Chemical Factors Influencing the Addictiveness and Attractiveness of Cigarettes in New Zealand

Final Report

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By

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Chemical Factors Influencing the Addictiveness and Attractiveness of Cigarettes in New Zealand

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SUMMARY

There is a long list of chemical additives in New Zealand cigarettes. Many of these serve to enhance the flavour of inhaled smoke and/or the neuropharmacological impact of the delivered nicotinic alkaloids. Among the added flavours are fruit extracts and sweeteners, which would probably increase the attractiveness of tobacco products to children. Some of the combustion products of these chemicals, such as acetaldehyde, may be addictive themselves when inhaled. Sugars, as additives, may therefore serve a dual purpose, for sweetening the bitter taste of cigarette smoke and contributing upon combustion to the formation of acetaldehyde, itself a chemical capable of altering endogenous alkaloid profiles in the brain and exerting potentially addictive effects. This specific case is one of concern as a high level of sugars and other sweeteners is listed in the New Zealand tobacco returns. The fact that quitting smoking is so difficult for so many people, even with the availability of nicotine replacement therapy, indicates that other factors besides nicotine alone are probably involved in the physiological addiction to cigarettes. Though some biological actions of a few of these chemicals are now starting to be known, there has been no systematic evaluation of the public health impacts of these additives or their combustion products in New Zealand or anywhere else in the world. Indeed, a regulatory framework to support such an evaluation is lacking and this is becoming a growing topic of concern for the WHO and overseas governments.

RECOMMENDATIONS

1. That the Ministry of Health consider adopting a regulatory framework for tobacco additives along the lines proposed by Bates et al. (1999), shown in this report.
2. That specific additives or characteristics of cigarettes, that are known or suspected to increase the bioavailability and uptake of nicotine and its related alkaloids, be quantified and reported for each brand sold in New Zealand. This would include total ammonia in smoke, smoke pH, puff number and volume, and total nicotinic alkaloid content and yield, as well as any compounds that prolong cigarette burn time.
3. That the total sugar and other sweetener content of each cigarette brand be reported and made publicly available. This would need to include liquorice, all forms of sugar, and sorbitol.
4. That the Ministry of Health require that any sweeteners, such as saccharin, if added to the cigarette filter or paper, be included in the returns.
5. That the presence of specific cigarette additives, or their combustion products, that have: a) pharmacological effects (such as acetaldehyde); b) deaden peripheral nerves (such as eugenol or menthol); or c) influence absorption of nicotine through bronchodilation or increased vascular permeability (such as theobromine and caffeine), be justified by the tobacco industry to the Ministry of Health.
6. That the New Zealand tobacco returns be re-structured so that the composition of individual cigarette brands can be quantitatively assessed and their additives regulated accordingly. This information should also be made public and subjected to public and regulatory scrutiny as is the case with other consumer products.

1. PURPOSE OF THIS REPORT

Hundreds of chemical ingredients are listed by tobacco companies for addition to the cigarettes that are marketed in New Zealand. The function and purpose of most of these compounds and extracts are not known. This report reviews current scientific knowledge on the chemical constituents of tobacco smoke or cigarettes that may influence the known addictive properties of cigarettes, or otherwise enhance their sensory attractiveness, especially for young children in their first experiences with smoking.

This report does not address the variety of social and behavioural aspects or advertising strategies surrounding the initiation of smoking or societal factors interfering with a person's efforts to quit smoking.

2. INTRODUCTION

The addictive property of cigarettes is widely attributed to the presence of the naturally-occurring nicotine alkaloid in tobacco (U.S. National Institute on Drug Abuse, 2000; U.S. Surgeon General, 1988). Signs of addiction to nicotine can be seen in a matter of days following initiation of smoking (Charlton et al., 2000), and addiction is firmly established by one year of smoking (RCP, 2000). However, although the physiological and biochemical impacts of nicotine on the central and peripheral nervous systems have been extensively studied and reviewed (U.S. Surgeon General, 1988), the process of addiction to tobacco is still not entirely understood. The long list of additives and ingredients used by the New Zealand tobacco industry is similar to lists from overseas jurisdictions (Covington and Burling, 1999; UK Department of Health, 1998). It is likely that there are many substances added to these products that may influence their marketability, either through manufacturing considerations or direct appeal to their consumers. It is likely that the 'appeal' of cigarettes to consumers would include added substances that influence taste and odour, as well as compounds that either directly or indirectly enhance tobacco's inherent addictiveness. There were no studies found in the open literature that examined the issue of additives and brand choice. However, factors influencing nicotine delivery, taste, odour, and membrane irritation would be expected to influence brand preference for the smoker.

The most comprehensive report on factors influencing addiction to nicotine was produced by the U.S. Surgeon General in 1988 (U.S. Surgeon General, 1988). This reference provides detailed summaries of experimental results, scientific observations, and hypotheses regarding how nicotine functions in the body. A more recent report on nicotine addiction by the Royal College of Physicians in Britain, reaffirms many of the earlier findings and concludes unequivocally that nicotine is highly addictive (RCP, 2000). In the present report, much of the technical information on the biology and neuropharmacology of nicotine is taken from the above references.

The purpose of this report is to review the current scientific knowledge on the chemical compounds reported in New Zealand cigarettes that may influence cigarette attractiveness, especially to children, as well as review the chemicals that may influence the absorption or pharmacological effects of nicotine or to be addicting themselves.

Chemical ingredients or smoke constituents of concern or that would require further study are identified if there is potential for these compounds to increase the addictiveness of cigarettes or enhance their attractiveness, particularly to young people.

Previous reports (Blakely and Bates, 1997; Fowles and Bates, 2000) have reviewed various aspects of cigarette chemical composition, focusing on nicotine content of NZ cigarettes, and reviewing the toxicological risks from chemicals found in cigarette smoke. Fowles and Bates (2000) reported a list of combined New Zealand 'returns' from tobacco companies regarding additives and ingredients in cigarettes. Over 600 compounds were present on this list covering what appear to be a range of functions that include among them sweeteners, flavourings, and compounds that mask membrane irritation. Many chemicals and ingredients added to cigarettes have unknown functions and yield unknown combustion products.

3. ADDICTION

The U.S. Surgeon General report (1988) defines addiction as: "the compulsory use of a drug that has psychoactivity and that may be associated with tolerance and physical dependence (i.e. may be associated with withdrawal symptoms after the cessation of drug use)". Most smokers are probably addicted to nicotine according to this criterion. Fewer than 7 per cent of those smokers in the U.S. who try to quit smoking unaided by various therapies are successful for one year or longer (National Institute on Drug Addiction, 2000). In contrast, it has been observed that roughly 10 per cent of smokers (referred to as "chippers") have the ability to smoke 5 or fewer cigarettes per day, can skip smoking for one or more days, and have little difficulty quitting (Benowitz, 1994). The reasons why these people are apparently not highly addicted to nicotine are currently unknown.

4. CHEMICAL FACTORS INFLUENCING ADDICTION

4.1 Nicotine and related Alkaloids in Tobacco

It is well accepted that nicotine and its related pyridine alkaloids are the primary addictive substances in tobacco (European Commission, 1999; Moxham, 2000). Nicotine-free tobacco or other plant materials do not completely satisfy the cravings of smokers (US Surgeon General, 1988). In the 1940's it was observed that "…smoking tobacco is essentially a means of administering nicotine just as smoking opium is a means of administering morphine" (Johnston, 1942).

Tobacco contains at least 20 different, but related, pyridine alkaloids (Table 1), 16 of which are shown in Figure 1. Of these the dominant alkaloid is nicotine, making up nearly 88% of the total alkaloid content of some tobaccos, and it has been reported that the average nicotine content of tobacco is 1.5% by weight (Benowitz et al., 1983). The remaining alkaloids are present in comparatively smaller amounts. The term 'nicotine' as defined in European legislation refers to the combined nicotinic alkaloids (European Commission 1999).

Table 1: Twenty alkaloids found in various Nicotiana tobacco species (Henry, 1939; U.S. Surgeon General, 1988).

2,3-Dipyridyl	Nicotine
N-nitrosonornicotine	Anatabine
Nicotyrine	Anabasine
Nornicotyrine	Anabaseine
Metanicotine	Iso-Nicoteine
Nicotimine	Nicotoine
Nicotine N-oxide	Nicotelline
Cotinine	Nornicotine
6'-Oxoanabasine	N-methylanatabine
Pseudooxynicotine	N-methylanabasine

Tobacco cultivars vary widely in their yield of nicotine and other chemicals by strain and growing condition. Cigarettes are therefore made from blended tobaccos to arrive at a target yield of nicotine delivery. 'Low nicotine' cigarettes are so termed not because the nicotine content of the tobacco is less, but because there is less total tobacco per cigarette, the puff count per cigarette, using machine testing, is lower, and there are added filtration mechanisms to remove tar and nicotine (U.S. Surgeon General, 1988).

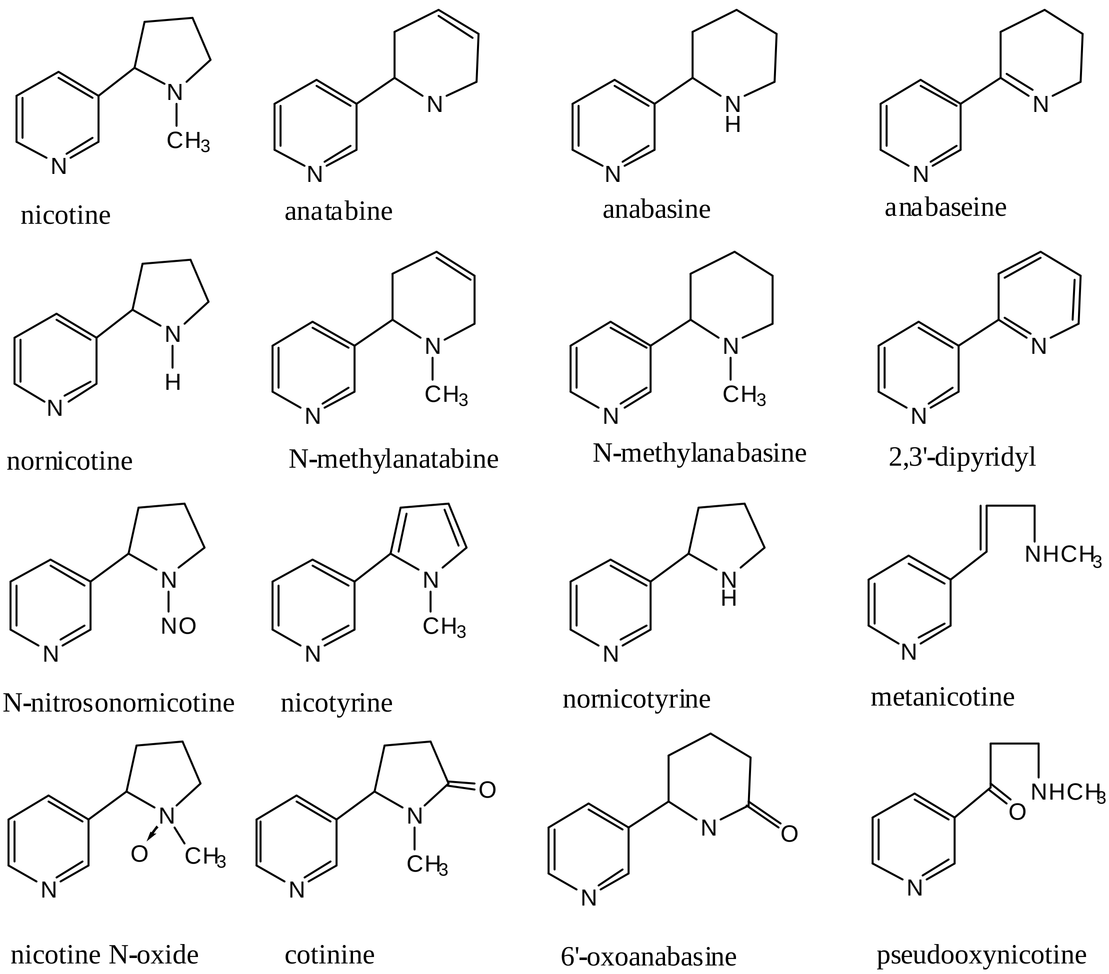
4.1.1 Pharmacological and toxicological effects of nicotine

Nicotine and its related pyridine alkaloids in tobacco are pharmacologically active substances. The relative pharmacological potency of nicotine is 1.2 – 2.5 times that of nornicotine and anabasine, depending on the test system and animal model used (U.S. Surgeon General, 1988). The alkaloid profile appears to vary substantially with different tobacco strains, but these additional alkaloids are not routinely quantified and their contribution to the pharmacological effect of nicotine is not precisely known. In addition to the pharmacologically active pyridine alkaloids found in tobacco, pyridine itself is added to New Zealand cigarettes, and this compound is also pharmacologically active through binding to the nicotine receptor (Bates et al., 1999b).

The pharmacological effects of nicotine do not by themselves account for the pharmacological or behavioural influences seen with smoking (Cherek et al., 1989; Pickworth et al., 1999). It has been demonstrated that nicotine replacement therapies do not completely mimic the neuropharmacological changes seen with smoking, even when the blood nicotine levels are essentially identical. For example, as shown by Cherek et al., (1989), operant avoidance responses were tested in a group of three smokers given low nicotine cigarettes, high nicotine cigarettes, or nicotine chewing gum. Smoking low or high nicotine cigarettes produced increased avoidance compared to baseline non-smoking rates. Chewing nicotine gum did not produce changes in avoidance responding, however, nicotine blood levels produced by chewing nicotine gum were similar to levels produced by smoking cigarettes (Cherek et al., 1989).

Nicotine is extremely toxic, with a lethal dose in adults of about 60 mg, or about 0.9 mg/kg (HSDB, 2000).

Figure 1: Chemical structures of 16 tobacco alkaloids (US Surgeon General, 1988)



A variety of behavioural effects from smoking may contribute to the observed chemical dependence. Laboratory tests have shown that rats exhibit improved learning in maze tests when given nicotine. Smokers similarly benefit from smoking in this manner (U.S. Surgeon General, 1988). This improvement in cognitive ability may add to the physiological craving for nicotine. However, although nicotine or smoking improves performance on some cognitive tasks for smokers, smoking and nicotine do not improve general learning when performance on these tasks are compared with that of non-smokers not exposed to nicotine

(U.S. Surgeon General, 1988). Therefore, smokers in abstinence of smoking experience deficits in cognitive performance, and this deficit is amended by doses of nicotine.

Epidemiology studies have revealed the unexpected finding that smoking prevalence is inversely related to the incidence of Parkinson's disease where brain nicotine receptor numbers are significantly lowered at autopsy compared with people without Parkinson's disease (Kelton et al., 2000; Mihailescu and Drucker-Colin, 2000). There is also indication that nicotine may help alleviate symptoms of Alzheimers disease (Kelton et al., 2000). This illustrates the potent neuropharmacological action of nicotine on the brain.

Because of the extensive neuropharmacological activity of nicotine in the brain, it is possible that certain individuals smoke in order to treat their own neurological disorders. It has become known, for example, that smoking prevalence is very high (i.e. more than double) among people who have been diagnosed as having attention deficit/hyperactivity disorder (ADHD). It has been hypothesised that these individuals smoke (subconsciously) as a way of using nicotine to medicate their disorder (Lambert and Hartsough, 1998; Riggs et al., 1999).

Because of nicotine's stimulation of epinephrine (adrenaline) release and increase in general metabolism, smoking is also known to reduce body weight. Smokers are, on average, 7 pounds lighter than non-smokers, and people who quit smoking often gain weight (Benowitz et al., 1994). This may add to a psychological dependence on smoking in the case of people trying to lose weight, particularly affecting young girls.

4.1.2 The Nicotine Receptor

Neuronal nicotinic acetylcholine receptors (nAChRs) represent a large family of ligand-gated cation channels with diverse structures and properties. In contrast to the muscular nAChRs, the physiological functions of neuronal nAChRs are not well defined to date. Behavioral studies indicate that brain nAChRs participate in complex functions such as attention, memory, and cognition, whereas clinical data suggest their involvement in the pathogenesis of certain neuropsychiatric disorders, including Alzheimer's and Parkinson's diseases, Tourette's syndrome, schizophrenia, and depression (Belluardo et al., 2000). For the majority of these disorders, the use of nAChRs' agonists (i.e. inhaled nicotine alkaloids in the case of smokers) may represent either a preventative or a symptomatic treatment (Mihailescu and Drucker-Colin, 2000).

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Nicotine binds to nicotinic receptors in the brain, augmenting the release of numerous neurotransmitters, including dopamine, serotonin, norepinephrine, acetylcholine, gamma-aminobutyric acid, and glutamate (Quattrocki et al., 2000). Several types of receptors for nicotine and related compounds can be found in the brain and peripheral nervous system, as well as in peripheral blood cells. The binding of nicotine to the receptor increases the production of acetylcholine receptors in neurons and affects neural tissue through this stimulus in the presence of acetylcholine. Acetylcholine is the major parasympathetic neurotransmitter in the body. The stimulation of the peripheral nervous system by nicotine is responsible for the elevated heart rate, blood pressure, and a host of other biological effects. The binding of nicotinic alkaloids to this receptor is the critical step in this cascade of events (U.S. Surgeon General, 1988).

Once in the brain, nicotine interacts with specific receptors and alters brain energy metabolism in a pattern that corresponds to its distribution in the brain. The result of chronic receptor-mediated stimulation of these tissues is an alteration of nearly all components of the neuroendocrine system including the corticosteroids, adrenal hormones, serotonin, and pituitary hormones (US Surgeon General, 1988).

Although the addiction to tobacco is a complex process and not easily measured, the binding of nicotinic alkaloids to the nicotinic receptor is clearly a critical step in the pharmacology of nicotine in the brain. Nicotine antagonists, such as mecamylamine, inhibit the cardioacceleratory and adrenaline releasing actions of nicotine in smokers (Zevin et al., 2000).

4.2 Factors that influence the absorption or delivery of nicotine

The standard measured nicotine yield of a cigarette is determined by:

?? The nicotine content of the tobacco
?? The static burn rate or amount of tobacco consumed during puffing
?? The pressure drop of the tobacco column
?? Porosity of the wrapper and or ventilation at the filter
?? The pressure drop of the filter
?? The filter material
?? The surface area of the filter material, and
?? The affinity of the filter material for nicotine particularly as a function of smoke pH.

The present review focuses on chemical factors that may influence addictiveness, therefore the physical characteristics of cigarette design (such as filter material), while important in nicotine yield, are not discussed.

4.2.1 Nicotine content and yield

Through the combination of the above variables, plant genetics, and commercial processes to remove nicotine from tobacco, it is possible to manipulate the machine-measured yield of nicotine from about 0.1 mg to 4 mg per cigarette (Baldinger et al., 1995; Benowitz 1989). However, in practice, the nicotine content and nicotine yields from so called “ultra-low” nicotine cigarettes do not in fact deliver less nicotine to smokers (Benowitz et al., 1983). Similarly, smoking fewer cigarettes per day does not necessarily translate into a lower tar or nicotine exposure for a smoker. This is because smokers compensate for the reduced nicotine in a conventional puff, and smoke much more intensively to achieve the desired nicotine blood level (Benowitz, 1986). Baldinger et al. (1995), showed that compensatory ‘oversmoking’ occurred in smokers smoking reduced tar and nicotine cigarettes, but not when smoking reduced nicotine cigarettes with regular amounts of tar. This supports the theory that there are non-nicotine factors in cigarette smoke that affect the cravings and compensatory oversmoking behaviours involved.

According to Benowitz and Henningfield (1994) the proportion of nicotine in cigarettes that is physically available for absorption is up to about 40%. This is thought to be the maximal amount of nicotine that can be absorbed from conventional cigarettes. If cigarettes were to be re-designed physically and/or chemically it is possible that this limit could change and the degree of bioavailability would need to be reassessed. However it is not clear that a simple measurement of nicotine yield would be sufficient for such an assessment. Optimally, a biological system containing a battery of tests for objectively and accurately measuring the bioavailability and biological activity of inhaled smoke should be developed. Chemical measurements and reported yields are unlikely to resolve questions about toxicological interactions in such a complex mixture.

4.2.2 Slowing the Cigarette Burn Rate

Cigarette manufacturers apparently design certain features into cigarette tobacco that can affect nicotine delivery during blending (Robertson, 2000). For example, cigarette filling power (bulk), pressure drop or resistance to draw, and static burn rate are all decreased with ascending stalk position on the tobacco plant. A decrease in the burn rate increases the puff count, and thereby results in the delivery of more nicotine to the smoker because less tobacco is burned between puffs (US Federal Register, 1995). However, increasing the burn rate, while having the effect of reducing the measured yields of nicotine and other constituents, does not necessarily mean the smoker receives a lower exposure, especially if they smoke each cigarette more intensively. In addition, a faster burn rate increases the ignition propensity of cigarettes, increasing the fire risk.

Chemicals that have the ability to retard the burn rate of cigarettes include some humectant chemicals and components that would be added to the cigarette paper to reduce permeability, but not necessarily reported in the current returns as they are not added to the tobacco itself. It is not widely known what these chemicals are, although burn-retarding agents are referred to in industry documents (Bates et al., 2000). This could be a gap in the New Zealand returns that may need to be filled should these products under go greater regulatory scrutiny.

4.2.3 Chemicals that affect pH changes in cigarette smoke

While the above factors influence the measured yield of nicotine, they do not measure its actual bioavailability or its ability to be absorbed. A number of chemicals are apparently added to cigarettes with the purpose of increasing or buffering the pH of the inhaled smoke (Fowles and Bates, 2000; Robertson, 2000). Ammonia compounds appear to be the chemicals of this type of the highest quantity in the New Zealand returns. Although a number of amino acids and other organic acids are also listed in the returns and serve an unknown function, their quantities and pKa values are such that they would exert an insignificant influence on pH in comparison to the ammonia compounds listed. The ammonia compounds therefore dominate the effect on pH, making the tobacco smoke more alkaline. A measurement of pH in cigarette smoke would allow for a scientific evaluation of the bioavailability of nicotine from cigarettes.

Nicotine is a weak base with a pKa of 8.0 (U.S. Surgeon General, 1988). This means that at a pH of 8.0, 50% of the nicotine will be ionised at equilibrium. As the pH of cigarette smoke increases, the relative amount of unionised nicotine (and other related alkaloids) will increase. This is important for two reasons. First, ‘free base’ compounds, including unionised nicotine, are more volatile than the ionised counterparts. As chemicals become more volatile and separate from the particulate (tar droplet) phase to the vapour phase, they diffuse more rapidly and are better distributed throughout the lung more quickly, gaining access to lung membranes (Pankow, 1999). In addition, the free base nicotine content in the tobacco rod has a lower boiling point, which means that more nicotine can be transferred from the tobacco to the aerosol. Second, unionised compounds traverse biological membranes with greater ease than the equivalent chemicals when ionised (Cassarett and Doull, 1994).

The pH of biological membranes is approximately 7.4, whereas smoke condensate without modification, tends to be slightly acidic (below 7.0). Therefore constituents that make the smoke more alkaline, serve to keep more nicotine volatilised and unionised and more easily pass the membranes of the lung. Ammonia, the pH adjusting chemical with the highest reported level in the New Zealand returns, has a pKa of 9.25, which effectively serves to elevate the pH of cigarette smoke and facilitates the delivery and absorption of unionised nicotine to the bloodstream.

Chemicals listed in the New Zealand returns (Covington and Burling, 1999) that influence pH in this manner include:

1. Ammonium hydroxide
2. Ammonium phosphate (dibasic)

Together, these added alkaline compounds could account for up to 1.5% by weight of the cigarette according to New Zealand returns (Appendix 1). Ammonium hydroxide added to tobacco would either react with inorganic phosphate or other anionic species to form alkaline salts, or volatilise as free ammonia. However, although these appear to be the main chemicals influencing pH, a wide range of alkaline chemicals could be substituted for the same purpose. These compounds can be expected to increase bioavailability and therefore the impact of nicotine on the smoker. Whether this plays a role in the initiation of smoking and nicotine addiction among youth is unknown and cannot be studied without product-specific information on the chemical content or (more preferably) the measured pH of the smoke from any given brand.

It has been argued that an elevated free-base nicotine content of cigarette smoke could result in a smoker achieving the same satisfaction from smoking fewer cigarettes, which could reduce harmfulness to smokers (Bates et al., 1999a; Bates et al., 1999b). However, this hinges on the assumption that a greater nicotine bioavailability per cigarette would not more quickly and easily addict a young smoker, resulting in a higher prevalence of smoking.

4.2.4 Bronchodilators – coffee and cocoa

Theobromine, the chief alkaloid in cocoa and chocolate, is known to be able to dilate bronchial airways and has pharmaceutical uses as a drug for asthmatics (Simons et al., 1985; Bates et al., 1999). For example, bronchodilation by theobromine can be measured by increased forced vital capacity, forced expiratory volume in the first second, forced expiratory flows at 25%, 50%, and 75% of vital capacity, and percent of forced expiratory volume in the first second (Simons et al., 1985).

Caffeine, the major alkaloid in coffee, has similar stimulant properties to theobromine and has been found to induce improved pulmonary function changes in asthmatics exposed to caffeine aerosols (Bukowskyj and Nakatsu, 1987).

The New Zealand returns indicate that up to 3.02% of cigarettes by weight are cocoa extracts, and an additional 0.21% chocolate, but there is no way to determine the corresponding theobromine content without testing or specific reporting of this compound by the industry. Similarly 'coffee extract concentrate – 0.01%' is listed in the returns, but the caffeine content of this extract is not available and remains unknown.

It may be that the doses of theobromine and caffeine per cigarette are too small to exert a bronchodilating effect on the lung, but without specific data on levels of these compounds in tobacco or in cigarette smoke, this issue cannot be resolved. However, assuming a cigarette contains 700 mg of tobacco, a content of 3.21% of chocolate or cocoa (see Appendix 1) would mean that up to nearly 23 mg cocoa product/extract is present in NZ cigarettes.

Bronchodilation by these types of compounds in cigarette smoke would contribute to increasing the lung surface area available for absorption of nicotinic alkaloids.

Apparently some tobacco companies, such as Lorillard, have replaced cocoa with an undisclosed proprietary substitute compound or extract (www.library.ucsf.edu/tobacco/cigpapers/book/chapter6/3.html). The identity of this compound is unknown and it is also unknown whether or not it is a bronchodilator.

4.3 OTHER COMPOUNDS IN CIGARETTE SMOKE THAT MAY INFLUENCE ADDICTION

Apart from nicotinic receptor binding and stimulation, cigarette smoke has other psychoactive properties. For example, nicotine inhibits monoamine oxidase (the enzyme responsible for breaking down the biogenic amine neurotransmitters norepinephrine, serotonin, and dopamine) in the brain. Various antidepressants also act through modulation of the biogenic amine neurotransmitter pathways. That the neural substrates modified by both smoking and antidepressant drugs overlap has been hypothesised to be relevant to smoking cessation (Quattrocki et al., 2000).

It has been observed in experiments that de-nicotinised cigarettes, while not exerting the same pharmacological effects as conventional cigarettes, do retain the ability to lessen some of the cravings of smokers in abstinence (Pickworth et al., 1999). Therefore, it is apparent that the pharmacology of cigarette smoking extends beyond nicotine alone.

4.3.1 Acetaldehyde

A number of published papers show that acetaldehyde exerts biological effects that may contribute to addiction (Wrona et al., 1997). Acetaldehyde is a metabolite of ethanol, and much of the research on this substance stems from a focus on alcohol dependence. It has been shown that nicotine is more reinforcing in patients with a prior history of alcoholism (Hughes et al., 2000). Acetaldehyde is suspected to act as a synergist with nicotine, though the precise mechanism has not been identified (Gray, 2000).

Acetaldehyde is known to inhibit aldehyde deydrogenase. It was originally observed that ethanol and acetaldehyde exposures in animals lead to a build up of cellular amines that are closely related to opioid compounds such as morphine (Smith, 1975). Cellular amino acid derivatives react with acetaldehyde *in vitro* to form alkaloids such as isoquinoline and carboline. These compounds have pharmacological activity in the nervous system that may help explain the withdrawal symptoms from alcohol. In the brain, acetaldehyde has been found to react with endogenous 5-hydroxytryptamine (5-HT) to form 1-methyl-6-hydroxy-1,2,3,4-tetrahydro-beta-carboline, and oxygen radical derivatives of this alkaloid (Wrona et al., 1997). Research is ongoing on the mechanisms of acetaldehyde neurotoxicity and the effects the ensuing biochemical changes in the brain may have in terms of addiction (Han and Dryhurst, 1996), as this chemical is derived from both smoking and alcohol consumption.

Acetaldehyde is formed from combustion of organic material, and is formed in particularly high concentrations upon combustion of sugars. It is present in high concentrations in cigarette smoke, with an average yield of about 700 micrograms per cigarette (Fowles and Bates, 2000). The high concentration of acetaldehyde in cigarette smoke may be explained by the relatively high level of sugars added to, or naturally occurring in, tobacco. A higher sugar content would be expected to increase the acetaldehyde concentrations in the smoke.

4.3.2 Nitrosamines

Nitrosamines are biologically reactive compounds formed by a reaction between secondary or tertiary amine groups and nitrate. Nitrates are found in tobacco naturally, particularly as a result of plant uptake from fertilisers (Fischer et al., 1990). The rate of the nitrosamine reaction is enhanced under heat and combustion. Many of the important nitrosamines in cigarette smoke are nitrosated derivatives of the nicotine alkaloids. For example, N-Nitrosonornicotine or NNN, and 4-N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone or NNK are the nitrosamine derivatives of nornicotine and nicotine, respectively. Although their toxicological (carcinogenic) properties are of primary concern, it is unknown whether these compounds themselves, as alkaloid derivatives, are still capable of binding the nicotine receptor and therefore contributing to the neuropharmacological impact of smoking. The binding kinetics of these compounds to the nicotine receptor has apparently not been reported in the literature. However, the concentrations of nitrosamines in cigarette smoke (combined) are less than 10% of the yield of nicotine (Fowles and Bates, 2000), which probably indicates that the receptor binding potential is relatively small.

4.3.3 Levulinic Acid

It has been reported that low concentrations of levulinic acid, an endogenous amino acid derivative, can bind to a distal site of the nicotine receptor, increasing the affinity of this receptor for nicotine (Bates et al., 1999b).

5. FLAVOURINGS AND SWEETENERS THAT MAY INFLUENCE THE ATTRACTIVENESS OF CIGARETTES

In general, tobacco products are sweetened and flavoured, although it is not possible with the current returns to ascertain the extent to which this is done for any given product. It is therefore not possible to use the returns to assess the contribution each flavour or sweetener may have on initiating and maintaining smoking.

Palatability is subjective and usually requires the formation of panels of test subjects. The long list of aromatic oils and fragrances in the New Zealand returns is testimony to the complexity surrounding the design of a set of products palatable to a wide range of consumers.

5.1 Sugars

A preliminary categorisation scheme for the various additives and ingredients in cigarettes has been proposed by Fowles and Bates (2000). In this list, it was found that up to 12.7% of a cigarette by weight may be added sugars and sweeteners. This value could be higher if the added sweetness from more complex carbohydrates (such as inulin from chicory added to cigarettes) is included. Undoubtedly the high sugar content affects the palatability and flavour of cigarettes to smokers. Since children are well known to seek out sweet tasting foods (Watt et al., 2000) it is not unreasonable to assume that any added sweetness in tobacco smoke would be received favourably by the child experimenting with smoking. De Graaf and Zandstra (1999) found that the optimal sucrose concentrations in taste tests increase in adolescents and even more so in children compared with adults.

5.2 Artificial sweeteners

One use of saccharin, a potent artificial sweetener, was apparently to serve as a sweetening agent added to the filter matrix of cigarettes rather than to the tobacco itself, effectively sweetening the smoke upon inhalation as it passed through the filter (Dr Louise Lee, California EPA, personal communication). Whether or not this is the case in New Zealand cigarettes is not known and would probably not be revealed under the reporting requirements in the current returns.

5.3 Licorice

In addition to the sugars and sweeteners reportedly added to cigarettes in New Zealand, licorice is also potentially added in quantities of up to 1.3% by weight. This is potentially significant since licorice has a long history of use in the food industry as a sweetening enhancer, essentially serving to make foods taste sweet when the amount of actual sugar may be quite low. The constituent of licorice, glycyrrhizin, is 50 times sweeter than sugar (http://www.go-symmetry.com/licorice.htm).

5.4 Coffee and Cocoa

Although a considerable percentage of cigarette weight could be cocoa and chocolate extracts (almost 3.5%), it is not known and could not be found to what degree this influences flavour of the inhaled mainstream or sidestream smoke, or more specifically how this might influence smoking initiation among youth. Similarly, the influence of coffee extract on inhaled smoke flavour is unknown.

5.5 Vanilla Flavours and Coumarin Derivatives

According to the 1999 tobacco industry returns to the Ministry of Health, the flavouring additives vanillin and ethyl-vanillin are apparently added in substantial quantities to tobacco to impart a vanilla flavour to the smoke. Vanilla, when compared with a range of spices was judged to be the most similar to sugar (Blank and Mattes, 1990). Therefore this would serve to effectively sweeten tobacco smoke.

In addition to vanilla itself, coumarin was used as a food additive due to its vanilla-like taste for many years until it became known that it could cause liver damage and was a suspected carcinogen. The concern over coumarin in tobacco led to a scientific review of the toxicological literature in 1977 with a conclusion that limits should be placed on the amount of coumarin allowed in tobaccos (Hunter Committee, UK, 1977) (Bates et al., 1999b). While coumarin itself does not appear on the New Zealand returns list, 3,4-dihydrocoumarin is listed at 0.01% (100 ppm). This is one of the metabolites of coumarin but its contribution to flavour of tobacco is unknown. In addition, coumarin derivatives are apparently introduced through extracts of botanicals, such as in the case of the coumestans in alfalfa (Covington and Burling, 1999).

6. SENSORY IRRITATION AND THE DEADENING OF PERIPHERAL NERVES

Cigarette smoke, like any smoke, is inherently irritating to the mucous membranes of the nasal and airway passages, as well as to the eyes. This irritation is a natural warning sign by the body of an ongoing harmful exposure. A number of additives in cigarettes appear to serve the purpose of temporarily lessening this sensation of irritation, essentially removing a natural barrier for avoidance of cigarette smoke. This would affect the attractiveness of cigarettes.

6.1 Clove oil (eugenol)

Eugenol is an organic compound found in clove oil, and has long been known to have local anaesthetic properties and was used for this purpose in surgeries (Wicker, 1994). Although the reported level of clove extract is only 0.0001% in the New Zealand returns, the amount of eugenol and its contribution to the numbing effect of the peripheral nerves in the upper airways is unknown.

6.2 Menthol

Menthol has local anaesthetic properties on nerves linked with taste and irritation of the mouth and throat (Green and McAuliffe, 2000). The New Zealand returns list menthol as 0.71% by weight. The reported limit in cigarettes is approximately equal to the amount of menthol that can be found in a typical cough drop, and probably serves to add flavour while simultaneously deadening local nerve endings to reduce the feeling of irritation from inhalation of the various combustion products. Presumably the high level of menthol pertains to those cigarettes advertised as 'mentholated'. However, it remains unknown to what extent this anaesthetic agent is added to other brands.

6.3 Glycols

Diethylene glycol, more commonly known as the key ingredient in automotive antifreeze, was historically added to cigarettes as a humectant. However, it does not appear in the New Zealand returns. Humectants assist with aerosol formation, dissolving more nicotine into tar droplets, and making the smoke less irritating to the smoker's throat and easier to inhale. In 1965, a tobacco industry internal panel for British American Tobacco advised against the use of diethylene glycol due to its known cumulative toxicity at low doses (www.library.ucsf.edu/tobacco/cigpapers/book/chapter6/3.html). The toxicity referred to being oxidative damage to the renal tubules of the kidney from oxalate formation and precipitation. In the reported discussions shown on this web site, it is clear that ethylene glycol was being used as a humectant, and that alternative humectants were being sought to avoid public criticism in the event that the list of ingredients ever became public. However, ethylene glycol did not appear on the list of additives in New Zealand submitted by the industry.

Glycerol and methylglycerol are also added to cigarettes as humectants, to decrease the sensory irritation of the inhaled smoke. Although not toxic by itself, when burnt, glycerol forms acrolein. Acrolein is a small reactive aldehyde that causes localised inflammation and membrane irritation when inhaled, or to the eyes (HSDB, 2000). Acrolein, was found to be the leading contributor from tobacco smoke to respiratory and eye irritation in a previous risk assessment (Fowles and Bates, 2000).

6.4 MASKING THE IRRITATION AND ODOUR FROM SIDESTREAM SMOKE

It has been reported that the tobacco industry has for many years and is currently researching ways to mask the unpleasantness of sidestream smoke for smokers and non-smokers (Connolly et al., 2000). Efforts to produce socially acceptable cigarettes include “Premier” by RJ Reynolds, “Vantage Excel”, and “Chelsea” (reintroduced in 1990 as “Horizon”). Though these brands did not succeed in the marketplace, research is apparently ongoing in this area and is likely to continue as regulations affecting sidestream smoke become more strict internationally.

Additives to the cigarette paper, including potassium citrate and aluminium and other metal hydroxides, have been patented by the tobacco industry as paper wrapper additives aimed to reduce particulate visibility by making droplet sizes smaller, though not affecting total emissions (Connolly et al., 2000).

A number of additives apparently have the purpose of reducing sidestream smoke unpleasant odour. These include acetylpyrazine, anethole, and limonene – compounds with low odour thresholds and few components that would affect the trigeminal nerve endings in the upper airways. Polyanethol, and cinnamic aldehyde pinanediol acetal produced a fresher “less cigarette-like” aroma than controls (Connolly et al., 2000). A summary table of additives that have been reported to reduce sidestream smoke irritation or alter sidestream smoke odour to lessen complaints is shown below in Table 2:

Table 2: Additives reported to reduce sidestream smoke odour, irritation, or visibility (Connolly et al., 2000)

Additive	**Document (Bates number)**	**Company**
Odour reduction		
Acetylpyrazine, anethole, beta-caryophyllene, cedrol, ethyl-3-methylvalerate, furaneol, limonene, p-anisaldehyde, patchouli alcohol, phenethyl alcohol, vanillin	2001300448	Philip Morris
Aromatek 150*, Aromatek 245*	2023356341	Philip Morris
Irritation reduction		
Aluminium sulphate Ammonium sulphate Sodium phosphate (monobasic)	566001816	Brown and Williamson
XLF-636*	505005495	B & W
XLF-662*, XLF-680*, XLF-775*	566001836	B & W

Table 2 (*continued*)

Smoke visibility reduction		
Albacar chalk, multifex chalk	2021354113	Philip Morris
Alumina sol-gel, magnesium carbonate sol-gel, phosphoric acid, potassium pyrophosphate	2020288104	"
Calcium carbonate, sodium carbonate	2022177532	"
Calcium chloride, citric acid, magnesium oxide, potassium acetate, potassium citrate, sodium hexametaphosphate	1003638777	"
Glutaric acid, hydromagnesite, malonic acid, potassium phosphate	2020326633	"
Magnesite, potassium succinate	2023398178	"
Magnesium carbonate	2021327427	"
Magnesium hydroxide	2021553268	'
Potassium phosphate – monobasic	2023394961	"
Phosphate, malonic acid	2021354113	"
"Studio 26 blend*", "XTH studio blend*".	2020397399	"

* The chemical identification of these compounds is not disclosed in industry documents and is likely to be protected under proprietary grounds.
The "Bates number" refers to a cataloguing system developed for the publicly available tobacco industry papers online.

7. EVALUATING THE IMPACT OF CIGARETTE ADDITIVES

The assessment of the safety of cigarette additives using conventional toxicological methods is difficult because there is insufficient information on the combustion chemistry of the additives to evaluate their relative contribution to the various toxicants or other biologically active compounds in cigarette smoke. As one tobacco industry paper indicated:

[A toxicologist] admits that ingredients with a long history of safe usage in foods "cannot be established for cigarettes" since "safe usage in foods does not automatically translate into safe usage when the ingredients is [sic] pyrolized and inhaled."

"A toxicologist, for example, may take a prosaic and `wholesome product', such as a Hershey Bar, and expalin [sic] what it consists of: thousands of sinister-sounding chemicals, many occurring naturally in chocolate," ... "many of which are used in cigarettes."
footnote 11. "The parallel is imperfect, of course -- we don't inhale the vapors of a burning Hershey Bar."

Reference: http://www.gate.net/~jcannon/liggett/fl/index.html

An additional difficulty in evaluating the additives and ingredients listed in the tobacco returns is that toxicological risk assessment does not typically consider neurobehavioural testing in a way that would identify mechanisms related to addiction. Therefore, it is conceivable that many compounds added to cigarettes may facilitate the pharmacological impact of nicotine or acetaldehyde without being toxic or pharmacologically active by themselves.

There are many examples of chemicals acting synergistically to exert greater than additive effects when administered simultaneously. Toxicological modelling by Pozanni et al., (1959) has resulted in the prediction that 2.5% of all chemical pair interactions, on average, will be synergistic (Beck et al., 1994). If there are about 4000 chemicals present in cigarette smoke, assuming they are present in smoke randomly and not for the specifically designed purpose of exerting synergy, this would result in approximately 100 synergistically acting pairs of toxicants.

If any synergy or addition to the effect of nicotine exists in cigarette smoke, that would likely affect the addictiveness of cigarettes. For example, synergism with other chemicals in cigarette smoke could occur at the nicotine receptor or through biochemical mechanisms that effectively block or retard metabolism of nicotine. Evidence for this has been observed in experiments with tobacco abstinence (Lee et al., 1987). In this experiment, it was expected that nicotine metabolism would be slower during abstinence than when individuals were smoking. To test this hypothesis, the disposition kinetics of intravenous nicotine were studied in 20 healthy smokers while smoking, after abstaining from smoking for 1 week, and (in six subjects) when smoking again. Cardiovascular responses to nicotine were also measured. Unexpectedly, total and non-renal clearance of nicotine increased by 36% and 39%, respectively, during abstinence. The increase in clearance after brief abstinence suggests that nicotine or its metabolites or another component of cigarette smoke inhibits nicotine metabolism in smokers. Cardiovascular responses to nicotine were greater after 1 week abstinence compared with overnight abstinence, consistent with a loss of physiological tolerance (Lee et al., 1987).

8. A PROPOSAL FOR A NEW REGULATORY FRAMEWORK FOR ADDITIVES IN CIGARETTES

Historically, the use of additives in cigarettes was not allowed before the 1970's. When low tar and nicotine cigarettes were introduced to the market, additives were allowed based on the assumption that additives would be needed to encourage consumer acceptance of lower tar yield cigarettes (Bates et al., 1999a). This in turn was anticipated to lead to health gains as people switched to lower tar and nicotine cigarettes. Despite this claim, there are no data indicating that these additives are in fact only used in lower tar and nicotine cigarettes. In addition, through compensatory mechanisms, it is now known that smokers of low tar and nicotine cigarettes are not exposed to less nicotine or fewer toxicants when smoking (Bates et al., 1999a; Gray 2000).

Bates et al. (1999a) through the United Kingdom based Action on Smoking and Health (ASH UK) have proposed a regulatory framework for tobacco products relating to additives. The proposed framework closely follows the general principles set out by the WHO in its advice on regulations governing tobacco products (WHO, 2000).

The eight parts of the ASH-UK framework are as follows:

1) **Disclosure**: manufacturers should be required to disclose all additives used in tobacco products, by brand, to a regulator.
2) **Public information**: Such information should not be confidential but be made available to the public through publications, the internet, or on request from the regulator
3) **Packaging**: Some additives should be listed on the packaging, depending on the value this would have for consumers
4) **Disclosure of purpose**: Tobacco companies should be required to disclose the purpose of an additive and any secondary consequences it may have for consumers.
5) **Conduct and disclosure of research**: Tobacco companies should be required to undertake toxicology and pharmacology research testing on all additives.
6) **Regulatory challenges**: Regulators should have the ability to challenge any of the existing 600 additives currently allowed and to have them removed until the manufacturer is able to show that no extra harm to the public arises as a direct or indirect result of the additive. In the absence of such evidence, the regulator should have the authority to ban the additive.
7) **Focus on pharmacologically active additives**: There should be an automatic challenge to any additive thought to have a direct or indirect pharmacological influence. New additives should only be permitted if the manufacturer can demonstrate that no extra harm or other net negative consequences arise from use of the additive.
8) **Permit essential additives**: Any regulatory framewok should permit additives necessary for the manufacture and storage of tobacco products providing these are safe, but should be challenged if they are suspected of influencing smoking behaviour.

It should be noted that regulatory frameworks exist internationally for the safety assessment of manufactured foods and drugs in which the above actions can be taken without undermining the ability to protect certain aspects of manufacturing from competitors.

An alternative proposal

Another similar, but stronger, approach that has been suggested by Dr Nigel Gray (personal communication), is to have all additives to cigarettes banned until each additive is demonstrated by the industry, to the satisfaction of regulators, not to impart any toxicological harm or direct or indirect pharmacological effect on the smoker that could contribute to addiction.

9. CONCERNS RAISED INTERNATIONALLY ABOUT ADDITIVES

European Union (EU) Directives in the late 1990's stipulated a reduction in tar content. The expert committee on cancer advising the EU made recommendations that "Any additives to be included should be demonstrated free of toxicity and other harmful effects on health, in burnt and unburnt form" (Consensus Conference on Tobacco, 1996).

In the United Kingdom, a number of medical groups, including the Royal College of Physicians, the British Heart Foundation, British Medical Association, Health Education

Authority, ASH, and the Cancer Research Campaign have called for the additives to cigarettes – especially those that increase addictiveness or improve taste for children or cause cigarettes to keep burning to be banned or at least subjected to rigorous public consultation (Alberti et al., 1998; Bates et al., 1999b). The European Commission is considering legislation that may further restrict nicotine and tar yields as well as the use of additives.

Public health and medical groups in the UK have called for full disclosure of additives and smoke constituents by brand, and that this information be made public. These groups have also called for all existing or new additives to meet a test for public health or public interest or be withdrawn from use. One proposal has been for a 10% per annum drop in tar and nicotine until levels of 5 mg tar and 0.5 mg nicotine are met (Bates et al., 1999a).

The widespread and increasing use of fruit extracts, syrups, and various forms of sugars or sweeteners to improve the palatability of cigarettes and make them more attractive to children is of great concern to the Department of Health in the UK (London Times, 24 Jan, 1999).

The Massachussettes Tobacco Control Program has articulated the view that "…no-one should be doing anything to tobacco products that adds to the already unacceptable health burden" (Bates et al., 1999b). This would include efforts to sweeten, de-sensitise peripheral nerves in the airways, or increase the addictiveness of the already addictive products.

At the meeting on the WHO Regulation of Tobacco Products meeting in Oslo, (WHO, 2000), a very strong and unanimous message was that the use of the terms "light" and "mild" which implied unsubstantiated health benefits, should not be permitted. Such claims are likely to dissuade smokers from quitting and should only be allowed once the company has demonstrated to the satisfaction of regulatory authorities that they are scientifically valid.

Parties present at the above WHO conference were also strongly in favour of requiring a full disclosure of all additives and ingredients to cigarettes, listed by brand and made public. There were no valid arguments voiced that these products should be treated differently than other consumer products that require publicising information to consumers in this regard.

10. UNCERTAINTIES

There are very large areas of scientific uncertainty in regards to the assessment of additives and smoke constituents that may influence the addictiveness and attractiveness of cigarettes in New Zealand and worldwide. The vastness of the list of ingredients excludes the possibility of precisely knowing the physiological impact of each and every ingredient. Some of the main sources of uncertainty include:

1) The widespread use of botanical extracts and resins, each in themselves complex mixtures. The combustion chemistry of any one of these extracts presents a huge source of unknown toxicological and physiological effects.
2) The impact of other alkaloids in tobacco and the possibility that natural compounds or pyrrolysis products from other plant extracts that may interact with the nicotine receptor.

3) The contribution of acetaldehyde to tobacco addictiveness, and the organic components of cigarettes such as sugar that increase acetaldehyde content of cigarette smoke.
4) The influence of sweeteners in encouraging kids to start and continue to smoke.
5) The impact of certain chemicals such as theobromine, pH adjusting chemicals, and plant extracts in facilitating delivery and absorption of nicotine and related alkaloids.

Although these uncertainties can be identified and subjected to various avenues of scientific inquiry, they should not become, according to the Precautionary Principle, hurdles to regulatory action.

11. CONCLUSIONS

There is a long list of chemical additives in New Zealand cigarettes, many of which serve to enhance the flavour of cigarette smoke and/or the neuropharmacological impact of the delivered nicotinic alkaloids. Many of the flavours used are fruit extracts and sugary sweeteners, which would probably increase the attractiveness of tobacco products to children. Some of the combustion products of these chemicals, such as acetaldehyde, may be addictive themselves when inhaled. Sugars, as additives, may therefore serve a dual purpose, for sweetening the bitter taste of cigarette smoke and contributing upon combustion to the formation of acetaldehyde, itself a chemical capable of altering endogenous alkaloid profiles in the brain and exerting potentially addictive effects. This specific case is one of concern as a high level of sugars and other sweeteners is listed in the New Zealand returns. The fact that quitting smoking is so difficult for so many people, even with the availability of nicotine replacement therapy, indicates that other factors besides nicotine alone are probably involved in the physiological addiction to cigarettes. Though some biological actions of a few of these chemicals are now starting to be known, there has been no systematic evaluation of the public health impacts of these additives or their combustion products in New Zealand or anywhere else in the world. Indeed, a regulatory framework to support such an evaluation is lacking and this is becoming a growing topic of concern for the WHO and overseas governments.

The structure of the New Zealand returns does not permit an examination of the actual sugar or sweetener content or any other additive in a particular brand. Therefore it is not currently possible to conduct a specific risk assessment on the products that are being sold, or to follow changes in these products which may be leading to increases in smoking initiation or addictiveness.

In order to create the regulatory and scientific capability for assessing the addictiveness and attractiveness of these products, the following steps would be necessary:

1) Require that the industry returns disclose to the Ministry of Health their additives and ingredients for all parts of the cigarette, by brand.
2) Require all existing and new additives and ingredients to undergo a test of scientific and public scrutiny and consultation. Have the industry demonstrate the safety of these additives when used as intended (i.e. when burned and inhaled chronically).

3) Require objective tests of sugar content of tobacco and sweetness of smoke to be developed and utilised for cigarette brands.
4) Require the testing of certain constituents and factors in the smoke: pH, puff number and volume, acetaldehyde, nicotine, and all of its related alkaloids.
5) Encourage the development of a test for biological nicotinic activity that can be used in the place of extensive chemical testing to ensure that the effective delivered nicotine content is measured.

Each of these steps is scientifically feasible, and the implementation of any one of these would result in a significant increase in our knowledge and ability to control the hazardous characteristics of these products and perhaps limit or reduce the public health impacts that they cause.

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APPENDIX 1

List of Additives and Ingredients in Cigarettes
from the 1998-1999 New Zealand Tobacco Industry Returns

Additive or Ingredient	**Max % (w)[a]**
A. Sweeteners	
Sugars	4.68
Honey	2.91
Sorbitol	2.00
Licorice root, fluid or powder	1.29
Prune juice and concentrate	1.08
Molasses extract	0.56
Apricot extract	0.35
Fig juice concentrate	0.35
Raisin juice extract	0.25
Plum juice and extract	0.24
Chocolate	0.21
Potassium sorbate	0.05
Caramel/caramel colour	0.025
Maltodextrin	0.01
Maltol	0.01
Apple juice concentrate	0.001
Fennel sweet oil	0.001
Malt and malt extract	0.001
Maple syrup and concentrate	0.0001
B. Other flavourings	
Cocoa, cocoa shells, extract, distillate, and butter	3.02
Menthol	0.71
Rum	0.15
Carob bean extract	0.12
Tamarind-seed gum	0.10
Fenugreek extract	0.06
Nutmeg powder	0.05
Chicory	0.03
Vanillin	0.03
Angelica root extract oil	0.01
Balsam peru and oil	0.01
Cassia bark oil	0.01
Chamomile flower oil	0.01

Cinnamaldehyde	0.01
Clary oil, sage Coffee, extract, concentrate	0.01 0.01
Ethyl vanillin	0.01
Lovage oil	0.01
Mandarin oil	0.01
Orange peel and extract	0.01
Peppermint oil	0.01
Rosemary oil and extract	0.01
Sage, oil and oleoresin	0.01
Styrax extract, gum and oil	0.01
Tolu balsam, gum and extract	0.01
Vanilla extract and oleoresin	0.001
Wine and sherry liqueurs	0.001
Bergamot oil	0.001
Caraway seed oil	0.001
Cinnamon leaf oil	0.001
Cinnamyl acetate	0.001
Ginger, ginger oil and oleoresin	0.001
Immortelle absolute and extract	0.001
Isoamyl alcohol	0.001
Kola nut extract	0.001
Lime oil	0.001
Mate leaf extract and oil	0.0001
Anise, anise star and oils	0.0001
Bay leaf oil	0.0001
Cardamom oleoresin, oil, extract, seed powder	0.0001
Carrot oil	0.0001
Celery seed extract, solid, oil, and oleoresin	0.0001
Cinnamyl cinnamate	0.0001
Citronella oil	0.0001
Clove stem oil, leaf oil, bud oil	0.0001
Cognac white and green oil	0.0001
Coriander extract and oil	0.0001
Dill herb oil Geranium rose oil and geranium oil	0.0001 0.0001
Jasmine absolute, concentrate, oil	0.0001
Lemon oil	0.0001
Mace powder, oil, and extract	0.0001
Myrrh oil, absolute and resinoid	0.0001
Parsley seed oil	0.0001
Patchouly oil and absolute (Pogostemon spp.)	0.0001
Pepper oil, black and white	0.0001

Petitgrain oil and absolute	0.0001
Pine needle oil Pine oil, Scotch	0.0001 0.0001
Rose absolute and oil	0.0001
Sandalwood oil, yellow	0.0001
Tarragon oil	0.0001
Thyme oil, white and red	0.0001
Violet oil and absolute	0.0001
C. Dyes and Pigments	
Beta carotene	0.0001
D. Solvents	
Ethyl alcohol	0.96
Benzyl alcohol	0.08
1-Butanol	0.01
Ethyl acetate	0.01
Ethyl hexanoate	0.01
Ethyl butyrate	0.001
Ethyl propionate	0.001
E. Solid state components	
Cellulose fibers	1.31
Diatomaceous earth	0.05
Titanium dioxide	
Beeswax	0.0001
F. Chemicals added that influence or buffer pH	
Ammonium phosphate dibasic	0.96
Ammonium hydroxide	0.48
Citric acid	0.70
Triethyl citrate	0.01
Acetic acid	0.001
L-Aspartic acid	0.001
Hexanoic acid	0.001
Lactic acid	0.001
Phosphoric acid	0.001
Pyruvic acid	0.001
Butyric acid Heptanoic acid	0.0001 0.0001
Propionic acid	0.0001
Sorbic acid	0.0001
G. Other chemicals (function unknown)	
Urea	0.33
Carboxymethyl cellulose	0.05
Dihydrocoumarin (3,4-)	0.01
Hydroxyphenyl-2-butanone (4-para)	0.01

Methoxybenzaldehyde (para-)	0.01
Methylacetophenone	0.01
Methylcyclopentenolone	0.01
Trimethylcyclohex-2-ene 1,4-dione	0.01
L-Valine	0.01
Acetanisole	0.001
Benzaldehyde	0.001
Benzoin resin and absolute	0.001
Caryophyllene (beta-)	0.001
Castoreum extract	0.001
Decalactone (delta-)	0.001
Dimethyl-1,2-cyclopentadione 3,4-)	0.001
Dimethyl-5,9-undecadien-2-one (6,10-)	0.001
Ethyl phenyl acetate	0.001
Ethyl heptanoate	0.001
Ethyl maltol	0.001
Ethyl-3-methyl pyrazine (2-)	0.001
Ethyl octadecanoate	0.001
Heptalactone (gamma-)	0.001
Hexen-1-yl acetate	0.001
Hydroxy-2,5-dimethyl-3(2H)-furanone (4-)	0.001
Isoamyl octanoate	0.001
Isoamyl phenylacetate	0.001
Isobutyl alcohol	0.001
Isobutyraldehyde	0.001
Isopropyl (2E,4E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate	0.001
Leucine (L-)	0.001
Linalool dimethyl-1,6-octadiene-3-ol(3,7-)	0.001
Methyl butyraldehyde (3-)	0.001
Methyl-2-pyrrolyl-ketone	0.001
Oak moss and oak moss absolute	0.001
Octalactone	0.001
Orris root concrete, oil and extract	0.001
Palmarosa Oil Phenethyl acetate	0.001 0.001
Phenethyl alcohol	0.001
Phenylacetic acid	0.001
Pipsissewa leaf extract (Chimaphila spp.)	0.001
Proline (L-)	0.001
Tetramethyl pyrazine (2,3,5,6-)	0.001
Trimethylcyclohex-1-enyl)but-2-en-4-one (4-(2,6,6-)	0.001

Trimethylcyclohexa-1,3-dienyl)but-2-en-4-one(4-(2,6,6-)	0.001
Cedarwood oil terpenes	0.0001
Acetophenone	0.0001
Acetyl pyrazine	0.0001
Acetyl pyridine (2-)	0.0001
Acetyl pyridine (3-)	0.0001
Acetyl thiazole (2-)	0.0001
Alanine (L-)	0.0001
Alfalfa extract and powder	0.0001
Amyl formate Amrys oil	0.0001 0.0001
Anisyl acetate	0.0001
Anisyl alcohol	0.0001
Benzophenone	0.0001
Benzyl benzoate	0.0001
Benzyl butyrate	0.0001
Benzyl cinnamate	0.0001
Bois de rose oil (Aniba spp.)	0.0001
Bornyl acetate	0.0001
Butanedione(2,3-)diacetyl	0.0001
Butyl acetate	0.0001
Butyl butyrate	0.0001
Butylidenephthalide(3-)	0.0001
Camphene	0.0001
Canaga oil	0.0001
Carvomenthenol(4-)	0.0001
Caryonphyllene oxide (beta-)	0.0001
Cassie absolute and oil (Acacia spp)	0.0001
Cedar leaf oil (Thuja spp)	0.0001
Cedarwood oil alcohols	0.0001
Cinnamyl alcohol	0.0001
Cinnamyl isovalerate	0.0001
Citral	0.0001
Citronella oil	0.0001
Citronellol (DL-)	0.0001
Costus root oil (Saussurea spp.)	0.0001
Cymene (para-)	0.0001
Cysteine(L-)	0.0001
Davana oil (Artemisia spp.)	0.0001
Decadienal (2-trans, 4-trans)	0.0001
Decalactone (gamma-)	0.0001

Decanal	0.0001
Decanoic acid	0.0001
Diethyl malonate	0.0001
Diethylpyrazine	0.0001
Dimethoxyphenol (2,6-)	0.0001
Dimethylpyrazine (2,3-)	0.0001
Dimethylpyrazine (2,5-)	0.0001
Dimethylpyrazine (2,6-)	0.0001
Dimethyl-1,3,4-octatriene(3,7-)	0.0001
Dimethyl-6-octenoic acid(3,7-)	0.0001
Dodecalactone (delta-)	0.0001
Dodecalactone (gamma-)	0.0001
Estragole	0.0001
Ethylbenzaldehyde(4-)	0.0001
Ethylbenzoate	0.0001
Ethylcinnamate	0.0001
Ethyldecanoate	0.0001
Ethylhexanol(2-)	0.0001
Ethylisovalerate	0.0001
Ethyllactate	0.0001
Ethyl laurate	0.0001
Ethyl levulinate	0.0001
Ethyl myristate	0.0001
Ethyl nonanoate	0.0001
Ethyl palmitate	0.0001
Ethyl phenol (para-)	0.0001
Ethyl-2-methyl butyrate	0.0001
Ethyl-3(5 or 6)-dimethyl pyrazine	0.0001
Ethyl-3-hydroxy-4-methyl-2-(5H)-furanone	0.0001
Ethylguaiacol(4-)	0.0001
Farnesol	0.0001
Furfuryl mercaptan	0.0001
Galbanum oil and extract	0.0001
Geraniol	0.0001
Geranyl acetate	0.0001
Geranyl butyrate	0.0001
Geranyl formate	0.0001
Glutamic acid (L-)	0.0001
Guaiac wood oil	0.0001
Guaiacol	0.0001
Heptadienal (2,4-)	0.0001
Heptanone (2-)	0.0001
Hepten-2-one (3-)	0.0001

Heptyl acetate	0.0001
Hexalactone (gamma-) Hexanal	0.0001 0.0001
Hexen-1-ol (3-)	0.0001
Hexenal (2-)	0.0001
Hexyl alcohol	0.0001
Hydrolyzed soy protein	0.0001
Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (2-)	0.0001
Hydroxybutanoic acid lactone (4-) butyrolactone (gamma-)	0.0001
Hydroxycitronellal Hydroxydihydrotheaspirane (6-)	0.0001 0.0001
Ionone (alpha-)	0.0001
Ionone (beta-)	0.0001
Isoamyl acetate	0.0001
Isoamyl butyrate	0.0001
Isoamyl formate	0.0001
Isoamyl isovalerate	0.0001
Isobutyl acetate	0.0001
Isobutyl cinnamate	0.0001
Isobutyl phenylacetate	0.0001
Isobutyl-3-methoxypyrazine (2-)	0.0001
Isobutyric acid	0.0001
Isoeugenyl methyl ether	0.0001
Isovaleric acid	0.0001
Linalool oxide	0.0001
Lysine (L-)	0.0001
Menthyl acetate	0.0001
Methoxy-4-methylphenol (2-)	0.0001
Methoxy-3-methyl pyrazine (2- or (5-or 6-)	0.0001
Methoxyphenyl-2-propanone (1-para)	0.0001
Methyl anisate	0.0001
Methyl anisole	0.0001
Methyl anthranilate	0.0001
Methyl benzoate	0.0001
Methyl butyraldehyde (2-)	0.0001
Methyl butyric acid (2-)	0.0001
Methyl cinnamate	0.0001
Methyl ester of rosin, partially hydrogenated	0.0001
Methyl heptanoic acid (2-)	0.0001
Methyl hexanoic acid (2-)	0.0001
Methyl linoleate and methyl linolenate	0.0001

mixed	
Methyl phenylacetate Methyl pyrazine (2-)	0.0001 0.0001
Methyl quinoxaline (5-)	0.0001
Methyl salicylate	0.0001
Methyl-2-furoate	0.0001
Methyl-3,5-heptadien-2-one (6-)	0.0001
Methyl-5-thiazole ethanol (4-)	0.0001
Methylthiomethylpyrazine	0.0001
Methylthiopropionaldehyde (3-)	0.0001
Mimosa absolute and extract	0.0001
Myristic acid	0.0001
Nonalactone (gamma-)	0.0001
Nonanal	0.0001
Nonanoic acid	0.0001
Nonanone (2-)	0.0001
Octadecadienoic acid (9,12-) (48%) and octadecatrienoic acid (9,12,15-) (52%)	0.0001
Octalactone (delta-)	0.0001
Octanoic acid	0.0001
Octen-3-ol (1-)	0.0001
Octenal (2-)	0.0001
Oleic acid	0.0001
Olibanum oil (Boswellia spp.)	0.0001
Opoponax oil and gum	0.0001
Pentadecalactone (omega)	0.0001
Pentanedione (2,3-)	0.0001
Phellandrene (alpha-)	0.0001
Phenethyl butyrate	0.0001
Phenethyl cinnamate	0.0001
Phenethyl isobutyrate	0.0001
Phenyl phenylacetate	0.0001
Phenyl-1-propanol (3-)	0.0001
Phenylacetaldehyde	0.0001
Phenylalanine (L-)	0.0001
Phenylpropionaldehyde	0.0001
Phenylpropionic acid	0.0001
Phenyl propyl acetate (3-)	0.0001
Pinene (alpha-)	0.0001
Pinene (beta-) Propenyl guaethol	0.0001 0.0001
Propylidene phthalide (3-)	0.0001
Pyridine	0.0001

Rhodinol	0.0001
Rum ether Salicylaldehyde	0.0001 0.0001
Sodium benzoate	0.0001
Sodium citrate	0.0001
Terpineol (alpha-)	0.0001
Terpinolene	0.0001
Tetramethyl-13-oxatricyclo(8,3,0,0[4,9])-tridecane(1,5,5,9-)	0.0001
Thymol	0.0001
Tolualdehydes (o-, m-, p-)	0.0001
Tolyl acetate (para-)	0.0001
Trimethyl pyrazine (2,3,5-)	0.0001
Trimethyl-1-hexanol (3,5,5-)	0.0001
Undecalactone (delta-)	0.0001
Undecalactone (gamma-)	0.0001
Undecanone (2-)	0.0001
Valeraldehyde	0.0001
Veratraldehyde	0.0001
Valerolactone (gamma-)	0.0001
Vetiver oil (Vetiveria spp.)	0.0001
Violet oil	0.0001