a halving of nicotine yield from 1.0 to 0.5 mg does not result in a halving of nicotine intake, but perhaps only a 10 to 20 percent reduction. The same applies for tar yields. This lack of a linear relationship has led some commentators to argue for an abandonment of stated nicotine yields on the sides of cigarette packets, as they are misleading to smokers (Henningfield et al, 1994). An alternative schema for the labelling of cigarettes was proposed by Henningfield et al (1994), based on using the yield test results, but not presenting them per se. Instead, categories of yields would be based on non-uniform divisions of yield results that would reflect meaningful differences in intake. The exact schema proposed by Henningfield et al (1994) was for nicotine yields as follows:

?? nicotine free (? 0.01 mg)

?? very low-nicotine (? 0.17 mg)

?? low nicotine (? 1.0 mg)

?? regular (> 1.0 mg).

The 0.17 mg and 1.0 mg nicotine yield divisions are superimposed on Figure 1, and suggest that there is likely to be, on average, a meaningful difference in intake between cigarettes less than or equal to 0.17 mg compared to cigarettes with a yield of between 0.17 and 1.0 mg. We endorse this approach, but propose some amendments for debate. First, the 0.17 mg level is based on the Benowitz and Henningfield (1994) paper proposing the option to reduce nicotine yields to below the addictive threshold. As such, the 0.17 mg figure was derived from assumptions, and conveys an air of over-precision; 0.20 mg would be more appropriate, and adequate. Second, simply having one range of nicotine yields from 0.2 to 1.0 mg would be insensitive to likely differences in intake across that range. Whilst it is recognised that compensation is definitely incomplete below yields of about 0.2 mg, it is likely that, on balance, there are also meaningful reductions in intake below about 0.5 mg nicotine yield (US Department of Health and Human Services, 1996). Third, if ceiling limits are imposed on the tar and nicotine yields of New Zealand cigarettes, as discussed previously, then it seems sensible to assign the highest possible category with the label 'high'. Therefore, for the purposes of debate, we propose the following schema:

- ?? nicotine free (? 0.01 mg)
- ?? very low-nicotine (? 0.20 mg)
- ?? low nicotine (? 0.5 mg)
- ?? medium nicotine (? 1.0 mg)
- ?? high nicotine (> 1.0 mg).

It is recommended that the Ministry of Health consider changing the labelling requirements for cigarettes from stated absolute yields to qualitative categories. Tar yields could be developed into similar categories.

A parallel consideration further endorses moving to some controlled schema for labelling of cigarette packets in relation to yield (or any future measure). The current use of descriptive labels like 'mild', 'supermild', and 'ultralight' that tobacco companies use on some products may be construed as misleading. In New Zealand a 'mild' cigarette (e.g. Benson and Hedges golden mild - 0.9 mg nicotine, 10 mg tar) may have the same tar and nicotine yield as the sales-weighted average for the United Kingdom, and greater than the sales-weighted average for Australia. Moreover, research has shown that the nicotine content and concentration of New Zealand-manufactured cigarettes is similar for 'mild' and 'regular' cigarette tobacco (Blakely et al, 1997). This means that, in New Zealand at least, the design features of the cigarette are used to determine the nicotine yield more than the actual nicotine content and concentration of the cigarette tobacco. Given the relative ease with which these design features are overcome (compensation), the New Zealand smoker of 'mild' cigarettes is probably extracting the equivalent amounts of tar and nicotine as a regular cigarette smoker.

## KEY POINTS FROM THE LITERATURE REVIEW

### **Health effects**

- ?? Lower tar and nicotine yield cigarettes do lower the risk of lung cancer
- ?? Lower tar and nicotine yield cigarettes probably lower the risk of pulmonary symptoms and disease
- ?? Lower tar and nicotine yield cigarettes possibly lower the risk of coronary heart disease
- ?? Confounding is unlikely to explain the associations of increasing tar and nicotine yields with increasing risks of disease, and exposure misclassification bias is likely to cause the actual associations to be underestimated.

### **Compensatory smoking**

- ?? In the natural setting, most studies find that smokers almost fully compensate for varying nicotine yields in the range of approximately 0.6 to 1.5 mg, obtaining on average about 1 mg of nicotine per cigarette smoked, regardless of nicotine yield
- ?? Most experimental studies find that smokers can compensate for varying nicotine yields, but that the compensation is not complete, being about 50 to 70 percent.
- ?? Below nicotine yields of about 0.6 mg, compensation becomes increasingly difficult and nicotine intake falls more rapidly.
- ?? Tar intake varies roughly in proportion to nicotine intake, although it may be modified by variation in the tar to nicotine ratio.
- ?? There is some evidence for a lower tar intake from a cigarette with low-tar, medium nicotine (maintained nicotine cigarette), compared to a low-tar, low-nicotine cigarette. However the difference in tar intake between these two types of cigarette appears to be relatively small.
- ?? Nicotine is probably the biggest determinant of compensatory smoking behaviour. Tar, taste, and other cigarette attributes probably also have a role, but less so than nicotine.

Recommendations are on page 11 of this report.

## APPENDIX 1: SUMMARIES OF THE METHODS AND RESULTS FOR STUDIES ON THE HEALTH EFFECTS OF VARYING LEVELS OF TAR AND NICOTINE

**Table 4: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with pulmonary function and disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Hawthorne and Fry 1978	Smokers were divided into four categories of tar: ?<17 mg ??17-22 mg ??23-27 mg ???28 mg.	<p><b>Methods</b></p> <p>??Three consecutive cross-sectional surveys in west central Scotland (1965-68, 1970-72, 1974-75), that were subsequently followed-up as cohorts.</p> <p>??Prevalence measures were bronchitis, shortness of breath, wheeze, phlegm, angina and possible myocardial infarction.</p> <p><b>Results</b></p> <p>??Baseline prevalences were reported as showing significant differences only for men in the 1974-75 survey. Among filter cigarette smokers, 23-27 mg smokers had a significantly (<math>p&lt;0.1</math>) raised prevalence of shortness of breath and wheeze compared to ?22 mg smokers, the relative risk being approximately 1.4 for both symptoms. Age and number of cigarettes per day were adjusted for.</p> <p>??No significant difference by tar yield was found for mortality during follow-up.</p> <p><b>Comments</b></p> <p>??A narrow range of tar yields for the first two surveys may have prevented finding significant differences in the prevalence of symptoms.</p> <p>??Most deaths were contributed from subjects in the first survey where there was little variation in the tar yields.</p>
Higgenbottam et al 1980	Smokers were divided into four tar yield categories on the basis of their usual brand: ??18 - 23 mg ??24 - 27 mg ??28 - 32 mg ??? 33 mg.	<p><b>Methods</b></p> <p>??Cross-sectional study of 7,600 smokers and 6,693 ex-smokers (Whitehall Study).</p> <p><b>Results</b></p> <p>??Tar yield was not associated with FEV<sub>1</sub>, adjusting for age, height and number of cigarettes smoked per day. (A subsequent re-analysis by Lee (1980) did show a significant effect, but the magnitude was small.)</p> <p>??Tar yield was associated with phlegm production, such that among smokers of 1-9 cigarettes per day the prevalence of phlegm production for high-tar smokers was over one and a half times the prevalence for low-tar smokers. However, the effect reduced to near negligible for smokers of more than 20 cigarettes per day.</p>

**Table 4: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with pulmonary function and disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Schenker et al 1982	<p>Tar was divided into three categories:            ??10-19 mg (low)            ??20-29 mg (medium)            ??? 30 mg (high)</p> <p>Mean tar content was 14.7 mg (sd 4.7).</p>	<p><b>Methods</b>            ??Cross-sectional study of 5,686 women (1,424 current smokers) administered a questionnaire determining chronic cough, chronic phlegm, wheeze and dyspnoea.</p> <p><b>Results</b>            ??Tar content was significantly (<math>p&lt;0.05</math>) associated with chronic cough. The relative risk for medium and high-tar smokers compared to low-tar smokers was 1.45 and 2.01 respectively, controlling for number of cigarettes smoked, depth of inhalation, socio-economic status and years smoked.            ??Tar content was nearly significantly (<math>p=0.077</math>) associated with chronic phlegm. The relative risk for medium and high-tar smokers compared to low-tar smokers was 1.28 and 1.59 respectively, controlling for the same factors above.            ??Tar content was not significantly associated with wheeze or dyspnoea.</p>
Petitti and Friedman 1985	<p>Tar was treated as a continuous variable, and relative risks reported per 5.0 mg increase in tar.</p> <p>About two thirds of the cohort smoked cigarettes greater than 15 mg in tar.</p>	<p><b>Methods</b>            ??Cohort study of 16,270 current, regular smokers enrolled in a health plan. Respiratory disease diagnoses registered on hospitalisation were the outcomes.</p> <p><b>Results</b>            ??Relative risk of diseases of respiratory system was 0.97 (95% CI 0.84-1.13), controlling for age, sex, race, BMI and number of cigarettes per day.            ??There were 110 respiratory disease cases only.</p>
Sparrow et al 1983	<p>Tar was treated as both a continuous and a categorical variable, the latter being:            ??0-16 mg            ??17-19 mg            ??20-21 mg            ??? 22 mg</p>	<p><b>Methods</b>            ??Longitudinal study of 1,355 men, including 383 current smokers and 555 former smokers. Both baseline and 5 year follow-up measures were taken.</p> <p><b>Results</b>            ??Tar content was evenly distributed between the four categories. (The actual range of tar contents was not stated, and it can only be assumed that most of the tar contents were distributed in the 15 to 25 mg range.)            ??Controlling for height, cigarettes per day and age, tar content was neither significantly associated with FEV<sub>1</sub> nor FVC at baseline.            ??Controlling for height, cigarettes per day, age and baseline pulmonary function, tar content was neither significantly associated with FEV<sub>1</sub> nor FVC at five year follow-up.</p>

**Table 4: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with pulmonary function and disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Brown et al 1991	<p>Smokers were divided into three categories of tar yield:</p> <ul style="list-style-type: none"> <li>??&lt;12 mg</li> <li>??13-14 mg</li> <li>??&gt;15 mg.</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cross-sectional health survey of 2,801 people that smoked, and nominated a preferred brand of cigarette.</li> <li>??Outcome was chronic cough and chronic phlegm.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??Women in the high-tar category had higher rates of chronic cough and chronic phlegm than women in the low-tar category (relative risk 1.20 and 1.22 respectively, <math>p &lt; 0.05</math> for both), controlling for cigarettes per day, number of years smoking and social class.</li> <li>??No significant differences were found for men.</li> </ul> <p><b>Comment</b></p> <ul style="list-style-type: none"> <li>??There was a narrow range of tar yields.</li> <li>??Control of confounding may not have been complete for women.</li> <li>??Few men were low-tar yield smokers (11.4%).</li> </ul>
Krzyanowski et al 1991	<p>Nicotine and tar yields were treated as continuous variables. Relative risk were reported per 10 mg of tar and 1 mg of nicotine. The distribution of yields was as follows:</p> <ul style="list-style-type: none"> <li>??median tar yield 10 to 12 mg (20<sup>th</sup> percentile 8.3 mg, 80<sup>th</sup> percentile 16.1 mg).</li> <li>??median nicotine yield 0.8 to 0.9 mg (20<sup>th</sup> percentile 0.6 mg, 80<sup>th</sup> percentile 1.06 mg).</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??690 cigarette smokers assessed in one or more of three consecutive health surveys.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??Significant (<math>p &lt; 0.05</math>) associations of both tar and nicotine yields were found with prevalent wheeze. This was after controlling for age, sex, number of cigarettes smoked, age of starting smoking and depth of inhalation. The associations were modified by the number of cigarettes smoked per day such that there were odds ratio of 1.70 and 1.35 for wheeze per 10 mg of tar for smokers of 5 and 15 cigarettes per day respectively. Likewise there were odds ratios of 2.64 and 1.69 per 1 mg of nicotine for smokers of 5 and 15 cigarettes per day respectively.</li> <li>??Non-significant (but positive) independent associations of both tar and nicotine were found with chronic cough, chronic phlegm and dyspnoea.</li> <li>??No significant independent associations of both tar and nicotine were found with FEV<sub>1</sub>, although there were complex interactions of tar and nicotine yields with number of cigarettes smoked per day.</li> </ul>

**Table 4: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with pulmonary function and disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Withey et al 1992	<p>Subjects were randomised to smoke one of three cigarettes:</p> <ul style="list-style-type: none"> <li>??low-tar (9.5 mg), middle nicotine (1.16 mg) (LM)</li> <li>??middle-tar (13.8 mg), middle nicotine (1.24 mg) (MM)</li> <li>??low-tar (9.7 mg), low-nicotine (1.04 mg) (LL).</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Randomised controlled trial of 643 men, randomly selected from the electoral roll.</li> <li>??Inclusion criteria was being male and a regular middle-tar (&gt; 12 mg; mean tar 15.3 mg and mean nicotine 1.43 mg) cigarette smoker.</li> <li>??Smokers were randomised to one of three cigarettes, and followed-up for 24 weeks.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??There were no significant differences between randomised groups at the end of the trial for cough, phlegm and PEFr, and only two statistically significant, but functionally inconsequential, improvements in respiratory function, both for the LL group.</li> </ul>
Tang et al 1995	-	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Prospective study, combining four cohorts of men studied between 1967 and 1982. The four cohorts were the British United Provident Association study, Whitehall study, Paisley-Renfrew study and the United Kingdom heart disease prevention project. As best we can determine, none of the other studies in this table report the same results by individual study for follow-up mortality related to tar yield.</li> <li>??Total of 56,255 men (12,400 smokers with known tar yield), followed-up for average of 13 years, and 2,742 deaths observed.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??The relative risks of chronic obstructive respiratory disease mortality for a 15 mg reduction in tar yield per cigarette was 0.78 (95% CI 0.40-1.48), adjusting for age, study and number of cigarettes per day</li> </ul>

**Table 5: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with coronary heart disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Hammond et al 1976	<p>Smokers were divided into three categories on the basis of both tar and nicotine yields</p> <ul style="list-style-type: none"> <li>??nicotine 2.0-2.7 mg and tar 25.8-35.7 mg (<i>high</i>)</li> <li>??nicotine &lt;1.2 mg (<i>low</i>, with very few exceptions the tar yields in this group were &lt;17.6 mg)</li> <li>??the remainder (<i>medium</i>)</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cohort study of over 400,000 smokers followed-up for 12 years.</li> <li>??Cigarette category was assigned at the beginning of the 12 year period, and again after six years.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??The coronary heart disease mortality rate ratio for high-yield smokers compared to low-yield smokers was 1.16 (p&lt;0.001), adjusting for age, race, cigarettes per day, urban/rural, occupational exposure, and pre-existent disease. The trend was consistent across time periods and sexes.</li> </ul>
Higenbottam et al 1982	<p>Smokers were divided into four tar yield categories on the basis of their usual brand:</p> <ul style="list-style-type: none"> <li>??18 - 23 mg</li> <li>??24 - 32 mg</li> <li>?? 33 mg.</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cohort study of 7,221 smokers (Whitehall Study)</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??Tar yield was associated with coronary heart disease mortality in 'inhalers', (p=0.07; adjusted for age, employment status and number of cigarettes smoked), but not in 'non-inhalers'. The effect in 'inhalers' was strongest among smokers of 1-9 cigarettes per day (relative risk 2.77 for high versus low-yield smokers), but weak for smokers of greater than 20 cigarettes per day (relative risk 1.19).</li> </ul>
Borland et al 1983	<p>Smokers were divided into three categories of CO yield:</p> <ul style="list-style-type: none"> <li>?? 18 mg (low)</li> <li>??18-20 mg (medium)</li> <li>??&gt; 20 mg (high)</li> </ul> <p>There was no correlation of nicotine or tar yields with CO yields, an unusual finding.</p>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cohort study of 4,910 male smokers with known CO yields, followed-up for 10 years</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??The odds ratio of coronary heart disease mortality (255 deaths in total) in high-yield smokers was 0.68 (95% CI 0.42-1.10) compared to low-yield smokers, controlling for age, grade of employment, cigarettes per day and tar yield.</li> <li>??Stratification by inhalation revealed significant associations such that for men reporting inhaling smoke high CO yield was protective, and for men not reporting inhaling smoke high CO yield was positively associated with coronary heart disease mortality.</li> </ul> <p>Results for tar yield are reported by Higgenbottam et al 1982.</p>

**Table 5: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with coronary heart disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Kaufman et al 1983	<p>Smokers were divided into categories of both nicotine and CO yields. Nicotine:</p> <ul style="list-style-type: none"> <li>??&lt;0.8 mg</li> <li>??0.8-0.9 mg</li> <li>??1.0-1.1 mg</li> <li>??1.2-1.4 mg</li> <li>???1.5 mg.</li> </ul> <p>CO:</p> <ul style="list-style-type: none"> <li>??&lt;10 mg</li> <li>??10-14 mg</li> <li>??15-17 mg</li> <li>??18 mg</li> <li>???19 mg.</li> </ul>	<p><b>Methods</b></p> <p>??Case control study of 502 men less than 55 years of age with acute myocardial infarction and 835 hospital-based controls</p> <p><b>Results</b></p> <p>??No association of myocardial infarction with nicotine or CO yield, controlling for number of cigarettes smoked, age, region, medical diagnoses, family history, personality score, alcohol, religion and marital status.</p>
Petitti and Friedman 1985	<p>Tar was treated as a continuous variable, and relative risks reported per 5.0 mg increase in tar. About two thirds of the cohort smoked cigarettes greater than 15 mg in tar.</p>	<p><b>Methods</b></p> <p>??Cohort study of 16,270 current, regular smokers enrolled in a health plan. Diagnoses registered on hospitalisation were the outcomes.</p> <p><b>Results</b></p> <p>??Relative risk of any cardiovascular disease was 1.15 (95% CI 1.03-1.29), controlling for age, sex, race, BMI, number of cigarettes per day, cholesterol, hypertension, and alcohol.</p>
Palmer et al 1989	<p>Smokers were divided into seven categories of nicotine yield:</p> <ul style="list-style-type: none"> <li>??&lt; 0.40 mg</li> <li>??0.40-0.63</li> <li>??0.64-0.75</li> <li>??0.76-1.00</li> <li>??1.01-1.06</li> <li>??1.07-1.29</li> <li>???1.30</li> </ul>	<p><b>Methods</b></p> <p>??Case-control study of 910 women with first myocardial infarct and 2,375 hospital-based controls.</p> <p><b>Results</b></p> <p>??No significant difference in odds ratios across nicotine yield categories of cigarettes, adjusting for age, hypertension, angina, diabetes, cholesterol, family history, menopausal status, BMI, Type A behaviour, exercise, education, area of residence, oral contraceptive use, caffeine and alcohol consumption.</p> <p>??Likewise, no significant difference in odds ratios across CO yield categories of cigarettes.</p>
Negri et al 1993	<p>Smokers were divided into four categories of tar yield:</p> <ul style="list-style-type: none"> <li>??&lt; 10 mg (&lt;0.6 mg nicotine)</li> <li>??10-15 mg (0.5-0.8 mg nicotine)</li> <li>??15-20 mg (0.8-1.3 mg nicotine)</li> <li>??&gt; 20 mg (0.5-1.8 mg nicotine).</li> </ul>	<p><b>Methods</b></p> <p>??Case control study of 916 people with acute myocardial infarction and 1,106 people hospital-based controls</p> <p><b>Results</b></p> <p>??No association across categories of tar yield controlling for number of cigarettes smoked.</p>

**Table 5: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with coronary heart disease**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Parish et al 1995	<p>Smokers split into two categories of tar yield:            ?? &lt; 10 mg (low)            ??? 10 mg (medium)</p> <p>Almost all were filter cigarette smokers.</p>	<p><b>Methods</b>            ?? Case-control study, utilising 3,341 cases and 5,448 controls (family member controls) that were smokers with tar yield information available. Non-fatal myocardial infarction was the end-point.</p> <p><b>Results</b>            ?? The odds ratio for non-fatal myocardial infarction for medium versus low-tar smokers was 1.10 (95% CI 0.99-1.22) for both sexes. Adjustment was made for age, sex and amount smoked.            ?? For 60-79 year olds the odds ratio was 1.166 (1.025-1.326), and for 30-59 year olds it was 1.010 (0.856-1.191).</p>
Tang et al 1995	-	<p><b>Methods</b>            ?? Prospective study, combining four cohorts of men studied between 1967 and 1982. The four cohorts were the British United Provident Association study, Whitehall study, Paisley-Renfrew study and the United Kingdom heart disease prevention project. As best we can determine, only Higgenbottam et als' study in this table report the same results as an individual study for follow-up mortality related to tar yield.            ?? Total of 56,255 men (12,400 smokers with known tar yield), followed-up for average of 13 years, and 2,742 deaths observed.</p> <p><b>Results</b>            ?? Mortality from smoking related diseases consistently decreased with decreasing tar. The relative risks of coronary heart disease mortality for a 15 mg reduction in tar yield per cigarette was 0.77 (95% CI 0.61-0.97), adjusting for age, study and number of cigarettes per day.            ?? Likewise, the relative risk for stroke was 0.86 (0.50-1.50)</p>

**Table 6: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with lung cancer**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Hammond et al 1976	<p>Smokers were divided into three categories on the basis of both tar and nicotine yields</p> <ul style="list-style-type: none"> <li>??nicotine 2.0-2.7 mg and 25.8-35.7 mg (<i>high</i>)</li> <li>??nicotine &lt;1.2 mg (<i>low</i>, with very few exceptions the tar yields in this group were &lt;17.6 mg)</li> <li>??the remainder (<i>medium</i>)</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cohort study of over 400,000 smokers followed-up for 12 years.</li> <li>??Cigarette category was assigned at the beginning of the 12 year period, and again after six years.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??The lung cancer mortality rate ratio for high-yield smokers compared to low-yield smokers was 1.35 (p&lt;0.001), adjusting for age, race, cigarettes per day, urban/rural, occupational exposure, and pre-existent disease. The trend was consistent across time periods and sexes.</li> </ul>
Higenbottam et al 1982	<p>Smokers were divided into four tar yield categories on the basis of their usual brand:</p> <ul style="list-style-type: none"> <li>??18 - 23 mg</li> <li>??24 - 32 mg</li> <li>?? 33 mg.</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cohort study of 7,221 smokers (Whitehall Study)</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??Tar yield was associated with lung cancer in 'non-inhalers' (p&lt; 0.03; adjusted for age, employment status and number of cigarettes smoked), but less so for 'inhalers'.</li> </ul>
Vutuc and Kunze 1982	<p>Smokers were divided into three categories of tar yield:</p> <ul style="list-style-type: none"> <li>??&lt;15 mg (low)</li> <li>??15-24 mg (medium)</li> <li>??&gt;24 mg (high)</li> </ul>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Case control study of 297 females with lung cancer (188 smokers) and 119 hospital-based controls.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??The relative risk of lung cancer was 2.6 (95% CI 0.8-8.3), 4.4 (2.9-6.5), and 8.9 (6.7-11.7) for the low, medium and high-tar smokers compared to never smokers. Age, years smoking and number of cigarettes per day were adjusted for.</li> </ul>
Borland et al 1983	<p>Smokers were divided into three categories of CO yield:</p> <ul style="list-style-type: none"> <li>?? 18 mg (low)</li> <li>??18-20 mg (medium)</li> <li>??&gt; 20 mg (high)</li> </ul> <p>There was no correlation of nicotine or tar yields with CO yields, an unusual finding.</p>	<p><b>Methods</b></p> <ul style="list-style-type: none"> <li>??Cohort study of 4,910 male smokers with known CO yields, followed-up for 10 years</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??The odds ratio for lung cancer mortality (90 deaths in total) in high-yield smokers was 1.49 (95% CI 0.72-3.10) compared to low-yield smokers, controlling for age, grade of employment, cigarettes per day and tar yield. The 95% confidence interval includes 1.0.</li> </ul> <p>Results for tar yield are reported by Higgenbottam et al 1982.</p>

**Table 6: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with lung cancer**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Vutuc and Kunze 1983	Smokers were divided into three categories of tar yield: <math>\leq 15</math> mg (low) 15-24 mg (medium) >24 mg (high)	<p><b>Methods</b></p> Case control study of 252 males with lung cancer (248 smokers) and 119 hospital-based controls. <p><b>Results</b></p> The relative risk of lung cancer was 10.9 (95% CI 3.8-30.7), 20.6 (12.3-34.8), and 36.7 (27.0-49.9) for the low, medium and high-tar smokers compared to never smokers. Age, years smoking and number of cigarettes per day were adjusted for.
Lubin et al 1984	Smokers were divided into six within country percentile groups of tar yield: 0-10%, 10-25%, 25-50%, 50-75%, 75-90%, and 90-100%. The mean tar yields for these six groups (across countries) was 15.6, 18.5, 20.6, 23.6, 25.2 and 29.8 mg respectively.	<p><b>Methods</b></p> Case-control study of 7,804 cases and 15,207 hospital based controls. <p><b>Results</b></p> For males, the odds ratios compared to the 0-10 percentile group for each of the remaining five groups were 1.2, 1.7, 1.3, 1.3 and 1.4 respectively. Number of cigarettes per day, years smoking and current smoking status were adjusted for. Test for linear trend was significant ( $p < 0.01$ ).                     For females, the odds ratios were 1.9, 1.3, 1.1, 1.5 and indeterminate respectively. Test for linear trend was significant ( $p < 0.01$ ). <p>Note, the studies of Vutuc and Kunze (1982 and 1983) are both of subsets of this data.</p>
Petitti and Friedman 1985	Tar was treated as a continuous variable, and relative risks reported per 5.0 mg increase in tar. About two thirds of the cohort smoked cigarettes greater than 15 mg in tar.	<p><b>Methods</b></p> Cohort study of 16,270 current, regular smokers enrolled in a health plan. Diagnoses registered on hospitalisation were the outcomes. <p><b>Results</b></p> Relative risk of cancer of trachea, bronchus or lung was 0.87 (95% CI 0.68-1.11), controlling for age, sex, race, BMI and number of cigarettes per day. There were only 35 cases of lung cancer.

**Table 6: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with lung cancer**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Zang and Wynder 1992	Assigned each smoker a total kg measure of tar exposure, using FTC data.	<p><b>Method</b></p> <ul style="list-style-type: none"> <li>??Case-control study of 2,296 cases of lung cancer (2,162 smokers) and 4,667 controls (2,907 smokers).</li> <li>??Assigned three measures of cigarette exposure: lifetime tar exposure (kg tar); most recent cigarettes per day (CPD); and pack years of smoking. They were all interdependent.</li> <li>??Analysed univariate odds ratios, then odds ratios for each of three measures with other two held constant or stratified.</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>??Univariate odds ratios for categories of CPD greatest, and those for cumulative tar exposure and pack years were roughly equivalent. Odds ratios were greatest for Kreyberg type I lung cancer.</li> <li>??There was a clear residual dose-response for lifetime tar when both CPD and pack years were held constant.</li> <li>??The authors estimated an approximate 15-20% decrease in Kreyberg type I lung cancer risk among long-term heavy smokers for every 10 mg reduction in the tar yield of cigarettes they smoked.</li> </ul>

**Table 6: Summary of methods and results for studies on the association of tar and nicotine in cigarettes with lung cancer**

Author	Tar and nicotine yields of comparative cigarettes	Summary of methods and results
Benhamou et al 1994	<p>Historical tar yields of French-manufactured cigarettes were used to determine the lifelong exposure of individuals. Smokers were then split into three categories:</p> <ul style="list-style-type: none"> <li>?(I) smokers of high-tar (?30 mg) cigarettes for ? 50% of their tobacco history</li> <li>?(II) smokers of high-tar cigarettes for 51-75% of their tobacco history</li> <li>?(III) smokers of high-tar cigarettes for &gt;75% of their tobacco history.</li> </ul> <p>The comparison group was life-long smokers of imported light 'cigarettes'.</p>	<p><b>Methods</b></p> <p>??Case-control study of 1114 male cases of lung cancer, and 1466 hospital based male controls. Subjects recruited in France from 1976 to 1980.</p> <p><b>Results</b></p> <p>??Compared to smokers of imported light cigarettes, the relative risk of lung cancer for group I was 2.9 (95% CI 1.5-5.4), group II was 4.3 (2.3-8.0), and for group III was 3.9 (2.1-7.2). Only age was adjusted for.</p> <p>??A logistic regression model including cigarettes per day, years smoking, depth of inhalation, current smoker, type of tobacco (light, mixed, dark), and filter, found the effect of tar was diminished (relative risks of 2.6, 3.1, and 3.3 respectively) such that the lower 95% confidence intervals were about 1.0 (0.9, 1.0, and 1.1 respectively).</p> <p>??For just the three tar categories of French cigarettes, there was no statistically significant dose response in either of the two above analyses.</p>
Tang et al 1995	-	<p><b>Methods</b></p> <p>??Prospective study, combining four cohorts of men studied between 1967 and 1982. The four cohorts were the British United Provident Association study, Whitehall study, Paisley-Renfrew study and the United Kingdom heart disease prevention project. As best we can determine, only Higgenbottam et als' study in this table report the same results as an individual study for follow-up mortality related to tar yield.</p> <p>??Total of 56,255 men (12,400 smokers with known tar yield), followed-up for average of 13 years, and 2,742 deaths observed.</p> <p><b>Results</b></p> <p>??The relative risk of lung cancer mortality for a 15 mg reduction in tar yield per cigarette was 0.75 (95% CI 0.52-1.09), adjusting for age, study and number of cigarettes per day.</p>

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