The Chemical Constituents in Cigarettes and Cigarette Smoke:

Priorities for Harm Reduction

A Report to the New Zealand Ministry of Health

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SUMMARY

This report discusses possible components of a harm reduction strategy for tobacco products. We describe what a harm reduction strategy might include and discuss how such a strategy can be justified from a public health viewpoint. The report reviews and summarises the available data and international policies relating to chemical constituents (excluding nicotine and tar) of cigarettes and cigarette smoke. Reported yields of toxic chemicals in smoke were taken from all available published sources. In all, 95 chemicals in cigarette smoke were identified. These 95 chemicals include 45 known or suspected carcinogens, according to the International Agency for Research on Cancer, and many other chemicals with non-cancer adverse health effects. We combined central estimates of the reported yields of these chemicals with their published cancer potency factor slopes or reference concentrations for non-cancer effects, obtained from the United States Environmental Protection Agency, to propose a risk-based priority-setting scheme for harm reduction of cigarettes.

Internationally, limits on these hazardous components of cigarette smoke do not exist. However, the Canadian Province of British Columbia has instituted mandatory industry reporting of 44 chemical quantities by cigarette brand and these results are published on the World Wide Web. The possibility of instituting such mandatory reporting is being discussed by several States or Governments.

This report also lists additives and ingredients in New Zealand cigarettes, from data supplied by industry returns to the Ministry of Health, grouped by what we viewed as the main purpose of the additive or ingredient. While most of these additives or ingredients are of low toxicity, most serve an unknown purpose, and many others appear to be added for enhancing flavour or influencing pH of the tobacco, which would influence the absorption of certain compounds, such as nicotine. The NZ returns do not provide a basis to examine product-specific risks as they are a combined list of all products.

We were unable to locate any information quantitatively relating additives or ingredients of cigarettes to resulting concentrations of chemicals in smoke. The knowledge of combustion chemistry linking these parameters is lacking internationally.

Suggested measures for consideration are provided to help guide Governmental policy development should any harm reduction strategy for tobacco products be pursued.

Introduction

Objectives of this Report

The objectives of this report are (1) to assemble and assess information on the types and quantities of chemical constituents, apart from nicotine and tar, that exist in cigarettes, tobacco, and tobacco smoke, with particular reference to the situation in New Zealand; (2) to develop priority list(s) of these chemicals for monitoring purposes; and (3) to propose a possible strategy for harm reduction based on the priority list(s).

Background

A previous report to the Ministry (Blakely and Bates, 1998) reviewed the available epidemiology studies on the relative health impact of varying tar and nicotine yields in tobacco products. Overall, the studies reviewed indicated that there was some reduction in adverse health effects including cancer, respiratory, and cardiovascular disease, among smokers of lower tar and nicotine yield cigarettes. However, the reduction in risk was not as much as would have been anticipated on the basis of a simple comparison in tar yields. This is probably because smokers of low nicotine yield cigarettes adjust their smoking behaviour, for example by blocking ventilation holes or taking deeper or more frequent puffs, to maintain their previous intake of nicotine, the main addictive component of cigarettes. This process is often referred to as "compensation".

The previous report (Blakely and Bates, 1998) concluded that a prudent option for New Zealand would be to gradually reduce nicotine and tar levels together, so long as tar levels were reduced proportionately as much as, or more than, nicotine levels. This report also noted that consideration should be given to other chemicals in tobacco smoke, other than just tar and nicotine, particularly chemicals in the gaseous phase, the intake of which would not be reduced by simply reducing tar.

This report follows on from the previous work on nicotine and tar, by considering other chemicals that smokers may be exposed to. This forms part of a "harm reduction" strategy. Ideally, all smokers would cease smoking entirely and, on that basis, efforts would be focused on getting them to quit (or not to start). However, experience shows that this is not a practicable objective in the near future. Therefore, there may be merit in regulating or encouraging changes in cigarettes, so that they are less harmful to those who smoke them. This is the basis of a harm reduction strategy for tobacco products.

As about 4,700 New Zealanders die from smoking-related diseases each year (17% of all deaths), even a small reduction in the toxicity of cigarette smoke would be beneficial in terms of public health gain. It is unlikely that a truly "safe cigarette" could ever be developed, as combustion products in smoke are inherently potentially harmful. Nevertheless, it may be possible to reduce some of the toxic potency of cigarettes if the most significant causative agents of disease can be identified and reduced or eliminated. However, it is important that such a strategy did not give the public the impression that

cigarette smoking had become a safe practice. Such a perception could counteract any gains made by the reduction of the toxicity of tobacco smoke. The 1998 ESR report therefore recommended that the Ministry of Health commission an independent monitoring programme of harmful constituents of cigarettes other than tar and nicotine.

The current report attempts to characterise the toxicological risks from individual chemical components of cigarette smoke so that priority chemicals can be identified in the event that a harm reduction strategy focusing on toxicological risks is undertaken in New Zealand. In addition to the identification and quantitative assessment of the toxicological risks from smoke constituents, it is important to identify additives or ingredients in cigarettes that are either harmful themselves, lead to the formation of harmful constituents in smoke, increase the absorption of nicotine, increase the addictiveness of cigarettes, or otherwise increase the prevalence of smoking.

Harm reduction strategies

There are several ways in which harm reduction from cigarettes might be effected, including:

1. Prohibition of specified additives in tobacco products
2. Direct regulation of the maximum permitted content or concentration of particular chemicals in tobacco products
3. Direct regulation of the maximum permitted yield of specified chemicals in tobacco smoke
4. Publication, either on or in the packets of tobacco products or at points of sale, of the content or concentration of particular chemicals in tobacco products or of the yield of prioritised chemicals in the smoke.[1] This would allow market forces to work in favour of products with lower levels of the particular chemicals.

Depending on the chemical in question, any of these approaches might be appropriate.

Methodology

General

The methodology had three main steps:

1. A comprehensive search, using the Internet and bibliographic databases, was carried out for published papers and reports dealing with the nature of tobacco additives and chemicals produced during the curing process, and constituents of tobacco smoke (in New Zealand and elsewhere), assessments of their toxic hazards, and actions taken by jurisdictions in other countries.

[1] It is widely accepted that the standard methods of measuring smoke yield do not necessarily reflect actual smoker intake of tobacco smoke.

2. Identified chemicals are examined in terms of the available evidence for an influence on the toxicity of cigarette smoke or for affecting the attractiveness or addictive qualities of tobacco products. For the toxicity of chemicals in smoke, a process of prioritisation (ranking) was applied. This process involved ranking the identified chemicals in terms of their comparative risks. The comparative risk assessment was based on published analytical results for mainstream and sidestream cigarette smoke combined with published toxicological potency information for cancer and non-cancer health effects. The methodology is explained in more detail in the following section.

3. Suggestions are made for possible actions related to harm minimisation that could be taken in New Zealand. These suggestions take into account the availability of appropriate analytical methods and, also, what other countries are currently doing or proposing to do about the same chemicals.

Risk ranking of tobacco smoke constituents

The risk-based prioritisation of chemicals in cigarette smoke was carried out by combining the reported yields (levels in smoke) of chemicals with their respective toxicological potencies, to arrive at a comparative risk estimate. The health effects associated with each chemical were divided into carcinogenic and non-carcinogenic endpoints, based on published international hazard assessments.

Cancer risk prioritisation

For prioritisation of cancer risks, known or suspected human carcinogens in tobacco smoke that had a published cancer potency factor were included. Chemicals reported to occur in cigarette smoke from any published source were included for consideration. Those chemicals designated as Group 1 (*known human carcinogens*) or Group 2A (*probably carcinogenic to humans*) or 2B (*possibly carcinogenic to humans*) by the International Agency for Research on Cancer (IARC) were included. This may lead to an underestimation of the true level of risk since there may be many carcinogenic compounds in tobacco smoke that have not yet been tested for carcinogenicity. In addition, other compounds, despite being suspected human carcinogens, have no published cancer potency factor available (e.g. isoprene, styrene). The cancer risks listed should only be taken as initial screening values for the purposes of prioritisation, and not as definitive levels of actual cancer risk.

Non-cancer risk prioritisation

For prioritisation of constituents with known non-cancer health effects, it was necessary to derive a hazard index (HI) based on target organ toxicity, with particular attention to cardiovascular, respiratory, reproductive, and other health effects. The HI for mainstream smoke was calculated using publicly available reference exposure levels (RELs) with respective target organs listed by the United States Environmental Protection Agency (USEPA) or California Environmental Protection Agency (USEPA IRIS database, 1999;

Cal/EPA 1999). A standard 20 m^3/day breathing rate default value was used for estimating exposures and converting RELs into units of ?g/person/day. Estimates of risks to passive smokers were complicated by uncertainties in estimating an "average" passive smoker exposure on a ?g/cigarette/person/day basis. For this reason, the relative risks from sidestream smoke are reported in arbitrary units normalised to 100% for the chemical constituent posing the greatest contribution to health risk.

Reference Exposure Levels (RELs)

Reference Exposure Levels were derived from human epidemiological data (e.g., from workplace studies) or from data obtained from experimental animals. These RELs can be viewed as practical threshold levels below which one would not expect to measure any adverse effects. The RELs contain margins of safety ranging from a factor of 1 to a factor of 1000, depending on the data used as the basis for the toxicological effect. These uncertainty factors are used to provide a margin of safety to account for variability in human response or uncertainties in extrapolation from controlled experimental conditions to what is actually experienced by the general public. The RELs are intended to provide a practical threshold below which adverse effects would not be expected with chronic exposure. These RELs have been used to calculate a hazard index for each chemical, relative to its measured concentrations in main and side stream smoke.

Hazard Index

The hazard index (HI) approach permits the assessment of the relative contribution of individual chemicals to the toxicity of a complex mixture, such as cigarette smoke.
The underlying assumption is that the toxicity of each individual chemical in a given mixture is additive with other chemicals that affect the same target tissue or organ system. All HIs assume there is a threshold exposure below which adverse effects are not expected to occur. The necessary components of a hazard index calculation are (1) a measured or estimated exposure to the chemical, and (2) a health risk benchmark concentration or reference dose for comparison (the reference exposure level or reference concentration). The REL is taken from the most sensitive effect reported in the toxicological or epidemiological literature combined with an appropriate margin of safety. The value used for comparison carries a specification as to the target organ or system for a given toxic effect. A chemical often has more than one target organ (e.g. dioxin), in which case, to be health protective, the benchmark level for the most sensitive effect is used for the other target organs. In this report, publicly available values from the US EPA or California EPA were used.

The HI was calculated as follows: $HI = E_1/REL_1 + E_2/REL_2 + \ldots E_n/REL_n$ where E = a measured or estimated exposure to a chemical, and REL is the chemical's reference exposure level for a given target organ effect. An HI > 1 implies that the threshold for toxic effects on the target organ has been exceeded. The HI calculations for mainstream smoke are based on the reported yields of a single cigarette. Clearly, most smokers consume more than a single cigarette per day. However, the purpose is to provide a comparative risk ranking of tobacco smoke constituents, rather than an assessment of actual risk. Therefore, it is not necessary to take into account the number of cigarettes

smoked. For the purposes of this report, the HI values provide a basis for prioritisation of non-cancer adverse health effect concerns about known chemicals in cigarette smoke. This prioritisation can be used to guide decisions on monitoring of chemicals.

Results

Results are presented separately for tobacco smoke constituents and tobacco itself. Both of these areas are considered in terms of the following subsections:

?? Nature of the chemicals and their known health-related effects

?? The current situation in New Zealand

?? The situation in other countries

?? Appropriate monitoring of chemicals in New Zealand

Tobacco smoke constituents

Chemicals in smoke

Cigarette smoke comprises a highly complex chemical mixture of non-specific products of organic material combustion, (such as acetaldehyde and formaldehyde) and chemicals that are specific to the combustion of tobacco and other components of the cigarette (e.g. tobacco-specific nitrosamines). For most of the compounds and substances added to tobacco, little is known of their combustion chemistry. This creates difficulties in determining the relationship between chemicals in tobacco and chemicals actually inhaled in the smoke.

It has been estimated that there are over 4000 chemical constituents in tobacco smoke (British Columbia Ministry of Health, 1998). Of these, about 400 have been measured or estimated in mainstream and sidestream smoke (Cal/EPA 1997). Of the 400, a significant amount of toxicology data exist for less than 100. Combined with its vast array of toxic constituents is the addictive quality of tobacco, which is largely due to naturally occurring high nicotine and related alkaloid levels. Some chemical constituents of tobacco, such as ammonia, influence the toxicity of the smoke indirectly by serving to increase the pH of inhaled smoke and therefore facilitate the absorption of nicotine in its unionised state
(U.S. Surgeon General report, 1988).

The following are brief details of some of the known components of cigarette smoke:

Carcinogens

Cigarette smoke contains numerous known or suspected human carcinogens. The International Agency for Research on Cancer (IARC) has listed 36 chemicals that are "known to cause cancer" (Group 1) in humans (IARC, 1999). Cigarette smoke contains at least 10 of these 36 compounds, plus many more mutagenic chemicals that are in the "probably carcinogenic" or "possibly carcinogenic" categories (IARC Group 2).

Accordingly, cigarette smoke is in the United States Environmental Protection Agency's (USEPA) Group A and the IARC Group 1 classification for carcinogens (known to cause cancer in humans).

"Tar"

"Tar" is defined as the nicotine-free, dry, particulate mass of tobacco smoke (U.S. Surgeon General, 1988). The particulate fraction of cigarette smoke contains many harmful carcinogenic constituents, including metals, PAHs, dioxins, and some non-volatile nitrosamines. The nature of the chemical components in tar and their toxicity vary widely across tobacco from various sources. Therefore, measurement of tar, per se, is only a crude measure of the relative toxic potential of tobacco combustion products.

Tar levels (yields) of cigarette brands have traditionally been measured by a standardised method involving a smoking machine. Results of such testing (and similarly for nicotine) are often published with the implication that the relative tar levels provide a measure of relative toxicity of the particular tobacco product. On the basis of these results cigarette brands have sometimes been classified as, for example, "high", "medium", and "low" yield cigarettes. However, a criticism is that the machine smoking is far from simulating actual human smoking behaviour and smokers have ways of increasing their intake, for example, by blocking ventilation holes and taking deeper or more frequent puffs. Recent data from British Columbia (B.C.) highlights some of these concerns. The first tests on cigarettes sold in B.C. showed that under the "realistic smoking condition", there is very little difference between 'light' and 'regular' cigarettes. Light cigarettes can even produce higher amounts of nicotine and carbon monoxide than the regular cigarettes tested in some cases. This is also true of the other compounds found in cigarette smoke, like cadmium, benzo[a]pyrene, and benzene.

Gases

In addition to the particulate fraction (tar) of tobacco smoke, many chemicals are found in the gaseous phase. The levels of these chemicals may or may not have a relationship to the yield of tar. The most widely reported of the gaseous chemicals is carbon monoxide (CO). Carbon monoxide is emitted in high concentrations (thousands of parts per million) in cigarette smoke. The toxicity of carbon monoxide is a function of its ability to form carboxyhaemoglobin, a stable chemical complex with haemoglobin. This effectively serves to remove oxygen-carrying haemoglobin from the circulating blood and to vital tissues. Carboxyhaemoglobin concentrations in the blood of about 2% or more of haemoglobin have been associated with angina pain in people with cardiovascular disease and can result in cardiac ischaemia and diminished blood flow to the heart. Some other important chemicals in tobacco smoke, such as benzene, are also found in the gaseous phase of the smoke, but are correlated with the amount of tar (Smith et al., 1997).

Nitrosamines

Nitrosamines are organic amines containing a nitro (-NO) group bound to an amine group through a nitrosation reaction. Organic compounds containing secondary or tertiary amine

groups are particularly susceptible to nitrosation. In tobacco, a number of amine-containing alkaloids chemically related to nicotine undergo nitrosation reactions, many of which are favoured under nitrate-rich conditions. Most of the nitrosamines that have been studied have been shown to cause DNA adducts and mutations. Several are known human carcinogens. It has been known for many years that there exist nitrosamines in tobacco and tobacco smoke, including some that are specific to the tobacco leaf, and some that are produced by the combustion of other materials in the presence of high concentrations of nitrate.

Non-specific nitrosamines of a volatile nature that have been reported to occur in tobacco smoke include N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosoethylmethylamine, N-nitrosodiethanolamine, N-nitrosopyrrolidine (NP), and N-nitroso-n-butylamine (NBA) (Mitacek et al., 1999).

The compounds that are specific to tobacco are commonly referred to as non-volatile Tobacco-Specific Nitrosamines, or TSNAs. There are four TSNAs that are widely reported in the literature: N-nitrosoanabasine (NAB), N-nitrosoanabatine (NAT), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and nitrosonornicotine (NNN). Of these, NNK and NNN appear to have the greatest mutagenic potential. NNK and NNN have been shown to cause DNA adducts associated with tumours in rodents and are classified as probable human carcinogens by IARC (Hecht, 1999; IARC 1999). Insufficient data currently exist to classify NAB and NAT as human carcinogens. However, regulatory agencies, including the USFDA and USEPA consider nitrosamines of any kind to be potential mutagens and cancer hazards just by virtue of their chemical structure (http://www.fda.gov/cvm/fda/TOCs/G3pt3g.html).

Tobacco industry data have been released for the yields of NNN, NNK, and NAT for a selection of different brands (Imasco Company data submitted to Health Canada). The data show that "Extra" low tar brands tend to have a significantly lower yield of TSNAs for the smoker by standard measurement methods (i.e. in absence of compensatory smoking mechanisms). However, the amount of TSNAs in sidestream smoke is similar.

The amount of TSNAs in cigarettes appears to vary widely from one country to another (Fischer et al., 1990b). It is also apparent that measured levels of TSNAs are not necessarily highly correlated with one another. For example, Polish cigarettes were reported as having 10 times the amount of NNN as compared with British cigarettes, yet the NNK levels were the same for both countries (Fischer et al., 1990b). The levels of NNN and NNK appear to vary more widely than the other volatile nitrosamines tested (Mitacek et al., 1999). Some have suggested that an increase in prevalence of the adenocarcinoma type of lung cancer tumours in smokers may be explained by increasing levels of some TSNAs, most notably NNK.

Nitrosamine formation is promoted by high levels of nitrate and nitrite. Tobacco nitrate levels have been reported to be correlated with the formation of NDMA, NDEA, NP, NBA, NAB and NAT, whereas the concentrations of NNK and NNN do not seem to be affected (Fischer et al., 1990a). This shows that the level of nitrosamines in cigarette smoke is a function of both existing levels of some types of NAs in tobacco (i.e. NNK and NNN), and those nitrosamines

that are products of chemical reactions during combustion in the presence of nitrate (NAB and NAT).

One recent review by tobacco company scientists reports a positive correlation in cigarette smoke between nitrate levels and 2-naphthylamine and 4-aminobiphenyl, both Group I carcinogens (Smith et al., 1997). These researchers concluded that a reduction in use of fertilisers high in nitrates and heavy metals would significantly reduce the carcinogenicity of cigarette smoke by reducing the levels of nitrosamines, cadmium, nickel, chromium, beryllium, arsenic, 2-naphthylamine and 4-aminobiphenyl.

Polynuclear aromatic hydrocarbons (PAHs)

Polynuclear aromatic hydrocarbons (PAH) compounds are formed through combustion of any organic material. Benzo(a)pyrene (BaP) is the most commonly studied and one of the most toxicologically potent of these compounds. The cancer risks associated with PAH exposures in chemical risk assessments are typically normalised to that of BaP. A detailed analysis of BaP levels in Canadian cigarettes showed average levels of 17 ng/cigarette mainstream smoke, but ultra and extra low tar yield brands had a mean value of about half this value under standard smoking conditions (Kaiserman and Rickert, 1992).

Chlorinated Dioxins and Furans

Chlorinated dioxins and furans (collectively referred to as "dioxins") are ubiquitous environmental contaminants formed through the reaction of organic matter and chlorine, often under conditions of combustion. A report on the levels of dioxins in the New Zealand environment has been recently published (Ministry for the Environment, 1999). This shows that the overall level of dioxin contamination in New Zealand is comparatively low by world standards. The dioxin content of cigarette smoke would be a function of the presence of dioxins in the cigarette itself, and the formation of dioxins from the chlorine and organic matter of the cigarette during the combustion process. A report on dioxin levels Swedish cigarettes showed dioxin levels of 1490 pg/20 cigarettes mainstream smoke (Lofroth and Zebuhr, 1992).

Tobacco smoke constituent reporting in New Zealand

In New Zealand, the Smoke-free Environments Act (1990), Sections 33 and 34 state:

> 33. **Annual testing for constituents** -
>
> (2) Every manufacturer and every importer of any class of tobacco product to which this section applies shall in each year conduct, in accordance with regulations made under this Part of this Act, a test for the constituents of each brand of that class of product sold by the manufacturer or importer, and the respective quantities of those constituents.
>
> 34. **Director-General may require further testing** -
>
> (1) Subject to subsection (3) of this section, in addition to the annual test required by subsection (2) of section 33 of this Act, the Director-General may, by notice of writing to the manufacturer or importer of any class of tobacco product to which that section applies, require a further test to be

carried out for the constituents of any brand of that class of product sold by the manufacturer or importer and the respective quantities of those constituents.

(2) Any such additional test shall be carried out in a laboratory nominated by the Director-General, but at the expense in all respects of the manufacturer or importer.

(3) The Director-General shall not, in any year, require tests under this section in respect of more than 10 percent of the brands of tobacco products sold by any particular manufacturer or importer.

These regulations provide a legal basis for the Director-General of Health to require testing for chemical constituents of tobacco products. However, to date, the tobacco companies have been required to report only nicotine and tar yields for cigarette products, on an annual basis. Reporting of carbon monoxide levels is also required under the Smoke-free Environments Regulations 1999, and will begin in the year 2000.

Tobacco smoke monitoring/reporting situation in other countries

Several countries or regions now have reporting requirements for constituents (other than tar and nicotine) in cigarettes and cigarette smoke. From February 1999, the State of Minnesota in the United States has required reporting of yields of ammonia, arsenic, cadmium, lead, and formaldehyde in cigarette smoke.

The British Columbia Ministry of Health currently has the most stringent reporting requirements for tobacco products (including cigarette tobacco, pipe tobacco, cigars and cigarellos, smokeless tobacco, and cigarette tubes). The Tobacco Act of 1997 requires companies to declare the yields of 44 constituents present in main and sidestream smoke under "normal" and "intensive" smoking conditions. Worldwide, this is the first such information to be made publicly available. The chemical analysis results for 11 Canadian brands can be found at the British Columbia Ministry of Health website for standard (non-intensive) smoking conditions. Yields and exposures to these constituents under intensive (compensatory) smoking conditions are higher, but the relative proportions of individual constituents do not change. The Canadian cigarette constituent reports are open to the public and are posted on the Websites of the British Columbia Ministry of Health (*http://www.cctc.ca.bcreports)* and Physicians for a Smokefree Canada
(http://www.smoke-free.ca/eng_issues/etsoutsmokers.htm)

Regulations governing the toxic constituents of cigarette smoke internationally are currently very limited. A search of international legislation found no legal limits placed on toxic constituents other than nicotine, tar, and carbon monoxide in cigarettes, tobacco, or tobacco smoke. The European Commission is currently (October 1999) considering a proposal to limit nicotine, tar, and carbon monoxide yields to levels of
1 mg, 10 mg, and 10 mg per cigarette, respectively. Regulations on nicotine and tar yields have been summarised in a previous report (Bates, 1998). Some regulations are very specific for labelling and reporting. In Canada, for example, the Tobacco Products Control Regulations

(http://www.hc-sc.gc.ca/ehp/ehd/tobacco/legislat/tobacco.pdf)

stipulate that nicotine, tar, and carbon monoxide levels be quantified and specified for consumer information on labels of packages for sale. The labelling requirements are very specific in terms

of placement, visibility, font size, etc. Similar laws apply in the United States and in New Zealand.

Development of a priority list for monitoring smoke constituents

An attempt was made to assemble a list of all known chemical constituents reported in cigarette smoke (Table 1). It is possible that there are other known chemicals that were not identified. However, we believe that the vast majority of the chemicals reported to exist in cigarette smoke are listed. In all, 95 chemicals were found, including some chemical classes, such as "chlorinated dioxins and furans". Where possible, Table 1 gives **(1)** an IARC cancer classification of Group 1 (known to be carcinogenic to humans) or 2a or 2b (probably or possibly carcinogenic to humans), or 3 (not classifiable as a human carcinogen); **(2)** a publicly available cancer potency factor (CPF); and **(3)** a published non-cancer reference exposure level (REL).

There were 14 chemicals in the British Columbia reporting requirements for which such indicators were not available, and so although quantitative measurements of concentrations in smoke exist, their cancer and non-cancer risks could not be quantitatively evaluated. Similarly, some chemicals in the IARC Group 2 cancer hazard classifications do not have published potency factors, and so statements about their toxicological risks can only be qualitative.

Table 1 lists the reported yields of chemical constituents in cigarette smoke used in this report for the purposes of risk assessment. Central estimates (i.e. the midpoint of a range) were used whenever possible. Yields of constituents from cigarettes smoked under standard conditions were used, as this provided a common denominator for comparison across different studies.

Table 1. Chemicals that have been reported to occur in cigarette smoke (listed alphabetically), with cancer classifications, cancer potency factors and non-cancer reference exposure levels

	Chemical	**IARC classification[a]**	**Cancer potency[b] (mg/kg/d)$^{-1}$**	**Non-cancer REL and target organ (? g/m^3)**	(µg/cigarette) **mainstream**	(µg/cigarette) **sidestream**
1	1,3 – Butadiene	2A	3.4	8 (repro/dev)	35.5 [c]	191 [c]
2	1-Aminonaphthalene				0.0096 [c]	0.0647 [c]
3	1-Methylpyrrolidine					
4	2-, 3- and 4-Methylpyridines					
5	2,5-Dimethylpyrazine					
6	2-Aminonaphthalene	1	1.8		0.007 [c]	0.039 [c]
7	3-Aminobiphenyl				0.0017 [c]	0.019 [c]
8	3-Ethenylpyridine				662 [e]	
9	4-Aminobiphenyl	1	21		0.0012 [c]	0.01 [c]
10	4-N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	2B			0.3 [f] - midpoint of reported range	0.195 [f]
11	Acetaldehyde	2B	0.01	9 (resp)	680 [c]	1571 [c]
12	Acetone				287 [c]	917 [c]
13	Acrolein	3		0.02 (resp/eye)	68.8 [c]	306 [c]
14	Acrylonitrile	2A	1	2 (resp)	8.9 [c]	86.2 [c]
15	Ammonia			100 (resp)	12.2 [c]	4892 [c]
16	Arsenic	1	12	0.03 (dev/card/nerv)	0.7 [g]	
17	Benz(a)anthracene	2A	0.39		0.045 [e] midpoint of range	
18	Benzene	1	0.1	60 (dev/card/nerv/ immune)	46.3 [c]	272 [c]
19	Benzo(a)pyrene	2A	3.9		0.0099 [c]	0.141 [c]
20	Benzo(b)fluoranthene	2B	0.39		13 [e] midpoint of range	
21	Benzo(j)fluoranthene	2B	0.39		0.00135 [k]	
22	Benz(k)fluoranthene	2B	0.39		0.009 [k]	
23	Beryllium	1	8.4		0.00025 [g] midpoint of range	
24	Bicyclohexyl					
25	Butyraldehyde				32.4 [c]	88.2 [c]
26	Cadmium	1	15	0.01 (kidney/resp)	0.103 [c]	0.736 [c]
27	Carbon Monoxide			10,000 (8 hr) (card)	13,609 [c]	42,451 [c]
28	Catechol	2B			88.2 [c]	164.9 [c]
29	Chlorinated dioxins and furans	1	1.3E5	0.00004 (dev/immune/resp/ end/alimentary)	0.000075 [h]	0.000152 [h]
30	Chromium (hex)	1	51	0.0008 (resp)	0.0042 [c]	0.054 [c]
31	Chrysene	3	0.039		0.05 [e]	
32	Crotonaldehyde	3			14.2 [c]	80.9 [c]
33	Cyclohexane					
34	Cyclopentane					
35	Dibenz(a,h)acridine	2B	0.39		0.0001 [e]	

36	Dibenz(a,j)acridine	2B	0.39		0.0027 [e]	
37	Dibenz(a,h)anthracene	2A	4.1		0.004 [e]	
38	7H-Dibenzo(c,g)carbazole	2B	3.9		0.0007 [e]	

Table 1 continued …

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	Chemical	**IARC classification[a]**	**Cancer potency[b] $(mg/kg/d)^{-1}$**	**Non-cancer REL and target organ (? g/m^3)**	(µg/cigarette) **mainstream**	(µg/cigarette) **sidestream**
39	Dibenzo(a,i)pyrene	2B	39		0.0025 [k]	
40	Dibenzo(a,l)pyrene	2B	39			
41	Dimethylamine					
42	1,1-Dimethylhydrazine	2B				
43	3-Ethenylpyridene					662 [d]
44	Ethylamine					
45	Ethylbenzene			1000 (dev/aliment/ kidney)		130[d]
46	Formaldehyde	2A	0.021	2 (resp/eyes)	33.0 [c]	407.8 [c]
47	Furfural					
48	Hydrazine	2B	17	0.2 (aliment/end)	0.034 [k]	
49	Hydrogen cyanide			3 (card)	118.4 [c]	106 [c]
50	Hydrogen sulphide			0.9 (resp)		
51	Hydroquinone				72.2 [c]	183.5 [c]
52	Indeno(1,2,3-c,d)pyrene	2B	0.39		0.012 [k]	
53	Isoprene	2B			264 [c]	1140 [c]
54	Lead	2B	0.042		0.0128 [c]	0.045 [c]
55	m + p cresol			4 (card)	14 [c]	79.6 [c]
56	Mercury			0.3 (nerv)	0.0052 [c]	
57	Methyl acrylate					
58	Methyl chloride					
59	5-Methylchrysene	2B	3.9		0.0006 [k]	
60	Methyl ethyl ketone			1000 (repro)	54.8 [c]	175.6 [c]
61	Methylamine					
62	Methylpyrazines					
63	Nickel	1	0.91	0.05 (resp/immune)	0.011 [c]	0.031 [c]
64	Nicotine					919 [d]
65	Nitric Oxide				37.7 [c]	1438 [c]
66	Nitrogen dioxide			20 (resp)		
67	2-Nitropropane	2B			0.001 [k]	
68	N-nitrosoanabasine (NAB)	3			0.019 [f]	
69	N-nitrosoanabatine (NAT)	3			72.2 [f]	52.3 [f]
70	N-nitroso-n-butylamine (NBA)	2B	11		0.012 [j]	
71	N-nitrosodiethanolamine	2B	2.8		0.03 [e]	
72	N-nitrosodiethylamine (NDEA)	2A	36		0.0083 [e]	0.0405 [e] midpoint of range used
73	N-nitrosodimethylamine (NDMA)	2A	16		0.0244 [e] midpoint of range for filtered cigarettes used	1.41 [e] midpoint of range for filtered cigarettes used
74	N-nitrosoethylmethylamine	2B	22		0.006 [k]	
75	N-nitrosomorpholine	2B	6.7			
76	N-nitrosonornicotine (NNN)	2B	1.4		1.9 [e] midpoint of reported range	49.8 [f]
77	N-nitrosopyrrolidine (NP)	2B	21		0.113 [e]	
78	o – cresol			4 (card)	5.7 [c]	31 [c]
79	Phenol			600 (aliment/card/	26.1 [c]	330 [c]

				kidney/nerv)		
80	Polonium-210					
81	Propionaldehyde				49.8 [c]	128.3 [c]

Table 1 continued …

Table 1 / p3

	Chemical	IARC classification[a]	Cancer potency[b] $(mg/kg/d)^{-1}$	Non-cancer REL and target organ (? g/m^3)	(µg/cigarette) mainstream	(µg/cigarette) sidestream
82	Pyridine				11.8 [c]	250.8 [c]
83	Pyrrole					402 [d]
84	Pyrrolidine					
85	Quinoline				0.356 [c]	10.1 [c]
86	Resorcinol				1.2 [c]	0.94 [c]
87	Selenium			0.08 (resp)		
88	Styrene	2B		1000 (nerv)	5.71 [c]	99.5 [c]
89	Toluene			400 (dev/nerv/ aliment)	72.8 [c]	499 [c]
90	2-Toluidine				0.115 [e]	
91	Trimethylamine					
92	Urethane	2B	1		0.029 [k]	
93	Vinyl acetate	2B		200 (resp)		
94	Vinyl chloride	1	0.27		0.0086 [g]	
95	Xylenes			200 (nerv/resp)		366 [d]

[a] IARC classifications can be found at: (*http://193.51.164.11/monoeval/grlist.html)*
1: known human carcinogens
2A: probable human carcinogens
2B: possible human carcinogens
3: unclassifiable as a human carcinogen

[b] cancer potency factors and RELs are those reported by the California EPA (1999; *http://www.oehha.ca.gov/scientific/other.html*).

[c] BC MOH: from the British Columbia website: *(http://www.cctc.ca/bcreports/)*,

[d] Daisey et al., 1998

[e] NTP 1998

[f] Imasco company nitrosamine data - Health Canada

[g] Smith et al., 1997

[h] Lofroth and Zebuhr, 1992

[i] Kaiserman and Rickert, 1992

[j] Mitacek et al., 1999

[k] CDC: US Surgeon General Report 1989

resp = respiratory system; repro/dev = reproductive or developmental processes; aliment = alimentary system (GI tract, liver); immune = immune system; card = cardiovascular system; nerv = nervous system; end = endocrine system

(California Environmental Protection Agency, *www.oehha.ca.gov*); US Environmental Protection Agency, *www.epa.gov/iris/*)

** US National Ambient Air Quality Standard (*http://www.arb.ca.gov/aqs/aaqs2.pdf*).

A. Comparative cancer risk rankings

Table 2 lists the results of comparative cancer risk estimate calculations. Reported concentrations of chemical constituents in main or sidestream tobacco smoke (Table 1) were combined with cancer potency factors (CPFs) derived by USEPA or Cal/EPA for cancer risk assessments. CPFs were not available for all carcinogenic compounds, and for some compounds, measured concentrations were available only for mainstream smoke.

A CPF for NNK was not found. Therefore, the published CPF for NNN was also used for NNK.

As an example of the underlying calculations, the exposure level for 1,3-butadiene (35.5 ug/cigarette) in mainstream smoke (see Table 1) was multiplied by the published cancer potency factor of 3.4 $(mg/kg/day)^{-1}$ to give a comparative cancer risk value of 8.6E-04 for a 70 kg person smoking for 35 years:

cancer risk = [0.0355 mg/cig/70 kg body weight] x 3.4 $(mg/kg/day)^{-1}$ x [35 years exposure /70 year lifespan] = 0.00086 per cigarette per day

Table 2a. Cancer Risks from individual Chemical Components in Cigarette Smoke: Mainstream Smoke

Cancer Risk Rank (Mainstream)	Chemical	Cancer Risk per Cigarette/day*	IARC Classification (as of October 1999)
1	1,3 - Butadiene	8.6E-04	2A
2	Chlorinated dioxins	7.0E-05	1
3	Acrylonitrile	6.4E-05	2B
4	Arsenic	6.0E-05	1
5	Acetaldehyde	4.9E-05	2B
6	Benzene	3.3E-05	1
7	NNN	1.9E-05	2A
8	NP	1.7E-05	2B
9	Cadmium	1.1E-05	1
10	Formaldehyde	5.0E-06	2A
11	Hydrazine	4.1E-06	2A
12	NNK	3.0E-06	2B
13	NDMA	2.7E-06	2A
14	NDEA	2.1E-06	2A
15	Chromium	1.5E-06	1
16	NEMA	1.3E-06	2B
17	NBA	9.4E-07	2B
18	2-Aminonaphthalene	9.0E-07	1
19	Dibenzo(a,i)pyrene	7.0E-07	2A
20	Nitrosodiethanolamine	6.0E-07	2B
21	Benzo(a)pyrene	2.8E-07	2A
22	Dibenz(a,h)anthracene	2.3E-07	2A
23	Urethane	2.1E-07	2B
24	4-aminobiphenyl	1.8E-07	1
25	o-toluidine	1.5E-07	2B
26	Nickel	7.2E-08	1
27	Benzo(j)fluoranthene	3.8E-08	2B
28	Benzo(b)fluoranthene	3.6E-08	2B
29	Indeno(1,2,3-c,d)pyrene	3.3E-08	2B
30	Benzo(k)fluoranthene	2.5E-08	2B
31	Dibenz(c,g)carbazole	2.0E-08	2B
32	5-methylchrysene	1.7E-08	2B
33	Vinyl chloride	1.7E-08	1
34	Beryllium	1.5E-08	1
35	Benz(a)anthracene	1.3E-08	2B
36	Dibenz(a,j)acridine	7.5E-09	2B
37	Lead	3.8E-09	2B
38	Chrysene	3.6E-09	3
39	dibenz(a,h)acridine	2.8E-10	2B

* Calculated using published cancer potency factors (see Table 1) combined with quantitative estimates of chemical content in mainstream cigarette smoke (Table 1). Risk estimates are calculated on a per cigarette/day basis for a 70 kg person smoking for 35 years out of an average 70 year lifespan, and 100% absorption from mainstream smoke delivery measurements under standard smoking conditions is assumed. No complex toxicokinetic parameters were used (i.e. no synergism or antagonism was assumed). These risk estimates are rough calculations and should be viewed as a means to compare and prioritise relative risks rather than quantify true cancer risk probability.

Table 2b. Relative Cancer Risks from Individual Chemical Components in Cigarette Smoke: Sidestream Smoke (ETS)

Cancer Risk Rank (Sidestream)	Chemical	Relative Risk Scale	IARC/USEPA Classification (as of August 1999)
1	1,3 – butadiene	100%	2A
2	Acrylonitrile	13.3%	2B
3	NNN	10.7%	2B
3	Benzene	4.2%	1
4	N-nitrosodimethylamine	3.5%	2A
5	Chlorinated dioxins/furans	3.0%	1
6	Acetaldehyde	2.4%	2B
8	Cadmium	1.7%	1
9	Formaldehyde	1.3%	2A
10	Chromium	0.43%	1
	N-nitrosodiethylamine	0.22%	2B
11	Benzo(a)pyrene	0.09%	2A
	NNK	0.04%	2B
7	4-Aminobiphenyl	0.03%	1
12	2-Aminonaphthalene	0.01%	1
13	Nickel	0.004%	1
14	Lead	0.0001%	2B

* Calculated using published cancer potency factors (Table 1) combined with quantitative estimates of chemical content in sidestream cigarette smoke (Table 1). For the purposes of this table, it is assumed that the bioavailability of each component is approximately equal to the passive smoker. Quantitative estimates of average exposure to ETS were not available and therefore quantitative cancer risks are not presented. The relative scale of cancer risk is given in the 3rd column, with the highest risk compound (1,3-butadiene) assigned an arbitrary value of 100%.

B. Non-cancer health effect rankings

The vast mixture of different chemicals in cigarette smoke can affect almost every organ system in the body, given sufficient duration of exposure. Major target organ systems in which non-cancer effects of smoking occur include the respiratory system, the heart and cardiovascular system, reproductive system, the eyes, and the nervous system. Foetal development, including birthweight, can also be affected. It is generally assumed that for these effects there is a threshold of exposure below which the effects would not occur (unlike the situation with cancer, for which it is often assumed there is no threshold).

Tables 3 through 6 show the hazard indices (mainstream smoke) and relative contributions to adverse health effects (sidestream smoke) calculated for all chemicals for which a non-cancer REL was available. The hazard index for mainstream smoke was calculated on a per cigarette per day chronic basis, assuming normal smoking conditions and no contribution from passive smoke. Estimates of yield for intense or compensatory smoking are often 2-3 fold higher than the values for normal smoking, and can be found at the website of the Physicians for a Smokefree Canada (*http://www.smoke-free.ca/eng_issues/etsoutsmokers.htm*). However, these will not alter the comparative risk rankings calculated on the basis of standard yields.

The relative scales of risk from passive smoking are constructed to allow prioritisation of constituents that result in the greatest health risk, but the absolute degree of hazard was not calculated due to the wide range of possible exposure scenarios one could construct to model the exposure of a passive smoker.

As seen in the tables below, even a single cigarette per day gives a mainstream delivery sufficient to exceed the hazard indices for both cardiovascular and respiratory effects, the latter by a very large margin (HI = 177).

Table 3. Cardiovascular effects - mainstream smoke

Chemical	**Reported concentrations**[a] (?g/cigarette)	**Reference Exposure Level**[b] (?g/m^3)	**Hazard index**[c]
Hydrogen cyanide	118.3	3	**1.973**[d]
Arsenic	0.7	0.03	**1.17**
m + p cresol	14	4	0.175
Chlorinated Dioxins/Furans	7.45E-5	4E-5	0.093
o cresol	5.7	4	0.071
Carbon monoxide	13,609	10,000	0.068
Benzene	46.3	60	0.039
Phenol	26.1	600	0.002
Total hazard index			**3.59**

[a] Table 1, this report

[b] Reference exposure levels are intended to protect sensitive individuals against chronic effects over a chronic period of continuous exposure.

[c] the HI is equal to reported concentrations ? Reference Exposure Level, assuming an average 20 m^3/day breathing rate.

[d] bold numbers indicate a hazard index greater than 1.0 which signals that adverse effects could be experienced by some people.

Table 4. Respiratory effects - mainstream smoke

Chemical	Reported concentrations[a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Hazard index[c]
Acrolein	68.8	0.02	**172**[d]
Acetaldehyde	680	9	**3.778**
Formaldehyde	33	2	0.825
Cadmium	0.103	0.01	0.515
Chromium	0.0042	0.0008	0.263
Acrylonitrile	8.9	2	0.223
Chlorinated dioxins/furans	7.45E-5	4E-5	0.093
Nickel	0.011	0.05	0.011
Ammonia	12.2	100	0.0006
Total HI			**177.7**

[a] from British Columbia Ministry of Health combined average for 11 leading cigarettes. Normal (non-intensive) smoking values were used.

[b] Reference exposure levels are intended to protect sensitive individuals against effects over a chronic period of continuous exposure.

[c] the HI is equal to reported concentrations ? Reference Exposure Level, assuming an average 20 m^3/day breathing rate.

[d] bold numbers indicate a hazard index greater than 1.0 which signals that adverse effects could be experienced by some people.

Table 5. Reproductive and developmental effects - mainstream smoke

Chemical	Reported concentrations[a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Hazard index[c]
Arsenic	0.7	0.03	**1.17** [d]
1,3 – butadiene	35.5	8	0.22
chlorinated dioxins	7.45E-5	4E-5	0.093
Benzene	46.3	60	0.039
Toluene	72.8	400	0.0091
Methyl ethyl ketone	54.8	1000	0.0027
Mercury	0.0052	0.03	0.00087
Total HI			**1.53**

[a] Table 1, this report

[b] Reference exposure levels are intended to protect sensitive individuals against effects over a chronic period of continuous exposure.

[c] the HI is equal to [reported concentrations ? (Reference Exposure Level *20)], assuming an average 20 m^3/day breathing rate.

[d] bold numbers indicate a hazard index greater than 1.0 which signals that adverse effects could be experienced by some people.

Table 6. Other effects - mainstream smoke

Chemical	Reported concentrations[a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Hazard index[c]
Eye irritation			
Acrolein	68.8	0.02	**172**[d]
Formaldehyde	33	2	0.825
Neurotoxicity			
Toluene	72.8	400	0.0091
Phenol	26.1	600	0.0022
Mercury	0.0052	0.03	0.00087
Styrene	5.71	1000	0.00029
Liver toxicity			
chlorinated dioxins	7.45E-5	4E-5	0.093
Toluene	72.8	400	0.0091
Phenol	26.1	600	0.0022
Kidney toxicity			
Cadmium	0.103	0.01	0.515
Phenol	26.1	600	0.0022

[a] Table 1, this report

[b] Reference exposure levels are intended to protect sensitive individuals against effects over a chronic period of continuous exposure.

[c] the HI is equal to [reported concentrations ? (Reference Exposure Level *20)], assuming an average 20 m^3/day breathing rate.

[d] bold numbers indicate a hazard index greater than 1.0 which signals that adverse effects could be experienced by some people

Sidestream Smoke

It is widely recognised that exposure to sidestream cigarette smoke is a cause of disease. Though the public health impact of sidestream smoke is much less than that of mainstream smoking, it was considered important to factor in sidestream smoking values and risks in this report. The estimation of relative health risks from sidestream smoke is complicated by the enormous variability in exposure. There is no general way to relate the amount of a chemical released from a burning cigarette to a precise chronic dose of chemical received by a passive smoker without taking into account variables such as specific room dimensions, room ventilation rates, and the amount of time spent in the presence of a smoker. Therefore, the risks in the table below are expressed only on a relative scale assuming each component has an equal chance of being inhaled by the passive smoker. The chemical with the greatest contribution to the toxicity to the specific target organ was assigned an arbitrary value of 100%, and each lesser contribution was scaled accordingly.

Table 7. Cardiovascular effects - sidestream smoke

Chemical	Reported concentrations[a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Relative Hazard Scale[c]
Hydrogen cyanide	106	3	100
m + p cresol	79.6	4	56.3
o cresol	31	4	21.9
Benzene	272	60	12.8
Carbon monoxide	42,451	10,000	12.0
Chlorinated Dioxins/Furans	1.5E-4	4E-5	10.6
Phenol	330	600	1.6
Arsenic	below detectable limit	0.03	not applicable

[a] Table 1, this report

[b] USEPA, 1999, or Cal/EPA 1999. Reference exposure levels are intended to protect against chronic effects over a chronic period of continuous exposure.

[c] the relative hazard is proportional to the ratio of reported concentrations to RELs. The scale is normalised to the chemical with highest risk at 100%

Table 8. Respiratory effects - sidestream smoke

Chemical	Reported concentrations[a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Relative Hazard Scale[c]
Acrolein	306	0.02	100
Formaldehyde	407.8	2	1.3
Acetaldehyde	1571	9	1.1
Cadmium	0.74	0.01	0.48
Chromium	0.054	0.0008	0.44
Ammonia	4892	100	0.32
Acrylonitrile	86.2	2	0.28
Chlorinated dioxins/furans	0.188	4E-5	0.025
Xylenes	366	200	0.012
Nickel	0.031	0.05	0.004

[a] Table 1, this report

[b] USEPA, 1999, or Cal/EPA 1999. Reference exposure levels are intended to protect against chronic effects over a chronic period of continuous exposure.

[c] the relative hazard is proportional to the ratio of reported concentrations to RELs. The scale is normalised to the chemical with highest risk at 100%

Table 9. Reproductive and developmental effects - sidestream smoke

Chemical	Reported concentrations [a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Relative Hazard Scale[c]
1,3 – butadiene	191	8	100
Benzene	272	60	19.1
Chlorinated dioxins	1.5E-4	4E-5	15.8
Toluene	499	400	5.2
Ethylbenzene	219	1000	0.92
Methyl ethyl ketone	175.6	1000	0.74
Mercury	not detected	0.03	---
Arsenic	not detected	0.03	---

[a] Table 1 this report

[b] USEPA, 1999, or Cal/EPA 1999. Reference exposure levels are intended to protect against chronic effects over a chronic period of continuous exposure.

[c] the relative hazard is proportional to the ratio of reported concentrations to RELs. The scale is normalised to the chemical with highest risk at 100%

Table 10. Other effects - sidestream smoke

Chemical	Reported concentrations[a] (?g/cigarette)	Reference Exposure Level[b] (?g/m^3)	Relative Hazard Scale[c]
Eye irritation			
Acrolein	306	0.02	100
Formaldehyde	407.8	2	1.3
Neurotoxicity			
Xylenes	366	200	100
Toluene	499	400	68.2
Phenol	330	600	30.1
Styrene	99.5	1000	5.5
Mercury	not detected	0.03	---
Liver toxicity			
chlorinated dioxins	1.5E-4	4E-5	100
Toluene	499	400	33.3
Phenol	330	600	14.7
Ethylbenzene	219	1000	5.9
Kidney toxicity			
Cadmium	0.736	0.01	100
Phenol	330	600	0.7
Ethylbenzene	219	1000	0.3

[b] USEPA, 1999, or Cal/EPA 1999. Reference exposure levels are intended to protect against chronic effects over a chronic period of continuous exposure.

[c] the relative hazard is proportional to the ratio of reported concentrations to RELs. The scale is normalised to the chemical with highest risk at 100%

Development of the priority list

Table 11 shows the summary results of the hazard ranking for mainstream and sidestream smoke for both cancer and non-cancer effects. This has been to derive the priority list of chemicals for monitoring in Table 13.

Table 11. Summary Table of Risk-Based Priorities for Toxic Constituents of Cigarette Smoke, as Smoked Under Standard Conditions

Effect	Mainstream smoke constituent	Cancer risk per cigarette/day	Sidestream smoke constituent	Relative risk scale
Cancer	1,3 – Butadiene	8.6E-04	1,3 – Butadiene	100%
	Chlorinated dioxins	7.0E-05	Acrylonitrile	13.3%
	Acrylonitrile	6.4E-05	NNN	10.7%
	Arsenic	6.0E-05	Benzene	4.2%
	Acetaldehyde	4.9E-05	N-nitrosodimethylamine	3.5%
	Benzene	3.3E-05	Chlorinated dioxins/furans	3.0%
	NNN	1.9E-05	Acetaldehyde	2.4%
	NP	1.7E-05	Cadmium	1.7%
	Cadmium	1.1E-05	Formaldehyde	1.3%
	Formaldehyde	5.0E-06	Chromium	0.43%
	Hydrazine	4.1E-06	N-nitrosodiethylamine	0.22%
	NNK	3.0E-06	Benzo(a)pyrene	0.09%
	NDMA	2.7E-06	NNK	0.04%
	NDEA	2.1E-06	4-Aminobiphenyl	0.03%
	Chromium	1.5E-06	2-Aminonaphthalene	0.01%
	NEMA	1.3E-06	Nickel	0.004%
	NBA	9.4E-07	Lead	0.0001%
	2-Aminonaphthalene	9.0E-07		
	Dibenzo(a,i)pyrene	7.0E-07		
	Nitrosodiethanolamine	6.0E-07		
	Benzo(a)pyrene	2.8E-07		
	Urethane	2.1E-07		
	4-Aminobiphenyl	1.8E-07		
	2-toluidine	1.5E-07		
	Nickel	7.2E-08		
	Benzo(j)fluoranthene	3.8E-08		
	Benzo(b)fluoranthene	3.6E-08		
	Indeno(1,2,3-c,d)pyrene	3.3E-08		
	Benzo(k)fluoranthene	2.5E-08		
	Dibenz(c,g)carbazole	2.0E-08		
	5-methylchrysene	1.7E-08		
	Vinyl chloride	1.7E-08		
	Beryllium	1.5E-08		

	Benz(a)anthracene	1.3E-08		
	Dibenz(a,j)acridine	7.5E-09		

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Non-cancer effects	Mainstream smoke	Hazard Index	Sidestream smoke	Relative risk scale
	Lead	3.8E-09		
	Chrysene	3.6E-09		
	Dibenz(a,h)acridine	2.8E-10		
Respiratory Effects	Acrolein	**172**	Acrolein	100%
	Acetaldehyde	**3.78**	Formaldehyde	1.3%
	Formaldehyde	0.83	Acetaldehyde	1.1%
	Cadmium	0.52	Cadmium	0.48%
	Chromium (hex)	0.26	Chromium (hex)	0.44%
	Acrylonitrile	0.22	Ammonia	0.32%
	chlorinated dioxins	0.09	Acrylonitrile	0.28%
	Nickel	0.011	Chlorinated dioxins	0.02%
	Ammonia	0.006	Xylenes	0.012%
			Nickel	0.004%
Cardiovascular Effects	Hydrogen cyanide	**1.97**	Hydrogen cyanide	100%
	Arsenic	**1.17**	m + p cresol	56.3%
	m + p cresol	0.18	o - cresol	21.9%
	Chlorinated dioxins	0.093	Benzene	12.8%
	o - cresol	0.071	Carbon Monoxide	12.0%
	Carbon Monoxide	0.068	Chlorinated dioxins	10.6%
	Benzene	0.039	Phenol	1.6%
	Phenol	0.0022		
Reproductive Effects	Arsenic	**1.17**	1,3 - Butadiene	100%
	1,3 - butadiene	0.22	Chlorinated dioxins	19.1%
	Chlorinated dioxins	0.09	Benzene	15.8%
	Benzene	0.04	Toluene	5.2%
	Toluene	0.0091	Ethylbenzene	0.92%
	Methyl ethyl ketone	0.0027	Methyl ethyl ketone	0.74%
	Mercury	0.00087		

(for mainstream smoke, the risk is per cigarette/day, assuming a 70 kg person). The cancer risk estimates should be viewed as rough screening values for the purposes of comparative estimation of risks, rather than a reflection of the true magnitude of cancer risk.

Table 12 lists the ten tobacco smoke constituents with the greatest comparative cancer risk values from main or sidestream smoke, plus those constituents with non-cancer HIs that exceed 0.1 (i.e. $1/10^{th}$ the concentration necessary to exceed a toxic threshold) for respiratory, cardiovascular, or reproductive/developmental toxicity, or relative contributions to non-cancer sidestream smoke risks greater than 10% for each effect.

It can be seen that the priority compounds for main and sidestream smoke are very similar. The result is a priority list of 16 chemicals (cresols and chlorinated dioxin isomers counting as one each). Eleven of the 16 chemicals in cigarette smoke identified in Table 12 are also required to be reported in British Columbia, Canada.

Although benzo(a)pyrene and other carcinogenic PAHs are widely cited as important carcinogens in cigarette smoke, our analysis showed that the risks from these compounds were low in comparison to many other compounds in smoke. Even if the risks from all the PAHs suspected to be carcinogens were combined, the risk would be lower than the 15th highest ranked compound, Chromium (VI). Therefore, we did not include PAHs on the final priority list.

Through communications with experts in the field of tobacco product analysis, it is clear that practicalities of constituent measurement need also to be considered. For example, in the analysis of NNN, the amounts of NNK can also be determined incidentally. Therefore, it may make sense to collect data on chemicals other than those on the list, if there is no additional cost to obtain them.

Table 12. Combined list of 16 priority chemicals in cigarette smoke
(listed alphabetically)

Chemical	Health Effect
1,3 – butadiene	cancer, reproductive/developmental
Acetaldehyde	cancer, respiratory irritation
Acrolein	respiratory irritation
Acrylonitrile	cancer, respiratory irritation
Arsenic	cancer, cardiovascular, reproductive/developmental
Benzene	cancer, reproductive/developmental
Cadmium	cancer
Carbon monoxide	cardiovascular
Chlorinated Dioxins and Furans	cancer, cardiovascular, reproductive/developmental
Chromium (VI)*	cancer, respiratory irritation
m + p + o Cresol	cardiovascular
Formaldehyde	cancer, respiratory irritation
Hydrogen cyanide	cardiovascular
N-nitrosonornicotine (NNN)**	cancer
N-nitrosodimethylamine (NDMA)	cancer
N-nitrosopyrrolidine (NP)	cancer

Note on ammonia: although ammonia toxicity is low by comparison with the other chemicals in cigarette smoke, ammonia levels influence pH, which affects nicotine absorption. There is, therefore, a case for including ammonia (and also pH) in the above list.
*It may not be possible to directly determine the hexavalent chromium levels separate from total chromium. In this case, default assumptions regarding the relative proportion of the hexavalent form would need to be included.

** Although the risks from NNK were somewhat lower than for NNN, analytical experts indicate that both NNN and NNK can be measured simultaneously, therefore it may make sense to include NNK as an incidental constituent.

Appendix A contains information on the availability of analytical methods for measuring the 16 identified priority substances in smoke, and the costs of these analyses.

Tobacco product constituents

Chemicals in tobacco products

Although it is the chemicals in cigarette smoke that are directly responsible for the health damage associated with smoking, it is important to understand the chemistry of tobacco products themselves, including the nature of the additives, of which there are at least several hundred. Many of these additives are used to affect the flavour and aroma of cigarettes and cigarette smoke. Other chemicals raise the pH of the cigarette smoke, thereby increasing the absorption of nicotine.

The following are some brief notes on the main chemical classes of additives in tobacco products.

Sweeteners

Sweeteners are used to affect the flavour, making cigarettes more appealing to some consumers. Some researchers are currently examining a proposed link between the presence of sugars in tobacco and the formation during combustion of acetaldehyde, a carcinogen and respiratory irritant. In addition, there has been concern that addition of sugars to cigarettes could encourage young people to start and continue smoking.

It appears that over 10% by weight of cigarettes could be sugars and various sweeteners. Sucrose and sucrose syrup, for example, may be used at up to 10% by weight.

Menthol

Menthol in cigarettes has a numbing effect on sensory nerve endings in the respiratory tract and helps to temporarily soothe sensations of discomfort in areas of inflammation and irritation. As such it may make smoking more tolerable to some smokers, including beginning smokers. The amount of menthol in cigarettes can be up to 0.71% by weight, according to industry data supplied to the NZ Ministry of Health. Information supplied to ESR from the UK indicates levels of menthol may be up to 2% by weight of some cigarettes (UK Department of Health, 1998).

Menthol is a commonly used ingredient in foods and topical ointments and throat lozenges. The 0.71% figure corresponds to roughly the equivalent of the amount of menthol in a typical cough drop (5-6 mg per gram of cigarette material). No information was available on how much of the menthol in a cigarette is inhaled when smoking.

Ammonia

Nicotine is most readily absorbed from the respiratory tract in its unionised chemical state. This state is achieved when smoke is inhaled under alkaline conditions (high pH), and smoke constituents, such as ammonia (from ammonium hydroxide and ammonium phosphate), facilitate

this effect. Ammonia treatment of tobacco facilitates this (Bates et al. 1999).

Naturally occurring chemicals

Tobacco is naturally rich in alkaloids, the most important being nicotine. There are at least 15 additional alkaloids that are structurally related to nicotine. The biological activity of most of these minor alkaloid chemicals is unknown. Several are known to have similar neuropharmacological actions to nicotine, although with less potency. Nornicotine and anabasine, for example, have similar pharmacological action to that of nicotine but only 20% to 75% potency (US Surgeon General, 1988). Some of these compounds, as secondary amines, are known to combine with nitrates to form carcinogenic nitrosamines that can be measured in tobacco smoke.

A wide range of toxic metals are also found in tobacco, depending largely on the soil content where the tobacco was grown. The use of fertilisers has been blamed for high concentrations of arsenic, mercury, lead, cadmium, chromium, polonium, and beryllium in tobacco (Smith et al., 1997).

No reports were found on levels of fungal mycotoxins in tobacco.

Pesticides in tobacco

Most tobacco crops are treated with pesticides, although generally the degree of monitoring of residue levels in the final product is likely to be low. A few studies from the 1970s indicated that organochlorine pesticide residues were commonly found in tobacco. The presence and types of pesticides found in tobacco will vary depending on the source country for the tobacco and regulations in force there. Some countries, such as Thailand, have regulatory limits for DDT residues in tobacco (the Thai maximum residue limit for DDT is 2 ppm in tobacco). The degree of transfer of pesticides or their breakdown products through mainstream or passive smoking is unknown. Another unknown is the nature and extent of the combustion products from these compounds. It is reported that benzo(a)pyrene (BaP) is a combustion product of DDT (*http://rampages.onramp.net/~bdrake/pest.html#cse50)*, but no peer-reviewed, published reports were found correlating BaP levels in smoke to DDT residues in the uncombusted product.

An internet site lists the major pesticides used on tobacco crops in different countries around the world (*http://rampages.onramp.net/~bdrake/pest.html#cse50)*. This list is reportedly based on a survey done by the USEPA in 1992, but the reference is not given and could not be found. The pesticides listed as used in New Zealand are methyl bromide and DDT (soil use only). However, tobacco is no longer grown commercially in
New Zealand, and DDT has been banned in NZ since 1989. There have been no exceptions for tobacco growing (John Reeve, personal communication).

The US Department of Health and Human Services (1998) make reference to the use of ethylene oxide as a fumigant for tobacco. However, no sources could be located that discussed the levels of ethylene oxide found in tobacco or tobacco smoke. Ethylene oxide forms stable reaction by-products (ethylene chlorohydrin and bromohydrin) in foods following fumigation.

These by-products are mutagenic, and possibly carcinogenic, but no reports on levels in tobacco or tobacco smoke were found.

The added health risks from pesticide residues in tobacco are unlikely to be significant as pesticide residues are likely to occur only in very low concentrations and be broken down through combustion into smaller non-specific organic chemical components.

Tobacco additive reporting in New Zealand

In New Zealand, tobacco companies are required to submit a set of annual "returns" to the Ministry of Health. These returns consist of a combined list of additives and ingredients from major manufacturers, and the maximum levels in tobacco products for each additive or ingredient. The New Zealand returns are very similar in length and content to lists supplied to other overseas agencies (e.g., UK, USA). The current reporting does not identify which tobacco products contain which additives. There is no requirement in New Zealand either to make the information currently supplied publicly available, or to keep it confidential.

Appendix B lists the additives reported in the most recent combined industry returns to the NZ Ministry of Health. Maximum percentages, which are upper limit concentrations, are provided. The NZ returns were categorised according to what appeared to be the obvious purpose of the additive (although this is not actually provided by the industry). Chemicals with unknown functions or effects are included in the "other" chemicals category at the end of the list.

Some of the additives listed in the NZ industry returns are foodstuffs or are derived from foods (e.g. chocolate, fruit juice extracts, etc.). These ingredients contribute to such things as improving the flavour of cigarettes, but it is not known whether they produce combustion products that either cause direct toxicological harm, or enhance the pharmacological addictive effects of nicotine or its absorption. There is evidence, for example, that xanthines such as theobromine from cocoa or caffeine from coffee cause central nervous system stimulation, cardiac stimulation, and bronchodilation (Reddy and Hayes, 1994). Inhaled bronchodilators could enhance nicotine absorption. Additionally, xanthines are secondary amines which may form nitrosamines in the presence of nitrate.

Tobacco additive reporting in other countries

There are few restrictions on the chemicals that may be added to tobacco products in various countries, and the levels of these additives are not regulated internationally.

In the UK, the regulation of tobacco additives follows a voluntary agreement between the tobacco industry and the UK Department of Health, established in March 1997 (UK Department of Health, 1998). Returns from the UK show that there are approximately 560 different additives in cigarettes, although which additives are used in which brands is either not known or not published, and the quantities added are also not known as these are regarded as proprietary secrets of the industry.

In the US, the Federal Cigarette Labeling and Advertising Act requires that each person who manufactures, packages, or imports cigarettes submit to the Secretary of Health and Human Services an annual list of ingredients added to tobacco in the manufacture of cigarettes. The Centers for Disease Control and Prevention's (CDC) Office on Smoking and Health collects and maintains these lists, which in total currently contain approximately 600 ingredients used in the manufacture of cigarettes. This information is defined by law as trade secret or confidential information and may not be released to the general public. However, in April 1994, six of the major tobacco companies released a list of over 600 ingredients added to tobacco in the manufacture of cigarettes in the US.

The State of Massachussettes has had legislation since 1997 requiring the reporting of added constituents in cigarettes. The information is not required to be made public.

The most specific and publicly available information on additives and ingredients comes from the Canadian British Columbia Ministry of Health website: (*http://www.cctc.ca.bcreports/ITLadditives)*. However, the list of ingredients is much smaller and more chemically specific than the list of additives supplied by the tobacco companies to the New Zealand Ministry of Health.

Thailand, in 1998, instituted national reporting requirements for tobacco industries to report to the Ministry of Public Health on additives in cigarettes, but again this requirement does not call for public release of the information.

Priorities for monitoring of tobacco products in New Zealand

The current situation does not lend itself to easy identification of priorities for monitoring or evaluation of additives in tobacco products in New Zealand. Although the Ministry of Health receives annual returns on additives used in New Zealand tobacco products (and these may be considered to be a form of monitoring), these returns are not product-specific.

As a first step to defining a list of additives that might justify more in-depth monitoring and evaluation, it would be appropriate to obtain additive information on a product-specific basis, so that the information supplied could be verified by independent analysis and so that evaluation of the possible health impacts of chemicals could take into account population-based exposures to these chemicals. This issue is covered further in the Discussion below.

Discussion

Ideally, policies to do with prevention of smoking would concentrate on preventing people from taking up the habit in the first place or assisting them to stop smoking entirely. However, such policies have been only partially successful and the proportion of the New Zealand adult population who are smokers has remained around 25 to 27% for most of the 1990s. We know that many smokers have considerable difficulty in quitting and a

substantial proportion of them will die prematurely and/or live for part of their lives with crippling diseases because of their habit. Presently the annual death toll in New Zealand attributable to smoking is about 4,700 people, and about 4 million worldwide. It is, therefore, appropriate to investigate ways in which the nature of the smoke inhaled may be modified to reduce the total mortality and morbidity. Potentially, a small percentage reduction in the toxicity of tobacco smoke could lead to the saving of many lives. This is the basis of harm reduction policies.

Harm reduction policies need to be concerned with both the addictive and the toxic components of the smoke. In the absence of either of these features, tobacco products would never have become the major public health problem that they are today. Ultimately, the focus must be on the nature of the tobacco product and its chemical content. However, continued scrutiny of the components of the smoke is essential for monitoring of the success of product modification strategies.

To date, most product modification efforts have focused on tar and nicotine levels in the smoke (yields). These efforts have had limited success, for a number of reasons, including:

1. Yields are measured by machines and the machine-measured yields are poor indicators of actual smoke intake by smokers. In particular, smokers are able to compensate for low nicotine yields by blocking ventilation holes and taking longer and deeper puffs. Measurement of yields under more realistic conditions (e.g., blocking ventilation holes of cigarettes) has shown that there is little difference between tobacco products with claimed high and low yields of tar or nicotine.

2. Tar is a fairly crude measure of toxic potential (although it is still one of the best indicators that we currently have available). Tar obtained from different tobacco products varies considerably in its degree of toxicity and carcinogenic potential (Gray et al., 1998). The nature of the tar will be dependent on the type of tobacco used and the additives included in the cigarette.

3. In New Zealand, as in probably all other countries, tobacco manufacturing companies have unregulated use of a wide range of additives and manufacturing processes that can be used to enhance the absorption of nicotine (e.g., ammonia, xanthines) or the attractiveness of tobacco products (e.g., sweeteners and flavouring agents). Potentially, these additives and processes could influence the toxicity or carcinogenic potential of tobacco smoke (e.g., by production of nitrosoamine compounds).

The tobacco companies, through their research, have gained much understanding of the way in which manufacturing methods and use of additives affects the acceptability of tobacco products by consumers. However, little of the underlying scientific information has been published in the peer-reviewed medical and scientific literature. Instead, it appears mainly to have been retained within the industry. The recent releases of tobacco company documents in the United States have brought much of this information to light. These documents also reveal the extent to which tobacco companies have sought to thwart regulatory harm reduction efforts based around control of smoke yield *(*http://www.cdc.gov/tobacco/industrydocs/*)*.

Consideration of these factors leads to the conclusion that there needs to be a greater focus on the composition of tobacco products. However, some monitoring of smoke and its constituents will remain critical, as it is the smoke that is inhaled and is responsible for the addiction and toxicity associated with tobacco products.

The specification for this project specified that we propose for monitoring a list of substances in smoke and in tobacco products themselves. On the basis of toxic potential we have been able to prioritise a list of substances likely to be found in smoke and for which monitoring would be appropriate (Table 12).[2] However, because of a lack of product-specific information on New Zealand tobacco additives, it has not been practicable to produce a prioritised list of substances for monitoring in tobacco products.

The tobacco company returns in New Zealand provide a list of additives (and maximum levels) that are stated to be used in tobacco products sold in this country. However, without accompanying information on the extent of the use of these additives, the list of several hundred additives makes it difficult to prioritise or to know where to concentrate any product regulation efforts.

Early returns of tobacco additives supplied to the Ministry of Health contained many more additives than were actually used in New Zealand. This made it even more difficult to prioritise monitoring and regulation efforts. That this was a deliberate strategy by the tobacco companies is strongly suggested by a recently released internal memo from
Philip Morris (Australia) Ltd, dated 18 January 1991, in which the New Zealand regulatory requirement for reporting a list of tobacco additives is discussed. In the memo it is stated that the list will be expanded "simply to obfuscate the mode", and also to protect their formulas from other tobacco companies. (Document can be viewed at:
http://www.philipmorris.com/getallimg.asp?DOCID=2023246519/6520)

The current situation, that has applied since about 1997, is that the list of additives is restricted to those actually used in all tobacco products sold in New Zealand. Although this is a major improvement, it is still difficult to prioritise monitoring efforts in the absence of information on the extent of use of each of these chemicals.

It is also not clear from the current New Zealand list whether the additives listed are included in the tobacco itself, or the paper or the filter. Nor is the purpose of many of the additives clear.

To remedy this information deficiency and to make possible harm reduction strategies based around an appropriate prioritisation of additives in New Zealand tobacco products, we suggest that consideration be given to adopting a set of requirements for tobacco

[2] A risk prioritisation report was prepared for the State of Massachusettes by Menzie-Cura and Associates, Inc. published in August of 1999. In that report, cancer and non-cancer health risks for mainstream cigarette smoke constituents were estimated using available exposure estimates and cancer potency factors or non-cancer RELs from various sources. It is noteworthy that their results are strikingly similar to those derived in this report. For example, of the chemicals giving the 10 highest cancer risks in the Massachusetts report, 8 are also in the top 10 of this report. Similarly, the compounds giving the highest non-cancer risks were acrolein, acetaldehyde, and hydrogen cyanide, which are also the highest contributors to non-cancer respiratory and cardiovascular effects identified in this report.

additive reporting, similar to that recently instituted by the Canadian province of British Columbia. This would involve reporting, on a product-specific basis, of the nature and quantities of all additives used in tobacco, cigarette papers, and filters, for all tobacco products sold in New Zealand. This reporting would occur at regular intervals, say once a year, and for new products introduced onto the market. We also suggest that this information be made public, as in British Columbia.

There would be a number of potential benefits of such a reporting requirement, including:

- It would be possible to appropriately prioritise and target harm reduction strategies based around not only the toxic or addictive potential of the additives, but also the extent of the population exposure to them (based on knowledge of product-specific additive levels and market shares).

- Verification of compliance with regulatory requirements would be made easier by knowledge of which products purported to contain which additives, and at what concentrations.

- Consideration together of comprehensive information on the composition of tobacco products and tobacco smoke might permit identification by researchers of product compositions that resulted in smoke of higher toxic or addictive potential.

- Comparison could be made with the composition of tobacco products available in other countries or jurisdictions with similar reporting requirements. Any unusual additives or combination of additives in New Zealand tobacco products could then receive appropriate scrutiny.

- It would permit identification of tobacco products containing tobacco additives "new" to New Zealand. These could be subjected to special scrutiny with regard to their potential impact on the public health.

- Publication of the information would allow individual smokers to choose tobacco products that minimised or avoided the use of particular additives.

A related issue would be verification of the accuracy of the tobacco industry reports if product-specific reporting were to be introduced. Some independent monitoring through analysis of the contents of a randomly selected sample of tobacco products would be appropriate for this purpose.

Suggested measures for consideration

On the basis of the above considerations, we suggest consideration be given to implementing the following measures to improve harm reduction for tobacco products in New Zealand:[3]

1. That tobacco companies be required to supply, at regular intervals (say, every 12 months), for each brand of cigarettes they market in New Zealand, the following information: Separately by tobacco, filter and cigarette paper, the nature of all additives and ingredients contained within each, identified by common or chemical names, as well as their chemical abstract numbers (when they exist), their functional purposes, and the range of concentrations for each of those additives or ingredients.

2. For cigarette brands with a market share of, say, 5% or more, consider implementing a tobacco smoke testing regime along the lines of that operated by the British Colombia Ministry of Health. The regime should use a risk-based priority list that identifies the chemicals contributing the greatest toxicological risks (e.g., Table 12 of this report, and accompanying footnote: acetaldehyde, acrolein, acrylonitrile, ammonia, arsenic, benzene, 1,3-butadiene, cadmium, carbon monoxide, chlorinated dioxins/furans, chromium, cresols, formaldehyde, hydrogen cyanide, NNN/NNK, NDMA and NP).

3. That the product-specific information on additives and smoke yields be made publicly available. In addition to providing consumers with information on which to make choices about tobacco products, this information would be very useful for researchers into tobacco and its effects.

4. An investigation be commissioned into the evidence for the use of additives to enhance the absorption or intake of nicotine, or the addictiveness or attractiveness of tobacco products. This investigation should follow and take into account the information on the constituents of New Zealand tobacco products obtained through implementation of the first of these suggestions. If appropriate, such an investigation should recommend appropriate restrictions on the use of additives in tobacco products.

5. That the industry-reported results for tobacco smoke constituent monitoring and product-specific additives be independently verified by analysis of a random sample of products in a reputable and experienced laboratory, and that such verification monitoring be carried out at regular intervals.

[3] We are aware that not all of our suggestions may be achievable under New Zealand legislation as it currently stands. However, we have taken the view that we should set out ideas for what we see as an appropriate approach, whatever their current legal feasibility. Legislation can always be amended.

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US Surgeon General Report 1989. Reducing the Health Consequences of Smoking: 25 Years of Progress. U.S. Department of Health and Human Services. Rockville, MD 20857 (Table 7).

Appendix A: Availability and Costs of Analytical Methods for Measuring Priority Substances in Tobacco Smoke

Standardised methods exist internationally for analysing all of the compounds shown in Table A1. A Canadian commercial laboratory (Labstat International, Inc.) routinely runs analyses for most of the chemicals, with the exception of dioxins and furans. However, the capacity to analyse samples for chlorinated dioxins and furans exists in New Zealand, and sample costs would be approximately $2,000 (NZ) each if done by ESR Analytical. However, it would first be necessary to obtain certified samples of tobacco smoke from accredited labs equipped with smoking machines. Obtaining certified samples for analysis may be possible through liaison with overseas companies, such as Labstat International, Inc., who perform similar sampling and analyses for overseas governments. The analytical methods for measuring constituents in cigarette smoke can be found at the following website: *http://www.hc-sc.gc.ca/ehp/ehd/tobacco/index.htm*. The Canadian Government has employed Labstat International, Inc. to provide analyses of the groups of compounds shown in Table A1:

Table A1. **Mainstream smoke analyses by Labstat, Inc** (personal communication with Dr Bill Rickert, October 1999; reprinted with permission)

Item	**Analysis of Mainstream Tobacco Smoke**	**Cost/sample** (Canadian $)	**Samples/ brand**	**Cost per item** (Canadian $)
1	ISO type smoking to include TPM, water, nicotine, PMWNF, CO, and puff number	$45	20	$900
2	Carbonyls (formaldehyde, acrolein, acetaldehyde, etc.)	$135	7	$945
3	Phenolics (phenol, cresol)	$125	7	$875
4	Benzo(a)pyrene	$325	7	$2,275
5	Aromatic amines (4-aminobiphenyl, 2-aminonaphthalene)	$435	7	$3,045
6	Nitric oxide	$115	7	$805
7	Hydrogen cyanide	$125	7	$875
8	Ammonia	$150	7	$1,050
9	Miscellaneous organics (benzene, toluene, 1,3-butadiene, styrene, isoprene, acrylonitrile)	$335	7	$2,345
10	Quinoline and pyridine	$310	7	$2,170
11	Trace metals (Pb, Cd, Hg, Ni, Sc, Cr, As)	$500	7	$3,500
12	pH	$115	7	$805
13	Tobacco specific nitrosamines (NNN, NNK, NAT, NAB)	$750	7	$5,250

Table A2. Sidestream smoke analyses by Labstat, Inc.

Item	Analysis of Sidestream Tobacco Smoke	Cost/sample (Canadian $)	Samples/ brand	Cost per item (Canadian $)
1	ISO type smoking to include TPM, water, nicotine, PMWNF, CO, and puff number	$130	7	$910
2	Carbonyls (formaldehyde, acrolein, acetaldehyde, etc.)	$160	7	$1,120
3	Phenolics (phenol, cresol)	$210	7	$1,470
4	Benzo(a)pyrene	$375	7	$2,625
5	Aromatic amines (4-aminobiphenyl, 2-aminonaphthalene)	$550	7	$3,850
6	Nitric oxide	$140	7	$980
7	Hydrogen cyanide	$160	7	$1,120
8	Ammonia	$180	7	$1,260
9	Miscellaneous organics (benzene, toluene, 1,3-butadiene, styrene, isoprene, acrylonitrile)	$425	7	$2,975
10	Quinoline and pyridine	$390	7	$2,730
11	Trace metals (Pb, Cd, Hg, Ni, Sc, Cr, As)	$620	7	$4,340
12	Tobacco specific nitrosamines (NNN, NNK, NAT, NAB)	$1,050	7	$7,350

Table A3. Tobacco analyses by Labstat, Inc.

Item	Analysis of cigarette filler	Cost/sample (Canadian $)	Samples/ brand	Cost per item (Canadian $)
1	Tobacco propionate	$75	3	$225
2	Tobacco sorbitol	$150	3	$450
3	Tobacco pH	$15	3	$45
4	Tobacco nitrate	$25	3	$75
5	Nicotine alkaloids	$50	3	$150
6	Tobacco specific nitrosamines (NNN, NNK, NAB, NAT)	$560	3	$1,680
7	Trace metals (Pb, Cd, Hg, Ni, Se, Cr, As)	$210	3	$630
8	Humectants (propylene glycol, triethylene glycol)	$90	3	$270
9	Triacetin plus triethylene glycol diacetate	$120	3	$360
10	Ammonia	$105	3	$315
11	Tobacco moisture	$10	3	$30

Table A4. Estimated cost per sample to obtain the analyses of the top 18 priority constituents in cigarette smoke

Test	Cost - main	Cost – side	Covers
Carbonyls	$135[a]	$160	acrolein, acetaldehyde, formaldehyde
Miscellaneous organics	$335	$425	1,3-butadiene, benzene, acrylonitrile
Metals	$500	$620	arsenic, cadmium, chromium
CO	$45	$130	carbon monoxide
Dioxins	$2000 (NZD)	$2500 (NZD)	chlorinated dioxins and furans
Hydrogen cyanide	$125	$160	hydrogen cyanide
Phenolics	$125	$210	m,p,o-cresols
Nitrosamines	$750	$1,050	NNN, NP
approximate total cost per sample (NZD)	$5,000 (NZD)	$6,600 (NZD)	All 15 high risk constituents

[a] costs are in Canadian dollars, except for dioxins, which were quoted in NZD. Total is calculated in NZD with the assumption that 1 NZD = 0.67 Canadian dollar.

Appendix B. List of Additives and Ingredients in Cigarettes from the 1998 New Zealand Tobacco Industry Returns

Additive or Ingredient	Max % (w)[a]
A. Sweeteners	
Sugars	4.68
Honey	2.91
Sorbitol	2.00
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
Licorice root, fluid or powder	1.29
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	0.01
Coffee, extract, concentrate	0.01

Appendix B continued …

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
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	0.0001
Geranium rose oil and geranium oil	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	0.0001

Appendix B continued …

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
Pine oil, Scotch	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	0.0001
Heptanoic acid	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

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
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	0.001
Phenethyl acetate	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

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
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	0.0001
Amrys oil	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

Appendix B continued …

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
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

Appendix B continued …

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
Hepten-2-one (3-)	0.0001
Heptyl acetate	0.0001
Hexalactone (gamma-)	0.0001
Hexanal	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	0.0001
Hydroxydihydrotheaspirane (6-)	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

Appendix B continued …

 B. Other flavourings

Additive or Ingredient	Max % (w)[a]
Methyl hexanoic acid (2-)	0.0001
Methyl linoleate and methyl linolenate mixed	0.0001
Methyl phenylacetate	0.0001
Methyl pyrazine (2-)	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-)	0.0001
Propenyl guaethol	0.0001

Appendix B continued …

App B / p9 **B. Other flavourings**

Additive or Ingredient	Max % (w)[a]
Propylidene phthalide (3-)	0.0001
Pyridine	0.0001
Rhodinol	0.0001
Rum ether	0.0001
Salicylaldehyde	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