



Report

Additives in Tobacco Products

Contribution of Carob Bean Extract, Cellulose Fibre, Guar Gum, Liquorice, Menthol, Prune Juice Concentrate and Vanillin to Attractiveness, Addictiveness and Toxicity of Tobacco Smoking



$\hbox{@}$ 2012 German Cancer Research Center (DKFZ), Heidelberg

Suggested citation:

German Cancer Research Center (ed.)
Additives in Tobacco Products:
Contribution of Carob Bean Extract, Cellulose Fibre, Guar Gum,
Liquorice, Menthol, Prune Juice Concentrate and Vanillin to
Attractiveness, Addictiveness and Toxicity of Tobacco Smoking
Heidelberg, Germany, 2012

Layout:

Sarah Kahnert, German Cancer Research Center, Heidelberg

Responsible for the content:
German Cancer Research Center
(Deutsches Krebsforschungszentrum, DKFZ)
Unit Cancer Prevention and
WHO Collaborating Centre for Tobacco Control

Head of Unit:

Dr. Martina Pötschke-Langer

Im Neuenheimer Feld 280 D-69120 Heidelberg, Germany

Phone: +49 (0) 62 21 42 30 07 Fax: +49 (0) 62 21 42 30 20 Email: who-cc@dkfz.de

Website: www.tabakkontrolle.de



Report

Additives in Tobacco Products

Contribution of Carob Bean Extract, Cellulose Fibre, Guar Gum, Liquorice, Menthol, Prune Juice Concentrate and Vanillin to Attractiveness, Addictiveness and Toxicity of Tobacco Smoking

Author: Dr. Urmila Nair

This report on tobacco additives, carob bean extract, cellulose fibre, guar gum, liquorice, menthol, prune juice concentrate and vanillin, has been created by the German Cancer Research Center (DKFZ), Heidelberg, Germany, and is available at DKFZ website http://www.dkfz.de/de/tabakkontrolle. Another report on 2-furfural, ammonium compounds, cocoa, glycerol, propylene glycol, sorbitol, sugars, acetaldehyde, created by the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, is available on the RIVM website http://www.tabakinfo.nl. The introduction is a common product. Photos are provided by the Federal Office of Public Health (FOPH), Switzerland.

The reports have been written in the context of the EU project Public InformationTobacco Control (PITOC) and aim to inform professionals on the general use, tobacco industry use and harmful health effects of selected tobacco additives. Simplified versions for the public, based on the fact sheets in the reports, have also been prepared and the originals in English are available at the DKFZ and RIVM websites. The simplified fact sheets aim to inform the public on the general use, tobacco industry use and harmful health effect of the selected tobacco additives; and have been translated by all 16 partners of the project to their national languages and will be disseminated through their websites.





Content

Introduc	ction	1
Genera	information on tobacco additives	2
	Carob Bean Extract	4
	Cellulose Fibre	7
	Guar Gum	11
	Liquorice	14
	Menthol	19
	Prune Juice Concentrate	25
	Vanillin	28

Additives in tobacco products Introduction

In the EU, smoking accounts for 695,000 preventable deaths per year1. In addition, almost 80,000 nonsmokers are estimated to die due to exposure to environmental tobacco smoke. Smoking also takes an enormous toll in health care costs and lost productivity. Still, some 30 % of all European citizens smoke. Most smokers start at young age; 90 % of all smokers start before the age of 18.

Tobacco additives may increase the consumption rate of tobacco products by making the product more palatable and attractive to the consumer, or by enhancing the addictiveness of the product. Additives may make individual brands taste more appealing and mask the taste and immediate discomfort of smoke. As such, additives may indirectly enhance tobacco related harm by increasing the consumption of these toxic products. The same effect will result from additives that enhance the addictiveness of tobacco components. Tobacco additives, especially when burnt, may also intrinsically increase the toxicity of the tobacco product. Many additives give toxic pyrolysis products when burnt. For instance, burning of sugars in tobacco will result in many toxic compounds including aldehydes.

This report is written in the context of the Tobacco Products Directive 2001/37/EC and the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), articles 9 and 102. The World Health Organization Framework Convention on Tobacco Control (FCTC) is a reaction to the worldwide tobacco epidemic and aims to contribute to the reduction of tobacco-related morbidity and mortality. Tobacco product control, including the attractiveness of tobacco products, is one of the means to this end. Articles 9 and 10 of the FCTC concern regulation of the contents of tobacco products and regulation of tobacco product disclosures respectively2. Of importance is the partial guideline of article 9, which states that regulating ingredients aimed at reducing tobacco product attractiveness can contribute to reducing the prevalence of tobacco use and dependence among new and continuing users. This prioritization of endpoints puts an emphasis in trying to regulate tobacco product attractiveness with guidance for addictiveness and toxicity being proposed at a later stage².

Chapters describe facts on the attractive, addictive and hazardous health effects associated with seven tobacco additives used by the tobacco industry most often and in highest quantities: carob bean, cellulose fibre, guar gum, liquorice, prune juice extract, menthol and vanillin available at http://www.dkfz.de/ de/tabakkontrolle. It aims to provide policy makers with evidence based background information required for proper tobacco product regulation. Facts concerning health hazards of the selected tobacco ingredients were collected through literature research, and were thoroughly and critically reviewed by an external expert in the field of tobacco product composition. The National Institute for Public Health and Environment (RIVM), Bilthoven, the Netherlands published a similar report on seven other additives, which are available at http://www.tabakinfo.nl.

- European Commission (2012) Health-EU (website). http://ec.europa.eu/health-eu/my_lifestyle/tobacco/ index_en.htm (accessed on 28 July 2012)
- Conference of the Parties of the WHO Framework Convention on Tobacco Control (FCTC) (2010) Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (Regulation of the Contents of Tobacco Products and Regulation of Tobacco Product Disclosures). FCTC/COP4(10), http://www.who.int/fctc/guidelines/Decisions9and10.pdf (accessed on 28 July 2012)

Additives in tobacco products General information on tobacco additives

The tobacco industry uses many additives in the manufacturing of tobacco products. Over 600 ingredients are known to be added to tobacco products. The modern American blend cigarette contains about 10 per cent additives by weight, such as sugars, cocoa, menthol liquorice1.

Reasons for adding additives to cigarettes

Additives are intentionally added to cigarettes by the tobacco industry to modify flavour, regulate combustion, moisturise the smoke, preserve the cigarettes, and in some instances to act as solvents for other additives1. Other non-reported effects of additives include the enhancement of attractiveness or consumer appeal and addictiveness of the tobacco products.

In the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) report published in 2010, attractiveness with regard to tobacco products is defined as the stimulation to use a tobacco product. The attractiveness of tobacco products may be increased by a number of additives but can also be influenced by external factors such as marketing, price, among others2. Specific additives can mask the bitter taste, improve the flavour and reduce the irritation of inhaled smoke. Examples of flavouring substances include sugars, benzaldehyde, maltol, menthol and vanillin. Spices and herbs can also be used to improve the palatability of tobacco products. Examples include cinnamon, ginger and mint. New techniques to deliver these attractive flavourings are continuously being developed and marketed by the industry. For example, a novel menthol product introduced in several countries employs a capsule in the filter that allows a high boost of menthol when crushed by the smoker almost twice that of an uncrushed capsule³. Altogether, these additives have the potential to enhance the attractiveness of cigarettes.

Nicotine is the main addictive component in cigarette smoke, but evidence is accumulating that additional

Additives in tobacco products e.g. menthol

can increase

- attractiveness.
- addictiveness and
- toxic emissions

therefore increase smokers' exposure to toxic smoke emissions

Increase

- health risk,
- cancer risk,
- morbidity and
- mortality

Lifetime smokers lose an average of 14 years of life

Smokers die younger

http://ec.europa.eu/health/tobacco/law/pictorial/index_en.htm

components present in cigarette smoke affect tobacco addiction. Sugars are an example of additives hypothesized to indirectly influence addictiveness of cigarette smoking by generating combustion products such as acetaldehyde. Acetaldehyde enhances the self-administration of nicotine in rodents presumably via the production of Harman. The generation of harman is the hypothesized indirect route through which acetaldehyde is presumed to increases the addictiveness to tobacco smoke4.

The adverse effects of additives are also elicited when toxic or carcinogenic components are generated upon combustion of the additives during smoking. Cigarette smoke is intrinsically highly toxic and additives, through generation of toxic pyrolysis products, can add to the composition of mainstream smoke and may increase levels of specific toxicants, including carcinogens.

GRAS and FEMA approval of tobacco additives

The tobacco industry claims that tobacco additives used in the manufacturing of cigarettes are approved for use by the Food and Drug Administration generally regarded as safe (GRAS) list and/or the Flavour and Extracts Manufacturers Association (FEMA) list.

However, the GRAS and FEMA lists apply to ingredients in foods or cosmetics, substances that are ingested or topically applied⁵. These lists do not apply to additives in tobacco, which are either transferred to inhaled smoke in pure form, or are burnt and converted into pyrolysis products, which could have a range of undesirable effects. Therefore, it is imperative to assess the possible risks of additives in tobacco in a different manner. Risk assessment should take into account the fact that inhalation is a completely different route of exposure in comparison to dermal or oral routes where these GRAS and FEMA lists are meant for. Inhalation exposure due to the large surface area in the lungs can have a profound effect on the addictiveness of a toxic product, as well as the inherent toxic potential of the additive through generation of toxic pyrolysis products. Any additive, used to ease the harshness or mask the flavour of tobacco smoke can also influence the attractiveness of cigarette smoking.

In summary, additives used in tobacco products are generally meant to enhance the attractiveness of cigarettes and may also directly or indirectly affect addictiveness; both of which results in increase in use and dependence. Additionally, toxic combustion products generated upon pyrolysis of additives have the potential to increase the exposure to toxic substances and thus increase the health hazard associated with cigarette smoking.

- Rabinoff M (2007) Pharmacological and Chemical Effects of Cigarette Additives. American Journal of Public Health 97: 1981-1991
- Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010) Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa. eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- German Cancer Research Center (DKFZ) (ed.) (2012) Menthol Capsules in Cigarette Filters -Increasing the Attractiveness of a Harmful Product. Vol. 17, Red Series Tobacco Prevention and Tobacco Control, Heidelberg, Germany, http://www.dkfz.de/de/tabakkontrolle/download/Publikationen/ RoteReihe/Band_17_Menthol_Capsules_in_Cigarette_Filters_en.pdf (accessed on 28 July 2012)
- Talhout R, Opperhuizen A & van Amsterdam JG (2007) Role of acetaldehyde in tobacco smoke addiction. Eur Neuropsychopharmacol 17: 627-636
- Wigand JS (2006) Additives, Cigarette Design and Tobacco Product Regulation. A Report to: World Health Organization, Tobacco Free Initiative, Tobacco Product Regulation Group, 28 June-2 July 2006, Kobe, Japan

Additives in tobacco products

Carob Bean Extract



Overview¹⁻²

Carob, also referred to as the carob pod, carob bean or locust bean, is the fruit of the large flowering evergreen shrub or tree (Ceratonia siliqua L.) belonging to the pea family. Each carob pod contains several seeds. The pulp is rich in sugars and therefore is a natural sweetener with a flavour, appearance and taste similar to chocolate. It is commonly used as a chocolate or cocoa substitute. It can be ground into fine powder or used in the form of an extract. The carob bean pods are used as flavourings in the form of alcohol, water or other extracts. Carob powder has been reported to contain the following sugars and cyclitols: sucrose, 25-40 %, fructose, 3-8 %, glucose, 2-6 %, pinitol, 5-7 % and myo-inositol, 0.5-1 %2.

The seeds of carob fruit represent about 10 % of the weight of the fruit and are a source of gum that is composed principally of neutral galactomannan polymer consisting of a main chain of D-mannose units and a side chain of D-galactose on every fourth or fifth unit. The gum-aqueous solution has a high viscosity even at low concentrations and is used as a substitute for pectins, agar and other mucilaginous substances. It is used as a thickener, food stabiliser and has several other applications in food as well as textile, cosmetic and pharmaceutical industries1. Carob bean extract is used to improve the organoleptic properties of tobacco smoke. Carob bean extract and gum is generally recognised as safe when used in food products, but this recognition is not applicable for their safety as a tobacco additive, due to the generation of likely pyrolysis products when burnt and inhaled or their ability to enhance the abuse potential of nicotine.

Chemical and Physical Information³

Carob bean extract (Ceratonia siliqua L. fruit extract)

Molecular structure

Locust bean extract, St. Johns bread extract

9000-40-2/84961-45-5

284-634-5

FEMA number

2243

Cosmetic, flavour and fragrance agents

GRAS (Generally Recognized As Safe)

Sweet, fruity, jammy, raisin-like, cocoa, chocolaty

Up to 1000 ppm in the finished non-tobacco products

Function of the Additive

Reports from tobacco manufacturers indicate that carob bean extract is used as a flavouring material. It can be applied directly to the tobacco during cigarette manufacturing or to the filter.4,5

Amount of Carob Bean Extract Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level, is now disseminated to public. In Germany, a brand-wise listing is available online from the Federal Ministry of Food, Agriculture and Consumer Protection⁶, and now various company web sites also provide information on their brands. Cigarette manufacturers in the United States used approximately 800,000 pounds in 1986. Usage level of 0.1-0.2 % of tobacco is reported by some manufacturers.

Pyrolysis and Reaction Products in Cigarette Smoke

Purge and trap studies conducted by tobacco industry, have shown that carob bean extract does not extensively distil at 100 °C, and at temperatures up to 900 °C carob bean extract pyrolyses extensively4. For example, pure carob powder pyrolysed at 700 °C gave rise to several compounds including furan, phenol, styrene, acetaldehyde and human carcinogen benzene5.

The considerable amount of inherent sugar of carob extract upon pyrolysis can caramelise and break down into a mixture of mainly organic acids and a variety of aldehydes, such as acetaldehyde, acrolein, and 2-furfural. These organic acids are reported to reduce nicotine delivery, leading to increased smoking frequency and deeper inhalation of smoke to enable higher absorption of nicotine in the airways. Sugars are converted via the Maillard reaction to form aminosugar complexes in tobacco, which can lead to the generation of other compounds including acrylamide and furfural and highly flavourful pyrazines.

International Agency for Research on Cancer classified human carcinogens (http://monographs.iarc.fr/ ENG/Classification/ClassificationsAlphaOrder.pdf) such as formaldehyde, polycyclic aromatic hydrocarbons, e.g. benzo[a]pyrene and benzene have been reported amongst their pyrolysis products.

Harmful Health Effects of Carob Bean Extract

Exposure

Direct adverse effects can occur due to the toxic and carcinogenic compounds formed during combustion as described above.

Toxicity

Combustion of the inherent sugars of carob extracts upon pyrolysis, as described above, can lead to formation of carcinogenic compounds such as polyaromatic hydrocarbons, and a variety of toxic aldehydes, such as acetaldehyde, acrolein and 2-furfural.

Addictiveness

The high sugar content of carob extracts upon pyrolysis caramelises and breaks down into a mixture of organic acids, which are reported to reduce nicotine delivery, leading to increased smoking frequency and deeper inhalation of smoke to enable higher absorption of nicotine in the airways. The aldehydes formed from sugars are very reactive and produce compounds such as harman, which is reported to have a mood-enhancing effect on the brain. Carob bean extract therefore has the potential to stimulate smoking behaviour.

Attractiveness

The addition of carob imparts a sweet and nutty taste, while the smoke flavour is described as 'rich'. Carob bean extract has a flavour similar to chocolate and the levels used are high, i.e. up to 0.2 % of the tobacco. Thus, it can impart similar chocolate/cocoa flavour notes, which is used to effect sensory perceptions by activating the olfactory receptors below the level of gustatory characterization, making the smoke more palatable and less irritating, creating a perception of safety. Moreover, the high sugar content contributes to the caramel flavours and Maillard reaction products generated through combustion of sugars in tobacco to improve taste, without imparting a distinct characterizing flavour or aroma. Sugars also mask bitter taste of tobacco smoke, lowering the pH, thus reducing the harshness of tobacco smoke and could facilitate smoking initiation. The attractive flavour of carob bean extract as well as the aldehydes, e.g. acetaldehyde produced from the high sugar content of the additive can contribute to the attractiveness and abuse potential of the tobacco product.

Conclusions

Carob bean extract contributes to the increase in attractiveness of smoking by improving flavour, thereby masking its bitter taste and reducing harshness of smoking. Upon pyrolysis, carcinogenic compounds, such as human carcinogen benzene are generated. The aldehydes acetaldehyde, acrolein, and 2-furfural can be generated from the combustion of the sugars contained in carob bean extracts and are transferred to cigarette smoke. Aldehydes are suspected in contributing to abuse potential, and are toxic. Overall, carob bean extract enhances the flavour and thereby the attractiveness of smoking also in naïve users. Thus, carob bean extract has the potential to directly stimulate smoking behaviour, thereby leading to deleterious effects by increasing the exposure to overall toxic substances, including carcinogenic compounds in cigarette smoke.

References

- Calixto FS & Caiiellas J (1982) Components of Nutritional Interest in Carob Pods (Ceratonia siliqua). J Sci Food Agric 33: 1319-1323
- Baumgartner S, Genner-Ritzmann R, Haas J, Amado R & Neukom H (1986) Isolation and Identification of Cyclitols in Carob Pods (Ceratonia siliqua L.). J Agric Food Chem 34: 827-829
- World Health Organization (1981) Carob (Locust) Bean Gum. Toxicological Evaluation of Certain Food Additives, WHO Food Additives Series No. 16, http://www.inchem.org/documents/jecfa/ iecmono/v16ie07.htm (accessed on 28 July 2012)
- Philip Morris USA (2002) Carob Bean Extract Summary of Evaluation for Use as a Cigarette Ingredient. Bates: 3006455098/3006455513, http://legacy.library.ucsf.edu/tid/qfp86a00 (accessed on 28 July 2012)
- Covington & Burling (1987) Summary of Data on Carob Bean Gum and Extract. 03 Aug 1987, Bates: 2029185667-2029185682, http://tobaccodocuments.org/bliley_pm/25808.html (accessed on 28 July 2012)
- Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) Tabakerzeugnisse (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)

Further Reading

- Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (2010) Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa. eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- Conference of the Parties of the WHO Framework Convention on Tobacco Control (FCTC) (2010) Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (Regulation of the Contents of Tobacco Products and Regulation of Tobacco Product Disclosures). FCTC/COP4(10), http://www.who.int/fctc/guidelines/Decisions9and10.pdf (accessed on 28 July 2012)
- Bates C, Connolly GN & Jarvis M (1999) Tobacco Additives: Cigarette Engineering and Nicotine Addiction. Action on Smoking and Health, London, U.K.
- Wigand JS (2006) Additives, Cigarette Design and Tobacco Product Regulation. A Report to: World Health Organization, Tobacco Free Initiative, Tobacco Product Regulation Group, 28 June-2 July 2006, Kobe, Japan

Additives in tobacco products Cellulose Fibre



Overview

Cellulose¹⁻⁸ is a natural polysaccharide, the principal component of the cell walls of higher plants and the most abundant carbohydrate in nature. Cellulose fibres can be obtained from various sources such as wood pulp, cotton linters, flax or hemp. The cellulose content of plants varies greatly from species to species, cotton is the purest natural form containing about 90 % cellulose while wood has around 50 % cellulose on a dry-weight basis. Celluloses are used as anticaking agents, emulsifiers, formulation aids, stabilizers, thickeners and texturizers. Carboxymethyl cellulose, a semi-synthetic cellulose, is used

in pharmaceuticals and cosmetics and has many functions such as emulsifier, thickener, binder, and viscosity control agent. Cellulose fibres occur naturally in leaf tobacco (~ 5-12 %), are also added as a binder and filler, and in reconstituted sheets which is made of tobacco wastes, dust, fines and particles, leaf ribs and stems and other ingredients and flavours, e.g. sugars and menthol, they can also be incorporated.

Cigarette paper consists essentially of cellulose. Cigarette paper plays a significant role, for example in the manufacture, visual appearance, as a carrier of agents

Chemical and Physical Information

Chemical name Cellulose Fibre

Molecular formula $[C_6H_{10}O_5]_n$

Molecular structure

Cellulose is a linear polysaccharide occurring naturally as a partially crystalline, high-molecularweight polymer, with many glucose units. The D-glucopyranosyl units are linked (1→4) and the

hydroxide groups of cellulose are on alternate sides of the chain, binding with others on cellulose molecules to form microfibrils or strong fibres. Partial acetylation of cellulose results in molecules differing in degree of acetylation, e.g. cellulose triacetate, cellulose acetate butyrate, cellulose acetate phthalate, and cellulose acetate propionate.

Cotton fibre; Cellulose powder; Cellulose gel, Wood pulp, bleached;

9004-34-6 (various, e.g. 232-674-9, 65996-61-4, carboxymethyl cellulose: 900-11-7)

EC number 232-674-9

~ 100,000-2,000,000

Practically insoluble in water or other solvents

such as vanilla, calcium carbonate and magnesium oxide to mask second-hand smoke and the yield of toxic chemicals of cigarette smoke. Increasing the fibre level results in increase in tensile strength of the paper, facilitating the run of the paper on cigarette making machine. However, this also results in increase in mainstream yields of toxic chemicals. Burn additives added to paper can also result in lower machine measured tar yields. Increasing the levels of potassium and sodium citrate results in faster burning papers and maintenance of burning even when the cigarette is not smoked. This reduces machine smoked tar yield per cigarette by reducing the number of puffs and also increases the risk of fire if discarded onto a flammable substance. Fibres can influence the paper porosity that also affects the burn rate and both main and side stream smoke yields and the end of draw. Increased cigarette paper permeability decreases the amount of tobacco consumed during a puff and reduces machine smoked tar yield. In reduced ignition propensity cigarettes, a double wrapping of the paper at intervals along the cigarette rod is employed to result in self-extinguishment of the cigarette if not puffed.

Cigarette filter is made mainly from cellulose acetate fibres bonded together (known as tow) with a hardening agent, triacetin plasticizer, to keep the filter in the required shape. Charcoal is also added to some filters. Cellulose is also used in filter wraps in which the filter is then wrapped and sealed with a line of adhesive.

Function of the Additive

Manufacturers report the use of cellulose as binding agent, filler in reconstituted tobacco and as a formulation aid. Cigarette paper is made of cellulose and may contain additives to provide whiteness, improve ash appearance and help ensure burn uniformity. However, information on burn accelerant or use of additives used to mask second-hand smoke is not provided. No information on additives was provided by the industry in the past, but the situation changed dramatically after the Tobacco Master Settlement Agreement, USA, in November 1998. The release of secret tobacco industry documents, their analysis and publication by independent scientist has resulted in increase in knowledge regarding additives and their function in smoking tobacco products.

Cellulose is also used in filter wraps. Cellulose acetate fibres, known as tow are used to make most cigarette filters. The fibres are bonded together with a hardening agent, triacetin plasticizer, and then wrapped in paper and sealed with adhesive8.

Amount of Cellulose Fibre Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level, is now disseminated to public. In Germany, a brand-wise listing is available online from the Federal Ministry of Food, Agriculture and Consumer Protection9, and now various company

web sites also provide information on their brands. Manufacturers report maximum level of use around 4-6.3 % used in various brands, and in cigarette paper, plug wrap and tipping paper.

Pyrolysis and Reaction Products in Cigarette Smoke

Cellulose fibre and related compounds are generally recognised as safe (GRAS) when used in food, pharmaceutical or cosmetic products, but this does not quarantee their safety as a tobacco additive due to the generation of pyrolysis products when burnt and inhaled. Cellulose does not transfer intact to the mainstream smoke but undergoes extensive pyrolysis. Pyrolysis and combustion of cellulose has been extensively studied and reviewed¹⁰⁻¹⁷. Nearly a hundred volatile products have been reported from pyrolysis of cellulose including laevoglucosan, carbon dioxide and carbon monoxide. A complex mixture of toxic and carcinogenic compounds7 such as polycyclic aromatic hydrocarbons including benzo[a]pyrene, phenols, benzene, toluene, naphthalene, catechol, furan and furan derivatives, volatile aldehydes and levoglucosan, formaldehyde, acetaldehyde, acetone and acrolein have been identified.

The pyrolysis products of polysaccharides and simple sugars are similar, but their yields differ. It is estimated that more formaldehyde and less acetaldehyde and acetone are generated from the pyrolysis of simple sugars compared to polysaccharides. However, the presence of oxygen greatly increases the yield of formaldehyde from cellulose pyrolysis. Cellulosic material, inherent and added, may account for up to 50 % of acetaldehyde in smoke. Formaldehyde, acetaldehyde, and acrolein are well-known upper respiratory tract irritants. In attempts to make the so called 'less hazardous cigarette', when cellulose in the reconstituted sheet replaced part of the tobacco, there was a reduction of tar and nicotine levels, but a significant increase in levels of human carcinogens such as formaldehyde, benzo[a]pyrene, benzo[a]anthracene, and o-,m-,p-cresols.

Harmful Health Effects of Cellulose Fibre

Exposure

Cellulose fibres undergo extensive combustion and pyrolysis and contribute to carcinogens and toxicant exposure to smokers and second hand smoke. Hazardous decomposition products are released upon combustion of cellulose. Cigarette paper can influence overall product performance more than any other non-tobacco component. The paper is made of cellulose fibre, with varying degree of porosity that can regulate the burning of tobacco. The paper characteristics have large influence on the smoke exposure from a burning cigarette. Burn additives

added to paper can result in lower machine measured tar yields. This reduces machine-smoked yields per cigarette without actual decrease in smoke toxicity and nicotine levels. Manufacturers also increase the ventilation of the filter to achieve the reduction in machine measured tar yields. Ventilation holes are positioned in the filter where smokers place their fingers, and are therefore easy to block unintentionally. Thus to regulate their nicotine intake smokers alter the way they smoke or compensate by smoking such cigarettes more intensively by taking more and deeper puffs and/or blocking the ventilation holes in cigarettes.

Toxicity

Added cellulose, similar to inherent cellulose, also contributes to the generation and exposure to human carcinogens and toxicants in cigarette smoke. Moreover, compounds formed such as formaldehyde, acetaldehyde, and acrolein are well-known upper respiratory tract and eye irritants. According to earlier reports, the use of chlorine-bleached cigarette paper, now banned in several countries, resulted in the formation and exposure to dioxins or carcinogenic polychlorinated dibenzodioxins in cigarette smoke. Cigarette additives have been developed that can be added during the paper making process to reduce or mask the aroma, visibility, and irritation of side stream smoke. This is a matter of concern, since the use of side stream altering additives could increase non-smokers' involuntary exposure to second hand smoke by reducing the normal warning signs of exposure to smoke toxins.

Addictiveness

By carefully designing paper porosity, paper filter ventilation and other paper design features, the manufacturers can control and possibly reduce the perception of toxicity of the smoke, enhance nicotine delivery and abuse potential. Aldehydes, e.g. acetaldehyde formed during pyrolysis can react with biogenic amines to form harman which may be responsible for its observed reinforcing effect.

Attractiveness

Industry has studied the contribution of cellulose to the flavour of tobacco smoke7. Good organoleptic properties, taste and aroma have been reported with use of carboxymethyl cellulose with tobacco as well as hydroxypropylcellulose with tobacco cigarettes compared to tobacco only cigarettes. Moreover, several patents on flavourant release upon pyrolysis have been registered by the industry. For example, one patent describes a method for a cellulosic polymer that releases flavours, such as vanillin or ethylvanillin under pyrolysis conditions. Flavour release additives are included during conventional paper making process with the slurry of cellulosic material and other ingredients. When such a paper wrapper is used for manufacture of cigarette, it enhances the aroma and masks the side stream smoke. Such technology and others aimed at reducing the visibility, aroma or irritability of the toxins in second-hand smoke are aimed to make socially acceptable products, thereby increasing non-smokers or bystander involuntary exposure to smoke toxins. In certain brands coloured and flavoured wrappers are used to increase attractiveness.

Conclusions

Natural and added cellulose contribute to the formation and exposure to human carcinogens and toxicants in cigarette smoke. Polycyclic aromatic hydrocarbons, e.g. benzo[a]pyrene, formaldehyde and benzene are all classified by IARC as human carcinogens. Formaldehyde, acetaldehyde, and acrolein are well-known upper respiratory tract and eye irritants. Aldehydes such as acetaldehyde, besides being toxic are also reported to potentiate the effect of nicotine addiction. The generation of harman as a condensation product of acetaldehyde and biogenic amines may be responsible for the observed reinforcing effect of acetaldehyde. Moreover, the characteristics of the cigarette paper can have a profound influence on the main stream and side stream smoke, and therefore it is important to regulate the composition of the paper also.

- Hoffmann D & Hoffman I (1997) The Changing Cigarette, 1050-1995. J Toxicology and Environmental Health 50: 307-364
- Bemiller JN (2008) Polysaccharides: Occurrence, Significance, and Properties. In: Fraser-Reid B, Tatsuta K & Thiem J (eds.) Glycoscience. Springer-Verlag, Berlin, Heidelberg

- 3 Baldry PJ, Cullis CF, Goring D & Hirschler MM (1988) The Combustion of Cigarette Paper. Fire and Materials 12: 25-33
- Case PD & Astl G (2003) Systematic Studies on Cigarette Paper. The Influence of Filler, Fibre and Natural Permeability on Paper Properties and Mainstream ISO Yields (TSRC). Paper presented at the 57th Tobacco Science Research Conference, September 21-24, Norfolk, Virginia, USA
- Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010)

 Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- 6 Wigand JS (2006) Additives, Cigarette Design and Tobacco Product Regulation. A Report to: World Health Organization, Tobacco Free Initiative, Tobacco Product Regulation Group, 28 June-2 July 2006, Kobe, Japan
- International Agency for Research on Cancer (IARC) (2004) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking. Vol. 83, Lyon, France, http://monographs.iarc.fr/ENG/Monographs/vol83/index.php (accessed on 28 July 2012)
- National Cancer Institute (2001) Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. Monograph 13, Smoking and Tobacco Control, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, http://cancercontrol.cancer.gov/tcrb/monographs/13/ (accessed on 28 July 2012)
- 9 Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) **Tabakerzeugnisse** (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)
- 10 Rosenburg MC (1985) **Cellulose and Carboxymethylcellulose (CMC)**: **Preliminary Survey**. Bates: 2000516369/6387, Collection Philip Morris, http://legacy.library.ucsf.edu/tid/kgb66e00 (accessed on 28 July 2012)
- Schlotzhauer WS & Chortyk OT (1987) Recent Advances in Studies on the Pyrosynthesis of Cigarette Smoke Constituents. J Anal Appl Pyrolysis 12: 193-222
- McGrath TE, Wooten JB, Geoffrey Chan W & Hajaligol MR (2007) Formation of Polycyclic Aromatic Hydrocarbons from Tobacco: The Link between Low Temperature Residual Solid (Char) and PAH Formation. Food Chem Toxicol 45:1039-1050
- Carmella SG, Hecht SS, Tso TC & Hoffmann D (1984) Roles of Tobacco Cellulose, Sugars and Chlorgenic Acid as Precursors to Catechol in Cigarette Smoke. J Agric Food Chem 32: 287-273
- 14 Baker RR (2006) The Generation of Formaldehyde in Cigarettes Overview and Recent Experiments. Food Chem Toxicol 44: 1799-1822
- Seeman JI, Dixon M & Haussmann HJ (2002) Acetaldehyde in Mainstream Tobacco Smoke: Formation and Occurrence in Smoke and Bioavailability in the Smoker. Chem Res Toxicol 15: 1331-1350
- Gori GB (ed.) (1980) Report No. 4. Toward Less Hazardous Cigarettes. The Fourth Set of Experimental Cigarettes. Smoking Health Program, U.S. Department of Health, Education and Welfare, Public Health Service, National Institute of Health
- 17 Paschke T, Scherer G & Heller WD (2002) Effects of Ingredients on Cigarette Smoke Composition and Biological Activity: A Literature Overview. Beiträge zur Tabakforschung 20: 107-247

Additives in tobacco products Guar Gum



Overview

Guar gum is obtained from the seed of the leguminous shrub; Cyamopsis tetragonoloba/guar plant belonging to the family Leguminosae. The seeds are dehusked, milled and screened to obtain the ground endosperm or the native guar gum. It is a water-soluble polymer with viscous fibre. It hydrates in cold

Chemical and Physical Information

Name

Guar Gum

Carbohydrate, plant gum

Molecular weight

Variable, ~ 220,000-250,000 or more

Molecular structure

Guar gum consists of high molecular weight polysaccharides composed of galactomannans consisting of a (1→4)-linked D-mannopyranose backbone with branch points from their 6-positions linked to D-galactose (that is, 1→6-linked-Dgalactopyranose). There are between 1.5-2 mannose residues for every galactose residue (~ 65 % mannose, 35 % galactose). There is about 10-12 % moisture content and 5-7 % protein content².

Yellowish-white

Nearly odourless

Guaran, Guar Flour, Jaguar

9000-30-0 (Guar depolymerised CAS# 68411-94-9) and others

166

412

232-536-8

GRAS (Generally Recognized As Safe)

Guar gum is hazardous when heated to decomposition, emitting acrid smoke and irritating fumes¹.

water to give highly viscous mucilaginous pseudoplastic solutions of low-shear viscosity. Processing techniques influence the properties, i.e. hydration rates, ease of dispersion into solution, and viscosity. Guar gum is used in the powder form or in derivative form as a thickener, binder, emulsifier and stabilizer. Regulators including the Joint FAO/WHO expert committee on Food additives (JECFA) have approved the use as food additive. It is used for example in breakfast cereals, dairy products, gravies, processed vegetables, baked goods. It is also approved in most countries for use in cosmetic and pharmaceutical industry^{1,2}. In the tobacco industry, guar gum is used as a binder for fragmented tobacco fines, stem and wastes etc. for the production of reconstituted tobacco sheet material and tobacco material. It is also used for the manufacture of various papers used for cigarette manufacture.

Function of the Additive

According to the industry guar gum products are used as binder and formulation aid in the tobacco as well as the paper^{3,4,8,9}. An industry patent describes the procedure to retain high levels of menthol in the final smoking product by adding menthol, sugar and guar gum to obtain the so called 'reconstituted tobacco with bonded flavourant'.

Amount of Guar Gum Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level is now disseminated to public. In Germany, a brand-wise listing is available online from the Federal Ministry of Food, Agriculture and Consumer Protection³, and now various company web sites also provide information on their brands. According to some manufacturers report, various guar products are used at a maximal use level of 0.6 % of the total weight of the tobacco as a binder in Germany, worldwide at levels below 1.1 % in selected brands, as formulation aid at 1.8 % level.

Pyrolysis and Reaction Products in Cigarette Smoke

Guar gum is hazardous when heated to decomposition, emitting acrid smoke and irritating fumes1. Studies conducted by tobacco manufacturers show that guar gum in tobacco does not extensively distil at 100 °C. At higher temperatures, guar gum would be pyrolysed extensively and the expected chemicals are like those from pyrolytic decomposition of polysaccharides⁴. International Agency for Research on Cancer classified human carcinogens such as formaldehyde, benzo[a]pyrene and benzene have been reported amongst the pyrolysis products.

Pyrolysis products of guar gum at 300 °C include 1-hydroxy-2-propane, acetic acid and 2-furanmethanol, formic acid, dihydro-methyl furanone, cyclohexanone, a methylbutraldehyde derivative, and an anhydrofuranose derivative and at 600 °C, propene, acetic acid, 1-hydroxy-2-propane, acetaldehyde, hexane, 2-butanone, diacetyl, furfural, cyclohexanone and levoglucosan, butyrolactone⁵. The most abundant compounds identified upon pyrolysis of guar gum were acetic acid, acetol, levoglucosan, 2,3-butanedione, 2-furfural, 5(hydroxymethyl) 2-furancarboxaldehyde and hexadecanoic acid, 2-propenal, toluene, benzene, 2-propanone, styrene, ethylbenzene, 3-buten-2-one and acetaldehyde6.

Harmful Health Effects of Guar Gum

Exposure

Irritating and toxic fumes, gases and acrid smoke can be formed when the additive is heated to decomposition as expected at high temperature up to ~900 °C occurring during smoking.

Toxicity

The toxicological properties of guar gum per se have not been fully investigated in this context. Inhalation of dust may cause respiratory tract irritation and may cause respiratory sensitization. Some individuals may develop a respiratory allergenic response to guar dust. Persons with a history of respiratory allergies may have those conditions aggravated by exposure to guar dust1.

Guar gum as an additive was tested by cigarette manufacturers, as part of a comprehensive evaluation of the toxicological effects of ingredients added to experimental cigarettes, using a tiered battery of tests and rat inhalation studies. The authors report that at the inclusion levels, there were minimal changes in smoke chemistry although a significant increase in the human carcinogen formaldehyde was observed. Based on the testing the authors concluded that there was a minimal effect of experimental inclusions even at exaggerated levels compared to those used in commercial cigarettes^{7,8}.

The caveat in such studies is that they are based on the premise that the toxicity of ingredients can be evaluated relative to that of the overall toxicity of tobacco products, rather than on the basis of their own absolute toxicity. However, the major drawback is that the ingredient being tested might be as toxic and carcinogenic as the tobacco smoke constituent. Moreover, the function of ingredients on the palatability and attractiveness of a toxic product, a point of great concern, is not addressed.

Addictiveness

No information available, but when guar gum in the tobacco product is combusted, several aldehydes

are generated as shown above, including acetaldehyde which intensifies the effect of nicotine on the brain in a synergistic manner and hence its addictive properties.

Attractiveness

A number of flavour compounds are generated during the heating of guar gum, such as furfurals and diacetyl. Furfural imparts a sweet woody flavour. Diacetyl has a butterscotch flavour and provides one of the characteristic flavours of caramelised foods. The generation of such compounds can add to the olfactory cue and attractiveness of the smoking product and play a role in reinforcing nicotine dosing through helping ease of inhalation and possible olfactory cueing.

Conclusions

Guar gum is important to the use of reconstituted tobacco sheet, which often carries agents to enhance tobacco use. Guar gum undergoes pyrolysis, giving rise to toxic/carcinogenic compounds. Regarding flavours, it is well known that the thermal degradation of sugars and carbohydrates at lower temperatures as in foods, contribute to complex aromas. Several flavour compounds have been reported due to pyrolysis reactions of guar gum. These flavour compounds singly or in combination with the thousands of other smoke constituents can act synergistically and contribute to the attractiveness of smoking by improving smoke flavour, thereby masking its bitter taste, reducing harshness of smoking, creating sensory cues, which all could contribute to optimization of nicotine dosing and enhance abuse potential.

- United States National Library of Medicine (NLM) Hazardous Substances Data Bank (HSDB). TOXNET, search term: guar gum, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (accessed on 28 July 2012)
- Food and Agricultural Organization of the United Nations (2006) Guar Gum. http://www.fao.org/ ag/agn/jecfa-additives/specs/monograph3/additive-218.pdf (accessed on 28 July 2012)
- Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) Tabakerzeugnisse 3 (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)
- Philip Morris (2002) Guar Gum Summary of Evaluation for use as a cigarette ingredient. Bates: 3006455471/3006455472, http://legacy.library.ucsf.edu/tid/efp86a00 (accessed on 28 July 2012)
- Walk RA (1994) Draft "White Paper" on Guar Gum. Bates: 2061999543-2061999567, Collection Philip Morris, http://tobaccodocuments.org/pm/2061999543-9567.html (accessed on 28 July 2012)
- RJ Reynolds (1993) Summary of Gums. Bates: 510636418/6425, http://legacy.library.ucsf.edu/tid/ 6 dfz53d00 (accessed on 28 July 2012)
- Coggins CRE, Edmiston JS, Jerome AM, Langston TB, Sena EJ, Smith DC & Oldham MJ (2011) A Comprehensive Evaluation of the Toxicology of Cigarette Ingredients: Essential Oils and Resins. InhalToxicol 1 (Suppl.): 41-69
- Baker RR, Massey ED & Smith G (2004) An Overview of the Effects of Tobacco Ingredients on Smoke Chemistry and Toxicity. Food Chem Toxicol 42 (Suppl.): S53-S83

- World Health Organization (1975) Toxicological Evaluation of Some Food Colours, Thickening Agents, and Certain Other Substances. WHO Food Additives Series No. 8: 38-43, http://www. inchem.org/documents/jecfa/jecmono/v08je06.htm (accessed on 28 July 2012)
- Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010) Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa. eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- International Agency for Research on Cancer (IARC) Agents Classified by the IARC Monographs, Volumes 1-105. http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf (accessed on 28 July 2012)

Additives in tobacco products Liquorice



Overview

Liquorice¹⁻⁴ is derived from the dried roots and rhizomes of Glycyrrhiza species, e.g. Glycyrrhiza glabra (Leguminosae family). Liquorice is used in two main forms: root and extract. Liquorice extract is produced by shredding and extracting the root. The extracted liquor is filtered and then either spray dried to produce a powder or concentrated to produce a solid block which generally has a stronger flavour than the powder. Liquorice extract is also sold as a liquid solid extract where the extracted material is dissolved/ suspended in a solvent to produce a syrup-like material. Liquorice root contains about 20 % of water-soluble extractives much of which (typically 3-5 % of the root, but up to 12 % in some varieties) is composed of glycyrrhizin, a mixture of potassium and calcium salts of glycyrrhizic acid. This intense sweetness can be traced to glycyrrhizic acid that consists of two sugar moieties attached to a steroid like triterpenoid. Sugars (glucose and sucrose) are also present. Glycyrrhizin constitutes 10-25 % of liquorice extract and is considered the primary flavour constituent.

Liquorice and its derivatives are generally recognized as safe (GRAS), and are widely used in the food industry as a sweetening agent, a flavour potentiator and a flavour modifier in drinks, candy, gum etc. They are also used in some over-the-counter drugs, cough syrups, throat pastilles, liquorice tea etc. in both traditional and herbal medicines. Liquorice shows a variety of pharmacological activities. It has been traditionally used for respiratory, gastrointestinal, cardiovascular, genitourinary, eye, and skin disorders, and for its antiviral effects. Liquorice acts as a bronchodilator, and in medicinal preparations and traditional medicine it is commonly used for several problems including as a demulcent, expectorant, antitussive and for sore throat. A major proportion of liquorice produced is used by the tobacco industry for flavouring cigarettes, cigars and chewing tobacco¹⁻⁴.

Function of the Additive

According to reports from tobacco manufacturers, liquorice extract (block, powder or liquid) is used in cigarettes as both flavour and casing material. The three forms may be used, but not interchangeably because of different flavour characteristics5. It minimizes rough smoke character by balancing out the overall flavour profile of the tobacco. Liquorice extract enhances and harmonizes the smoke flavour, reduces dryness in the mouth and throat. It improves moisture holding characteristics of tobacco, increasing stability and shelf life and acts as a surface active agent for ingredient application, thereby improving the rate of absorption of flavours uniformly into tobacco2. Liquorice is used as an adjunct to boost the sweetness of tobacco products. The taste of liquorice to the smoker is that of a mellow sweet woody note which, at proper use levels, greatly enhances the quality of the final product. The smoothing effect of liquorice is probably due to glycyrrhizin, which is renowned for its demulcent therapeutic property⁶. Such smoothing is possibly done by interaction with transient receptor potential channel receptors7.

Amount of Liquorice Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level, is now disseminated to public. In Germany, a brand-wise listing is available online from the Federal Ministry of Food, Agriculture and Consumer Protection⁸, and now various company web sites also provide information on their brands. Liquorice extract (block, powder or liquid) is used in cigarettes both as flavour and casing material at levels of about 1-4 %5. According to some manufacturers report, liquorice is used as casing at a maximal use level of 0.74 % of the total weight of the tobacco, liquorice extract, fluid and powder as flavouring at maximum use about 0.4 % in Germany or worldwide liquorice use at maximum use levels 0.9 %.

Pyrolysis and Reaction Products in Cigarette Smoke

Although liquorice extracts are recognised as safe when used in food products, their safety as a tobacco

Chemical and Physical Information

Liquorice

Liquorice extract, Liquorice Fluid Extract, Powder, and Root

68916-91-6: 84775-66-6

2628, 2629

218

Natural extract, not completely defined complex mixture (see characteristics below)

Liquid or dry extract, brown or glossy black

Flavouring agents

Odour type

Light slightly spiced scent

Intensely sweet

GRAS (Generally Recognized As Safe)

When heated to decomposition it emits acrid smoke and irritating fumes.

More than 400 compounds have been isolated from Glycyrrhiza species. Liquorice contains as its major active principle the triterpene glycoside glycyrrhizin (also known as glycyrrhizic or glycyrrhizinic acid) in concentrations ranging from 1 to 24 %, depending on sources and methods of assay. Glycyrrhizic acid (CAS no. 1405-86-3) is a conjugate of Glycyrrhetinic acid and two molecules of glucuronic acid. Other constituents of liquorice include flavonoids, isoflavonoids, chalcones, coumarins, triterpenoids, sterols, 2-20 % starch, 3-14 % sugars (glucose and sucrose), lignin, amino acids, amines (asparagine, betaine, choline), gums, wax, and volatile oil consisting of many aroma chemicals1. The crude dried aqueous extracts (also known as "block liquorice") may contain 4-25 % glycyrrhizinic acid in the form of calcium, magnesium and potassium salts. The ammoniated salt is manufactured by acid treatment of the aqueous extracts, followed by neutralization of the precipitated material with diluted ammonia. The monoammonium salt is then further purified by solvent extraction and other separation techniques. Both glycyrrhizinic acid and ammonium glycyrrhizinate are chemically defined flavouring substances and they are used because of their sweet taste (33-200 times sweeter than sucrose).

Chemical and Physical Information on Glycyrrhizin

Molecular formula

$$C_{42}H_{62}O_{16}$$

Molecular structure

Molecular weight

823

Synonyms

20ß-carboxy-11-oxo-30-norolean-12-en-3ß-yl-2-oß-d-glucopyranuronosyl-d-glucopyranosiduronic acid; d-glucopyranosiduronic acid, (3ß,20ß)-20-carboxy-11-oxo-30-norolean-12en-3-yl-2-oß-d-glucopyranuronosyl; glycyron; glycyrrhetinic-acid-glycoside; glycyrrhizicacid; glycyrrhizinic acid; liquorice; sweet-root; liquorice-root-extract

CAS registry no.

1405-86-3

Light, slightly spiced scent, intensely sweet taste

220 °C decomposes

Octanol/water partition coefficient

 $Log K_{ow} = 2.80$

additive, where the additive is burnt and inhaled is not assured. Pyrolysis studies conducted by the industry at simulated tobacco burning temperatures up to 900 °C showed that all forms of neat liquorice extracts pyrolysed extensively with no indication that liquorice extracts would transfer intact to mainstream smoke5. Around 60 compounds were identified, including toxic and/or carcinogenic compounds such as benzene, toluene, phenol and acetaldehyde. As a single ingredient added to cigarette tobacco, block liquorice extract at 12.5 % increased smoke constituents including selected polycyclic aromatic hydrocarbons (PAH), arsenic, lead, phenol and formaldehyde while liquorice extract powder at 8 % increased select PAH, phenol and formaldehyde on a total particulate matter basis. Lower levels (including typical application levels) of block, powder or liquid liquorice extract did not significantly alter the smoke chemistry profile.

Harmful Health Effects of Liquorice

Exposure

Tobacco industry is a major consumer of liquorice. About 90 % of the liquorice consumed in the USA is used by the tobacco industry. Major exposure to liquorice combustion products occurs during smoking¹. International Agency for Research on Cancer classified human carcinogens such as formaldehyde, benzo[a] pyrene and benzene have been reported amongst the pyrolysis products.

Toxicity

Industry has reported the potential genotoxic and cytotoxic effects of liquorice extract on smoke, and the inhalation toxicity of smoke in a rat model. In subchronic 90-day rat inhalation studies, the mainstream smoke from cigarettes with 12.5 % added block and 8 % added powder liquorice extract contained higher formaldehyde concentrations compared to control cigarette smoke. Female rats in the 12.5 % block liquorice extract exposure group displayed an increased incidence and severity of epithelial hyperplasia in the nose. Liquorice extract added to cigarette tobacco at levels of up to 5 %, did not discernibly alter the smoke chemistry or biological effects normally associated with mainstream cigarette smoke5.

The caveat in such a study is that it is based on the premise that the toxicity of ingredients is evaluated relative to that of the overall toxicity of tobacco products, rather than based on the ingredient's absolute toxicity. This means that the ingredient being tested might be as toxic and carcinogenic as the tobacco smoke constituents themselves. A recent reevaluation of tobacco industry data has revealed that toxins in cigarette smoke increase substantially because of hundreds of additives (including prune juice extracts) that were tested by the industry in different combinations with the tobacco matrix9. Nevertheless, the main function of ingredients on the enhancement of palatability of a toxic product is not addressed. For example, several flavour compounds are also generated during

combustion of liquorice, which can interact with other smoke constituents to impart the required effect. This interaction and effect on attractiveness although not investigated, in all likelihood, as a consequence enhances nicotine delivery and abuse potential.

Addictiveness

The harsh and irritating character of tobacco smoke provides a significant barrier to experimentation and initial use. Liquorice concentrate boosts the sweetness of smoke and enhances attractiveness of tobacco products by facilitating delivery of optimal dose of nicotine. When used as an additive in cigarette, the carbohydrates and sugars present in liquorice also affect the smoke chemistry. When the sugars, in the tobacco product are combusted, various aldehydes are generated such as formaldehyde, acetaldehyde, propanal, 2-butenal, 2-methylpropenal, butanal, methylbutanal, furfural, benzaldehyde, methylfurfural, methoxybenzaldehyde. Aldehydes, e.g. acetaldehyde are known to potentiate the effect of nicotine, thus enhancing addictiveness. Organic acids derived from sugars have been reported to ameliorate the harshness of smoke and reduce nicotine delivery, leading to increased smoking frequency and deeper inhalation of smoke. This enables optimal absorption of nicotine but also modulates exposure to toxic and carcinogenic smoke constituents in the airways.

Attractiveness

Glycyrrhizin is the active substance of liquorice and has a sweet taste. The taste and flavour of tobacco with liquorice/liquorice root added are described as sweet, woody and round and adding liquorice also has the objective of mastering the adverse taste of tobacco and its toxins including nicotine. Glycyrrhizin is a bronchodilator although it is not clear whether the levels present are sufficient for this effect, although a synergistic effect with other compounds in cigarette smoke can be expected. Compounds which have bronchodilating properties (opening/broadening the airways) would enable the smoker to inhale deeper (a larger volume of) tobacco smoke implying an increase in the bioavailability of nicotine¹⁰. Moreover, by creating the perception of soothing the oral and throat mucosa, it masks the harsh effects of smoke and nicotine. Liquorice reduces dryness in the mouth and throat of smokers¹¹. Liquorice (extracts) is used to smoothen and mildly sweeten the smoke enhancing the delivery and optimization of nicotine. The sugar component of liquorice can enter into the Maillard browning process to impart a sweet caramel flavour improving the organoleptic properties of smoke and reduce harshness. Sugars form amino-sugar complexes in tobacco which can lead to the generation of compounds such as furfural and pyrazines as well as toxic acrylamide. Compounds such as pyrazines which are highly flavourful enhance perception, attractiveness and mask toxins. Liquorice is used to improve the organoleptic properties of tobacco smoke, thereby enhancing the attractiveness of smoking and stimulating the use of nicotine dosing. Sensory cues can arise from a range of neural responses including smell via olfactory nerve; irritation via trigeminal nerve, and taste via facial, glossopharyngeal and vagal nerves. Sensory cues are important in the perceptions of pending reward and craving reduction, trigger for a learned behaviour and smoking topography all of which contribute to optimal nicotine dosing and thus enhances abuse liability¹².

Conclusions

Liquorice is a moisturizing, sweetening, flavouring and also a flavour harmonizing agent. Liquorice is used to mellow nicotine harshness and to increase smoothness and body of tobacco smoke. This is accomplished by the creation of sensory cues from head and neck

receptors. Liquorice enhances the attractiveness of tobacco smoke and allows optimal nicotine dosing by masking the undesirable characteristics of tobacco smoke in particular nicotine. It provides a hard to detect pleasant sweet undertone to the smoke. According to the industry, liquorice is used as an adjunct to boost the sweetness of tobacco products. The taste of liquorice to the smoker is that of a mellow sweet woody note which greatly enhances the attractiveness of the final product. Liquorice extracts are used to improve the organoleptic properties of tobacco smoke, making the harsh cigarette smoke palatable, thereby enhancing the attractiveness of smoking, more so to naïve users leading to deleterious health effects by facilitating and increasing use and exposure to toxic and addictive tobacco products.

- United States National Library of Medicine (NLM) TOXNET Databases on toxicology, hazardous chemicals, environmental health, and toxic releases. http://toxnet.nlm.nih.gov/index.html (accessed on 28 July 2012)
- Vora PS (1984) Characteristics and Applications of Liquorice Products in Tobacco. Tobacco International (April 27): 15-20
- 3 Andel van I, Wolterink G, Werken van de G, Stevenson H, Aerts van LAGJM & Vleeming W (2003) The Health and Addiction Risk of the Glycyrrhizic Acid Component of Liquorice Root Used in Tobacco Products. RIVM report 340630001/2003
- 4 Isbrucker RA & Burdock GA (2006) Risk and Safety Assessment on the Consumption of Liquorice Root (Glycyrrhiza sp.), Its Extract and Powder as a Food Ingredient, with Emphasis on the Pharmacology and Toxicology of Glycyrrhizin. Regul Toxicol and Pharmacol 46: 167-192
- Carmines EL, Lemus R & Gaworski CL (2005) Toxicologic Evaluation of Liquorice Extract as a Cigarette Ingredient. Food Chem Toxicol 43: 1303-1322

- Bates C, Connolly GN & Jarvis M (1999) Tobacco Additives: Cigarette Engineering and Nicotine Addiction. Action on Smoking and Health, London, U.K.
- Tobacco Products Scientific Advisory Committee (TPSAC) (2011) Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations. Submitted to FDA: March 23, 2011, Final edits from the July 21, 2011 meeting are included, http://www.fda.gov/downloads/ AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ UCM269697.pdf (accessed on 28 July 2012)
- Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) Tabakerzeugnisse (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)
- Wertz MS, Kyriss T, Paranjape S & Glantz SA (2011) The Toxic Effects of Cigarette Additives. Philip Morris' Project Mix Reconsidered: An Analysis of Documents Released through Litigation. PLoS Med 8: e1001145
- Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010) Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa. eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- Tobacco Documents Online, Profiles: Licorice. http://tobaccodocuments.org/profiles/licorice.html (accessed on 28 July 2012)
- Megerdichian CL, Rees VW, Wayne GF & Connolly GN (2007) Internal Tobacco Industry Research on Olfactory and Trigeminal Nerve Response to Nicotine and Other Smoke Components. Nicotine Tob Res 9: 1119-1129

Further Reading

- 13 Conference of the Parties of the WHO Framework Convention on Tobacco Control (FCTC) (2010) Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (Regulation of the Contents of Tobacco Products and Regulation of Tobacco Product Disclosures). FCTC/COP4(10), http://www.who.int/fctc/ guidelines/Decisions9and10.pdf (accessed on 28 July 2012)
- 14 Wigand JS (2006) Additives, Cigarette Design and Tobacco Product Regulation. A Report to: World Health Organization, Tobacco Free Initiative, Tobacco Product Regulation Group, 28 June-2 July 2006, Kobe, Japan
- 15 International Agency for Research on Cancer (IARC) Agents Classified by the IARC Monographs, Volumes 1-105. http://monographs.iarc.fr/ENG/Classification/ ClassificationsAlphaOrder.pdf (accessed on 28 July 2012)

Additives in tobacco products

Menthol



Overview

Menthol¹⁻⁶ is one of the most used tobacco additives worldwide. Natural plant sources of menthol include several members of the mint family *Labiatae* (*Lamiaceae*), most prominently members of the Mentha genus such as peppermint (*Mentha piperita*), cornmint (*Mentha arvensis*) and spearmint (*Mentha spicata L.* or *Mentha viridis L.*). Menthol is a widely used flavour in familiar over-the-counter dentifrices, foods, cosmetics and pharmaceuticals, such as lozenges, topical preparations and vapour inhalation products by virtue of its antipruritic and antitussive properties. Menthol is used primarily for its chemosensory effects of creating perceptions of cooling, minty taste and smell. Menthol is also used in compounding artificial mint flavours.

The largest end-use for menthol, in particular synthetic or natural I-menthol, is as a flavouring additive for cigarettes and other tobacco products. Menthol cigarettes are one of the only marketed cigarette brands identified and promoted by the flavour additive. Menthol cigarettes comprise a substantial proportion of market in several countries worldwide including the U.S., Japan and Philippines. Historically the first brand to incorporate the local analgesic menthol as an additive in the 1920's was the Spud cigarette in U.S.A. Aimed to counteract and suppress the harsh symptoms of tobacco smoking it was promoted and marketed as such to smokers, so that they could continue smoking even when suffering from cold or other respiratory ailments. It offered health protection, which is clearly an illusion, but a novelty became a wide-spread brand category within the industry. As of the 1960s, twenty-five per cent of the U.S. market was menthol predating the introduction of light cigarettes.

The Tobacco Product Scientific Advisory Committee of FDA, based on comprehensive review of evidence-based literature, concluded that menthol has the population impact of contributing to youth initiation and helping adults to continue to smoke. Moreover, the availability of menthol cigarettes has an adverse impact on public health by increasing the numbers of smokers with resulting premature death and avoidable

morbidity¹. Currently the FDA is deliberating on this expert report and expected to take action soon.

Function of the Additive

According to tobacco industry reports, a variety of "flavouring" substances are employed in the manufacture of conventional American blended cigarettes to provide distinctive, brand-specific "flavour" to the mainstream smoke. The most familiar of these flavouring ingredients and only one that is advertised and branded is menthol⁴. Menthol can be applied directly to the tobacco and/or reconstituted tobacco sheet during cigarette manufacturing, and thus may be subject to pyrolysis-type reactions when smoked. It can also be applied to the inner foil of menthol cigarette packages and quickly diffuse into the tobacco to impart its sensory characteristics to the cigarette or may also be applied to the filter as a flavouring material. A new menthol product introduced in several countries employs a capsule in the filter that allows a high boost of menthol when crushed by the smoker almost twice that of an uncrushed capsule⁷.

Amount of Menthol Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level, is now disseminated to public. In Germany, a brand-wise listing is available online from the Federal Ministry of Food, Agriculture and Consumer Protection⁸, and now various company web sites also provide information on their brands. The concentration of menthol in tobacco products varies according to the product. It is present in 90 % of all tobacco products in the U.S., both "mentholated" and "non-mentholated"³, many at undetectable levels and at a characterizing level in 26 % of U.S. cigarettes with the intended effect of mild or more intensive sensation of cooling depending on the target group for a particular brand.

Chemical and Physical Information

Menthol

I-Menthol: 2216-51-5; D-Menthol: 15356-70-4, D/L-

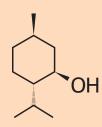
Menthol: 89-78-1; Menthol: 1490-04-6,

FEMA (Flavouring Extract Manufacturer's Association) 2665

GRAS (Generally recognized as safe)

Molecular formula $C_{10}H_{20}O$, FW = 156

Molecular structure



Monocyclic terpene alcohol having three asymmetric carbon atoms in the cyclohexane ring

I-menthol: 212 °C (FCC, 1996)

Melting point

I-menthol: 43 °C (FCC, 1996)

Octanol/water partition coefficient $Log K_{ow} = 3.4$

Odour/flavour

Minty

Peppermint absolute: CAS# 8006-90-4 Spearmint oil: CAS# 8008-79-5

A number of isomers of menthol have also been

developed.

Menthol characteristics

Menthol is a monocyclic terpene alcohol having three asymmetric carbon atoms in the cyclohexane ring, yielding a variety of isomers. Menthol is subject to all of the chemical reactions typical of a cyclic secondary alcohol, including dehydrogenation or oxidation to menthone [10458-14-7] and isomenthone [491-07-6] and esterification to menthyl acetate [16409-45-3] and other esters. The I-menthol isomer exhibits the characteristic balanced peppermint odour and flavour and exerts a cooling effect when applied to the skin. The other menthol isomers exhibit significantly different taste characteristics and are lacking in the familiar cooling sensation imparted by I-menthol. While I-menthol constitutes the predominant isomer in natural botanical sources, the racemic mixture dl-menthol is produced synthetically and is similarly employed to impart the characteristic cooling menthol perceptions in various consumer product formulations. The dl racemate exhibits about half of the cooling properties of menthol, and finds use mainly in topical skin care products. Both I-menthol and dl-menthol are used in tobacco products4.

Menthol is added as a continuum of concentrations i.e. from imperceptible amounts of menthol (approximately 0.01-0.03 % of cigarettes' tobacco weight) to about 1.0 %. The taste, aroma and cooling sensations imparted by menthol vary according to concentrations. At lower application levels, menthol can be used to increase smoothness and reduce harshness in cigarette smoke. This is likely the main reason for use of menthol as an additive in non-menthol brands3. Smokers can distinguish the taste of menthol only above the level of 0.03 %. A slight menthol flavour effect is apparent at tobacco addition rates of 0.1-0.2 %, and a stronger "flavour" is achieved at 0.25-0.45 %. While earlier reviews of menthol usage in cigarettes stated that addition rates did not typically exceed 0.3 %, several major US cigarette manufacturers have recently released information indicating that some cigarette tobaccos may contain up to 2 % w/w menthol4.

In addition, several additives and formulations are also used to simulate menthol effects. For example, peppermint oil, spearmint oil and other menthol enhancers like thyme oil, eucalyptus oil, anethole and methyl salicilate can be used to increase cooling and menthol perception³. A number of menthol targeted analogues of menthol have also been developed, e.g. some remove the aroma or taste of mint leaving only a strong cooling sensations. These analogues were also developed for the razor companies who wished to remove the eye irritation of the aroma of menthol while returning the cooling sensation.

Pyrolysis and Reaction Products in Cigarette Smoke

In one study, pyrolysis of neat dl-menthol at 860 °C resulted in 16 % menthol unchanged and the formation of several compounds including the human carcinogens benzo[a]pyrene and benzene. At 600°, 78 % menthol was recovered and no benzo[a]pyrene was formed. Subsequent studies by the tobacco

Table: Summary of physiological effects of menthol as tobacco additive^{2,3}

Effects	Description/impact	Implications
Cooling	 Stimulation of cold receptors Irritation (perceived as cool) Counteract harshness Long-lasting impact 	 Substitute perceived smoke "effect" Menthol perception Mask irritation of smoke, enabling initiation and increased inhalation and uptake
Anaesthetic	Anti-irritant or counter-irritantReduced pain sensations	 Mask irritation of smoke, enabling initiation and increased inhalation and uptake in children and first time users
Sensory	Increase smoothnessReduce harshness	 Enable deeper inhalation and increased uptake
Respiration	 Increased sensation of airflow Inhibition of respiratory rates Allow increase lung exposure to nicotine, tar and toxic constituents 	 Enable deeper inhalation Change inhalation patterns (frequency, volume) increased breath holding Increase addiction and toxicity potential Mask early warning of respiratory diseases
Nicotine impact	Increased bite or strengthStimulation of nociceptors	 Provide substitute for nicotine in low-tar cigarettes
Central nervous system	■ Brain stimulant or depressant	 Enhance tobacco reinforcement and addiction Provide substitute for nicotine, possibly alter effects of nicotine
Electrophysiological	Increase nerve activity	Enhance tobacco reinforcement
Drug absorption	 Increase absorption and lung permeability of smoke constituents 	Increase nicotine and carcinogen uptake
Drug metabolism and toxicity	 May decrease nicotine/cotinine metabolism & modulate carci- nogen metabolism 	 Elevated dose of nicotine and increased addiction potential Increase carcinogen exposure

industry have reported that when burning was carried out in the presence of tobacco matrix 98.9 % of menthol is transferred unchanged into mainstream smoke and 0.5 % is found as pyrolytic products4.

Harmful Health Effects of Menthol

Exposure

Although the main functions of menthol are described below, there is some evidence that pyrolysis of menthol can result in exposure to carcinogens such as benzo[a]pyrene and benzene.

Menthol acts as a penetration enhancer in drug delivery studies suggesting that it not only permeates the epidermis well but also acts to increase the accessibility of other molecules. It may increase the absorption and lung permeability of smoke constituents, thereby, increasing nicotine and carcinogen uptake and thus the health hazards of smoking. Menthol in cigarettes may inhibit nicotine oxidation and glucuronidation thereby enhancing systemic nicotine exposure.

Toxicity

Menthol is not toxic in its pure and un-burnt form, as used in the food, pharmaceutical and cosmetic industry. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established an acceptable daily intake of 0-0.2 mg/kg for menthol. However, the safety assessments and regulatory approvals were not intended to address safety of its use in tobacco products which are toxic and whose smoke is inhaled4. Besides, other relevant factors that need to be considered are that toxicants and carcinogens can be formed during combustion at high temperature attained during smoking and the pharmacological effect of the additive that can facilitate increased inhalation and absorption of nicotine and toxic smoke emissions.

The exposure and toxicity studies comparing menthol and non-menthol cigarettes have resulted in mixed results because of several reasons, including study design, sample size or ethnicity. Based on those results, manufacturers have concluded that there is no increased physical harm from the addition of menthol to cigarettes. However, such a narrow definition of harm is not appropriate in dealing with the issue of menthol or cigarettes, and its broader negative public health impact9. A recent reevaluation of the tobacco industry data has revealed that toxins in cigarette smoke increase substantially because of hundreds of additives, including menthol, that were tested by the industry in different combinations with the tobacco matrix¹⁰. Cigarettes are responsible for high mortality and morbidity and in this context, the focus on menthol toxicity alone is meaningless. This only distracts from the real harm associated with menthol in cigarettes, which is increasing attractiveness and nicotine abuse.

Addictiveness

The abuse liability of cigarettes is influenced by a number of factors including chemosensory perceptions. Additives that affect the senses create perceptions that facilitate initiation, maintenance of smoking and enhance the addictiveness by allowing the smoker to deliver optimal doses of nicotine11. Menthol facilitates abuse liability of nicotine and tobacco product by chemosensory effects⁵⁻⁶. The tobacco industry has conducted research on menthol's cooling, anaesthetic and analgesic properties that ameliorate the harshness and irritation of tobacco smoke, in particular, nicotine. Owing to its physiological effects, menthol contributes to the sensory effects of the smoke and in turn, affects smoking topography delivery of nicotine at an optimal dose. Even in cigarettes with subliminal and undetected levels of menthol, menthol's non-flavour-related cooling effects decrease unfavourable aspects of smoking cigarettes while assuring optimal nicotine dose. Thus, they encourage initiation, reinforce addiction and deter cessation^{12,13}.

Menthol enhances the dermal penetration of a variety of drugs, and might enhance the pulmonary absorption of nicotine and/or tobacco carcinogens. Menthol can act synergistically with nicotine, can modulate nicotine effects and may act directly on nicotinic cholinergic receptors to alter nicotine response. Significant increases in puff volume and puff frequency and increased breath holding have been reported with mentholated brands. Among long term smokers, higher levels may allow deeper and more prolonged inhalation of tobacco smoke, resulting in greater smoke/nicotine intake per cigarette.

According to tobacco industry documents, menthol at high levels can simulate an increased bite or impact of nicotine by activating nociceptors, or pain receptors and providing a substitute for nicotine's impact in very low nicotine yield cigarettes. Menthol increases electrophysiological nerve activity and consequently enhances tobacco reinforcement and addiction and provides a substitute for nicotine.

Attractiveness

Attractiveness of additives refers primarily to effects on taste, smell and tactile perceptions. Menthol modulates several transient receptor potential (TRP) receptors. These include TRPM8 (cooling effect), TRPV3 (warm sensation) and TRPA1 (analgesic effect)1. The cooling sensation ascribed to menthol is due to the stimulation of the nerve endings, by interfering with the calcium conductance across sensory neuronal membrane. The cooling effect of menthol masks irritation of smoke, facilitates easy and depth of inhalation by first time young smokers, thus making smoking initiation easier.

The anaesthetic and analgesic properties of menthol are mediated through a selective activation of -opioid receptors. At high concentrations, menthol numbs the throat and masks the harshness of smoke, facilitating deeper inhalation of smoke. Its action as anti-irritant or counterirritant at higher levels reduces pain sensations and masks irritation of nicotine and smoke. Such effects may contribute to perceptions of a "soothing" or safer product enabling product use among smokers with respiratory concerns. Mentholated tobacco products users more often than not believe that this flavouring offers some health protection as compared to non-menthol cigarettes.

Menthol can act on both thermal (low level) and nociceptive receptors (very high level) resulting in both cooling and irritant effects. Repeated exposure results in menthol desensitizing receptors by which free nicotine produces pain and irritant effects, thereby, reducing the irritation from nicotine in tobacco smoke and making smoking attractive by 'treating the throat scratch' associated with smoking.

Starter products, dependence and cessation

Menthol can mask the taste and harshness of tobacco smoke. In cigarettes formulated with lower levels of menthol, the menthol flavour and effect are less dominant and menthol primarily masks harshness. The tobacco industry identified mildness, smoothness, and less harsh tasting cigarettes as being important preferences for younger smokers3.

Menthol cigarette use is significantly more common among newer, younger smokers in the U.S. with 50 % of adolescent smokers beginning with a menthol brand. Younger smokers may be better able to tolerate menthol cigarettes with their milder sensory properties better than harsher non-menthol cigarettes. Subsequently, adolescents who experience fewer adverse physiological effects from smoking may be more likely to progress from experimentation to regular smoking and switch to non-menthol cigarettes as nicotine dependence increases.

Menthol cigarette smoking youth have significantly higher scores of nicotine dependence compared with non-menthol smokers, controlling for demographic background, length, frequency and level of smoking. Menthol smokers are less likely to attempt cessation, more likely to relapse after successfully quitting, and less likely to report sustained smoking cessation than non-menthol smokers. At high levels of menthol, the profound cooling effects can diminish health concerns in long term smokers, which can delay quitting.

The tobacco industry's document research and empirical studies show that consumers perceive that menthol cigarettes offer some form of implicit health protection or medicinal benefit that non-menthol cigarettes do not provide. Consequently, menthol flavouring enhances abuse liability, making it easier to start and harder for smokers to quit¹.

Conclusions

A narrow definition of harm is not justified in dealing with multifunctional additives like a menthol. Menthol is an effective antitussive agent and the increased sensation of airflow and inhibition of respiratory rates allow an increased lung exposure to nicotine, tar and toxic constituents, while masking reaction like coughing or

any early warning signs of respiratory disease. It affects multiple sensations: taste, aroma and tactile smoothness, enhance abuse liability. Its pharmacological actions reduce the harshness of smoke and the irritation from nicotine, and may increase the likelihood of nicotine addiction in adolescents and young adults who experiment with smoking, and discourage quitting.

Adding menthol is not benign, it enhances the attractiveness of toxic tobacco products. The harm of menthol is in its masking of the harshness of tobacco smoke, its use in starter products for children, its interference with quitting and staying quit, and the deliberate targeting of menthol cigarettes to vulnerable populations. Any tobacco product design characteristic that makes toxic tobacco products attractive and palatable eventually increases dependence and impacts negatively on the public health. Overall, the unique sensory effects of menthol, at higher or subliminal levels, contribute to the reinforcing effects of nicotine and smoking, thereby contributing substantially to the tobacco related morbidity and mortality.

- Tobacco Products Scientific Advisory Committee (TPSAC) (2011) Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations. Submitted to FDA: March 23, 2011, Final edits from the July 21, 2011 meeting are included, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf (accessed on 28 July 2012)
- 2 Ahijevych K & Garrett BE (2004) Menthol pharmacology and its potential impact on cigarette smoking behavior. Nicotine Tob Res 6 (Suppl. 1): S17-28
- Ferris Wayne G & Connolly GN (2004) **Application, Function, and Effects of Menthol in Cigarettes: A Survey of Tobacco Industry Documents.** *Nicotine Tob Res* 6 (Suppl. 1): S43-54
- 4 Heck JD (2010) A Review and Assessment of Menthol Employed as a Cigarette Flavouring Ingredient. Food Chem Toxicol 48 (Suppl. 2): S1-38
- Kreslake JM, Wayne GF& Connolly GN (2008) The Menthol Smoker: Tobacco Industry Research on Consumer Sensory Perception of Menthol Cigarettes and Its Role in Smoking Behavior. Nicotine Tob Res 10: 705-715

- Kreslake JM & Yerger VB (2010) Tobacco Industry Knowledge of the Role of Menthol in Chemosensory Perception of Tobacco Smoke. Nicotine Tob Res 12 (Suppl. 2): S98-101
- German Cancer Research Center (DKFZ) (ed.) (2012) Menthol Capsules in Cigarette Filters Increasing the Attractiveness of a Harmful Product. Vol. 17, Red Series Tobacco Prevention and Tobacco Control, Heidelberg, Germany, http://www.dkfz.de/de/tabakkontrolle/download/Publikationen/RoteReihe/Band_17_Menthol_Capsules_in_Cigarette_Filters_en.pdf (accessed on 28 July 2012)
- Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) **Tabakerzeugnisse** (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)
- Olark PI & Gardiner P (2011) Menthol Should Not Be Given a Free Pass Based on Studies of Biomarkers of Toxicity. Cancer Epidemiol Biomarkers Prev 20: 1269-1271
- Wertz MS, Kyriss T, Paranjape S & Glantz SA (2011) The Toxic Effects of Cigarette Additives. Philip Morris' Project Mix Reconsidered: An Analysis of Documents Released through Litigation. PLoS Med 8: e1001145
- Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010)

 Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- Yerger VB & McCandless PM (2011) Menthol Sensory Qualities and Smoking Topography: A Review of Tobacco Industry Documents. Tob Control 2 (Suppl.): ii37-43
- 13 Lee YO & Glantz SA (2011) Menthol: Putting the Pieces Together. Tob Control 20: (Suppl. 2): ii1eii7

Further reading

- 14 Addiction (2010) Special Issue: The Role of Mentholated Cigarettes in Smoking Behaviors in United States Populations. Vol. 105 (Suppl. 1): 1-140
- Nicotine & Tobacco Research (2010) Menthol Cigarettes: Moving Toward a Broader Definition of Harm. Vol. 12 (Suppl. 2): 85-153
- 16 Tobacco Induced Diseases (2011) Mentholated Cigarettes and Public Health. Vol. 9 (Suppl. 1): S1-S7
- 17 Tobacco Control (2011) Menthol Cigarettes. Vol. 20 (Suppl. 2): 1-56

Additives in tobacco products Prune Juice Concentrate



Overview

Plum is the common name of tree of many species belonging to the genus Prunus of Rosaceae family and also for its fleshy fruit. Prunes are ripe plums dried without fermentation. Prune juice concentrate is predominantly prepared from Prunus domestica, using water extraction at low temperature followed by vacuum evaporation to a concentration of about 70 % soluble solids. Pectinase treatment can reduce viscosity and the flavour may be enhanced by adding volatile oils separated during concentration or threonine. Prune juice concentrate is widely used in bakery, confectionery and dairy manufacturing as a colour/flavour enhancer, e.g. as sugar

substitute, to sweeten and colour natural baked goods, as natural syrup for yogurts and ice cream, as a humectant to maintain moisture in cakes and cookies, as a filling for hard candies and chocolate and as a binding agent in cereal bars. The flavour of dried plums is compatible with other fruits, spices and chocolate. In fact, dried plums act in a manner similar to vanilla to round out and enhance other flavours and reduce the bitterness associated with the bran fractions of whole grain^{1,2}.

Prune juice concentrate is used in casing and as a flavour additive for cigarettes. Different compositions such

Chemical and Physical Information

Prune juice concentrate

Prunus domestica fruit extract or powder, Prunus, Prune extract, Plum extract

90082-87-4 (Prune Concentrate: CAS: 83173-17-5)

290-179-3

Natural fruit extract, not completely defined complex mixture, 70 Brix Concentrate 85-95 % of dry solids are reducing sugars (see characteristics below).

Amber to dark brown

Category

Flavouring agents

Odour type Fruity

Prune concentrate characteristics

Chemically prune juice is a complex mixture¹⁻³. Carbohydrates can constitute as much as 95 % of concentrate and there is a preponderance of mono- and di-saccharides fructose, glucose, xylose and sucrose. The carbohydrate fraction also contains soluble "gums" such as hemicellulose, protopectin, pectin and higher sugars such as melezitose. Fifteen amino acids, the major being aspartic acid, aspargine, tyrosine and cysteine have been reported. Amino acids impart taste and aroma such as sweet, nutty or earthy to the smoke. Eight organic acids including quinic, malic, phosphoric and glucuronic acids, which play a role in smoothness, volatile compounds such as furans, phenols and degradation products of carotenoids, and also ammonia have been reported in prune juice extract. Malic acid, for example, is an effective flavour enhancer. Prune extract also contains benzoic acid, levulinic acid and 5-hydroxymethylfurfural.

as prune extract, prune extract-oleoresin, prune juice/ concentrate are also reported (see below). Prune juice extracts/concentrates addition to cigarettes, little cigars and blunt wraps are legally banned in Canada (the Bill C-32-An Act to amend the Tobacco act, 2009) as products from processing of fruits and similarly in Brazil.

Function of the Additive

Industry categorise the function of plum juice concentrate, plum extract, prune extract and prune juice concentrate as flavour/casing ingredients. Casing is the sauce composed of a variety of ingredients such as humectants, sugars, cocoa, liquorice, fruit extracts applied to tobacco in early processing stage.

Amount of Prune Juice Concentrate Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level, is now disseminated to public. In Germany, a brand-wise listing is available online from the Federal Ministry of Food, Agriculture and Consumer Protection⁴, and now various company web sites also provide information on their brands.

Various extracts are reported by manufacturers, e.g. plum juice concentrate (CAS: 90082-87-4, 0.004 %), plum extract (CAS: 90082-87-4, 0.004 %), prune extract (CAS: 90082-87-4, 1.09 %) and prune juice concentrate (CAS: 90082-87-4, 1.09 %) as flavour ingredients⁵. According to some manufacturers report, prune juice concentrate is used as casing at the maximum level of 0.47 % dryweight of the tobacco and use of prune extract, prune extract-oleoresin, and prune juice/concentrate as flavouring at maximum use of 0.00136 %, 0.00054 %, 0.01792 % respectively is reported for domestic cigarettes in Germany.

Pyrolysis and Reaction Products in Cigarette Smoke

Prune extracts are generally recognised as safe when used in food products, but this does not guarantee their safety as a tobacco additive due to the generation and inhalation of likely pyrolysis products when burnt. No direct pyrolysis studies have been reported on prune juice concentrate. However as carbohydrates/sugars constitute as much as 95 % of the concentrate, the addition of prune extracts to tobacco would affect the smoke chemistry in a similar way as with the addition of sugars. Pyrolysis of sugars leads to formation of carcinogenic compounds such as polyaromatic hydrocarbons. Sugars caramelise and break down into a mixture of mainly organic acids and a variety of aldehydes, such as acetaldehyde, acrolein, and 2-furfural. These acids have been reported to affect nicotine delivery, smooth the harshness of smoke, possibly, leading to increased smoking frequency and deeper inhalation of smoke to enable optimal absorption of nicotine as well as toxic and carcinogenic smoke constituents in the airways.

Harmful Health Effects of Prune Juice Concentrate

Exposure

The combustion of the inherent sugars of prune extract/ concentrate can lead to formation of carcinogenic polyaromatic hydrocarbons, a variety of aldehydes, such as acetaldehyde, acrolein, and 2-furfural and a mixture of organic acids. These organic acids are reported to reduce nicotine delivery, leading to increased smoking frequency and deeper inhalation of smoke to enable higher absorption of nicotine in the airways together with toxic and carcinogenic smoke constituents.

Toxicity

Prune juice concentrate was tested for multiple toxicological endpoints, as a mixture of additives and individually in a number of studies by the industry in experimental cigarettes⁵⁻⁷. They reported no significant effects of tested ingredients on overall toxicity of cigarette smoke. However, these publications are based on the premise that the toxicity of ingredients should be evaluated relative to that of the overall toxicity of tobacco, rather than on the basis of their own absolute toxicity. The drawback in these studies is that the ingredient being tested might be as toxic and carcinogenic as the tobacco smoke constituents. Reevaluation of such studies has revealed that toxins in cigarette smoke increase substantially because of hundreds of additives including menthol that were tested by the industry in different combinations with the tobacco matrix8. Moreover, the main important function of ingredients on the palatability and attractiveness of a toxic product is ignored.

Addictiveness

The harsh and irritating character of tobacco smoke provides a significant barrier to experimentation and initial use. Prune juice concentrate improves the organoleptic properties of tobacco smoke, stimulates the ease of nicotine delivery by smoothening and sweetening the harsh smoke, enhance smokers ability to optimize nicotine delivery to the brain, thereby increasing the abuse potential.

Attractiveness

Prune juice concentrate is used to smoothen and mildly sweeten the smoke making the smoke more palatable. Prune juice concentrate is reportedly used in combination with other natural flavours or commercial tobacco flavour improvers to "smooth or mildly sweeten the smoke and to blend the various natural smoke flavour ingredients"2.

The high sugar component of prune concentrate can caramelise to impart a sweet caramel flavour improving the organoleptic properties of smoke and to reduce harshness. Sugars can be converted via the Maillard reaction to form amino-sugar complexes in tobacco which can lead to generation of other compounds including (amadori compounds), acrylamide and furfural and pyrazines. The highly flavourful compounds such as pyrazines may effect perceptions of harm by masking toxins and increasing palatability and attractiveness. Sensory cues can arise from a range of neural responses including smell (via olfactory nerve), irritation (trigeminal nerve), and taste (facial, glossopharyngeal and vagal nerves) from the compounds produced by the Maillard browning process. Sensory cues produced by these compounds are important in the stimulation of cues, such as pending reward, craving reduction and triggering a learned behaviour, play an important role in enhancing nicotine delivery⁹.

Conclusions

Prune juice concentrate is used as a casing and flavouring. It smoothens and mildly sweetens the tobacco smoke making it more palatable, leading to enhanced nicotine delivery. High inherent also contributes to the Maillard browning process generated flavours as well as toxic compounds associated with the pyrolysis of sugars. Prune juice extract is used to improve the organoleptic properties of tobacco smoke, making the harsh cigarette smoke palatable, thereby optimizing the delivery of nicotine and increasing the abuse liability particularly for naïve users leading to deleterious health effects of smoking.

References

- Sanders SW (1991) Using Prune Juice Concentrate in Whole Wheat Bread and Other Bakery Products. Cereal Foods World 36: 280-283
- 2 Lorillard (1992 est.) Prune Juice Concentrate. Bates: 87068672-87068682, Collection Lorillard, http://tobaccodocuments.org/lor/87068672-8682.html (accessed on 28 July 2012)
- Melstead JL & Brandwein BJ (1966) The Isolation, Identification and Quantitative Determination of Some Organic Constituents of Prunus domestica. Proc SD Acad Sci 45: 185-195
- Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) **Tabakerzeugnisse** (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)
- Baker RR, Massey ED & Smith G (2004) An Overview of the Effects of Tobacco Ingredients on Smoke Chemistry and Toxicity. Food Chem Toxicol 42 (Suppl.): 53-83
- Baker RR, Pereira da Silva JR & Smith G (2004) **The Effect of Tobacco Ingredients on Smoke Chemistry Part I: Flavourings and Additives.** *Food Chem Toxicol* 42 (Suppl.): S3-37
- 7 Coggins CR, Wagner KA, Werley MS & Oldham MJ (2011) A Comprehensive Evaluation of the Toxicology of Cigarette Ingredients: Carbohydrates and Natural Products. *InhalToxicol* 1 (Suppl.): 13-40
- Wertz MS, Kyriss T, Paranjape S & Glantz SA (2011) The Toxic Effects of Cigarette Additives. Philip Morris' Project Mix Reconsidered: An Analysis of Documents Released through Litigation. PLoS Med 8: e1001145
- Megerdichian CL, Rees VW, Wayne GF & Connolly GN (2007) Internal Tobacco Industry Research on Olfactory and Trigeminal Nerve Response to Nicotine and Other Smoke Components. Nicotine Tob Res 9: 1119-1129

Further Reading

- 10 Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010)

 Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- Conference of the Parties of the WHO Framework Convention on Tobacco Control (FCTC) (2010) Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (Regulation of the Contents of Tobacco Products and Regulation of Tobacco Product Disclosures). FCTC/COP4(10), http://www.who.int/fctc/guidelines/Decisions9and10.pdf (accessed on 28 July 2012)
- Bates C, Connolly GN & Jarvis M (1999) Tobacco Additives: Cigarette Engineering and Nicotine Addiction. Action on Smoking and Health, London, U.K.
- Wigand JS (2006) Additives, Cigarette Design and Tobacco Product Regulation. A Report to: World Health Organization, Tobacco Free Initiative, Tobacco Product Regulation Group, 28 June-2 July 2006, Kobe, Japan

Additives in tobacco products Vanillin



Overview

Vanilla aroma is naturally produced in the seedpods of the Mexican orchid Vanilla planifola and is widely used as flavouring material in food and cosmetic industries¹⁻³. Vanilla flavour is used in several types of food such as yogurts, ice creams, confectionery, beverages and baked goods, either as a characterizing flavour that imparts the typical flavour of vanilla or as a segment of a more complex flavour system.

Chemical and Physical Information

Name

Vanillin

4-hydroxy-3-methoxybenzaldehyde, para-vanillin, vanillic aldehyde 4-hydroxym-anisaldehyde, methylprotocatechuic aldehyde, 3-methoxy-4-hydroxybenzaldehyde hydroxy-4-methoxy-3-benzaldehyde

Molecular structure

Aldehyde

Chemical formula

C₈H₈O₃

Boiling point

285 °C

Melting point

~ 81 °C

Molecular weight

152.14

Octanol/water partition coefficient

 $Log K_{ow} = 1.37$

Thermal decomposition or burning may release carbon monoxide or other hazardous gases, acrid smoke and irritating fumes.

White to yellowish, non-hygroscopic crystalline powder

Pleasant aromatic vanilla odour

Pleasant vanilla taste, sweet taste

CAS number

121-33-5

204-465-2

3107

GRAS (Generally Recognized As Safe)

In the complex flavour system, vanilla is used to enhance the flavour of caramel, coffee and dairy products and to mask the off flavours that develop because of oxidative degradation. Vanilla (CAS: 8024-06-4) has a delicate, sweetish/aromatic odour and a low threshold of odour recognition. The immature pods are dried, fermented and extracted with alcohol to obtain vanilla extract with a high content of aromatic compounds, the major component vanillin (4-hydroxy-3-methoxybenzaldehyde) constituting up to two per cent of weight of vanilla beans. The vanilla flavour is a combination of gustatory, olfactory and tactile stimuli that result in an interplay between the complex mixture of aromatic esters, alcohols and aldehydes.

As natural vanilla is expensive, synthetic vanilla flavour substances, vanillin and ethyl vanillin (CAS No. 121-32-4, FEMA 2464, Synonym 3-ethoxy-4-hydroxy-benzaldehyde, MP: 285 °C) are used instead to reduce costs. Vanillin is one of the most universally accepted popular aromatic chemicals, ranking it as number one with respect to its consumption in tonnage. Vanillin is mainly used as an additive to food and beverages (60 %), but considerable amounts are used for flavour and fragrances (20-25 %), while 5-10 % is used for intermediates for pharmaceuticals. Vanillin is added to a whole range of food and beverage products in concentrations, depending on the product category, from 0.00002 % up 0.1 %. As fragrance ingredient for perfumes vanillin is added at concentrations ranging from 0.005 % to 0.8 %. The various vanilla flavouring substances are generally recognized as safe (GRAS) when used in these products.

Vanillin is used as an additive to improve the organoleptic properties of tobacco smoke, thereby enhancing the attractiveness of smoking. Vanilla flavour, natural and or synthetic, not only imparts a sweet characterizing vanilla taste, flavour and aroma to tobacco smoke but it is also used to mask the odour of second hand smoke. The data is limited on combustion of vanillin and its transfer to the body through the lung, when used as a cigarette additive. However, due to its strong chemosensory effect, it enhances the abuse potential by masking the harshness of nicotine and other toxins. Besides, by masking second hand smoke, it reduces the perception of bystanders to smoke toxins, a strategy used by the tobacco industry to manufacture 'socially acceptable' products.

Function of the Additive

According to the cigarette manufacturers, vanillin is used as a flavouring material. Vanillin or vanillin releasing compounds can be applied directly to the tobacco during cigarette manufacturing and to the paper or filter.

Amount of Vanillin Added to Cigarettes

The mandatory listing of tobacco ingredients added above a specified level is now disseminated to public. In Germany, a brand-wise listing is available

online from the Federal Ministry of Food, Agriculture and Consumer Protection⁴. Cigarette companies also report various levels on their individual websites, for example, vanilla bean extract 0.001 %, vanillin 0.005 %, ethyl vanillin 0.05 % of the tobacco weight reported as flavour in German cigarettes by one company, vanilla oleoresin 0.01 %, vanillin 0.05 %, ethyl vanillin 0.025 % at a maximum use level in any cigarette brand as flavour; or vanilla extract 0.00022 %, vanilla oleoresin 0.00045 %, vanillin 0.00443 %, ethyl vanillin 0.00022 % maximum use in German domestic cigarettes is reported by others.

Pyrolysis and Reaction Products in Cigarette Smoke

Thermal decomposition or burning of vanillin may release hazardous products such as carbon monoxide or other hazardous gases, acrid smoke and irritating fumes3. High temperature pyrolysate products of vanilla extract included aromatic hydrocarbons, their nitrogen containing analogs and phenols⁵. Vanillin was shown to transfer intact to mainstream smoke of filter cigarettes at low temperatures (200 °C), with approximately 0.1 % degradation to 2-methoxyphenol, phenol, o-cresol and, 2-hydroxy benzaldehyde at 200-800 °C.6

Harmful Health Effects of Vanillin

Exposure/Toxicity

The exposure and toxicity studies comparing cigarettes with and without additives like vanillin in a mixture of additives or individually have been done by the industry, with the conclusion that there is no increased harm from the addition of vanillin to cigarettes and there is no increase in the overall toxicity of cigarette smoke7. These publications are based on the premise that the toxicity of ingredients should be evaluated relative to that of the overall toxicity of tobacco products, rather than based on their own absolute toxicity. The main drawback with this interpretation is that the ingredient being tested might be as toxic and carcinogenic as the tobacco smoke constituents. A recent reevaluation of such studies has revealed that toxins in cigarette smoke increase substantially because of hundreds of additives (including vanilla, vanillin and vanilla oleoresin) that were tested by the industry in different combinations with the tobacco matrix8. Besides, such studies have little relevance when the main function of the additive is to enhance the palatability and attractiveness of an addictive and toxic product.

Addictiveness

The harsh and irritating character of tobacco smoke provides a significant barrier to experimentation, initial use and conversion. Vanilla flavour enhances attractiveness of tobacco by masking these effects through chemosensory stimulation that also masks harm and increases abuse potential.

Attractiveness

Vanilla flavour is one of the most popular flavours worldwide and is used to enhance the organoleptic properties (pertaining to taste, colour, odour, and feel involving use of the sense organs) of tobacco smoke, to make the product more attractive to consumers, thereby, promoting and sustaining tobacco use, especially by young people and first time users9. Sensory cues can arise from a range of neural responses including smell via olfactory nerve, irritation via trigeminal nerve, and taste via facial, glossopharyngeal and vagal nerves. Sensory cues are important in the determination of smoking satisfaction, reinforcement of a learned behaviour, reward and craving reduction. Vanilla flavour is used to mask the harshness and smell of tobacco smoke, thereby reducing perceptions of harm and toxicity of mainstream and second hand smoke not only for the smoker but exposed nonsmokers. Industry documents reveal that, amongst side stream flavouring, vanillin received high score of acceptability. Several flavour release reagents that on pyrolysis release either a single flavour or a mixture of flavours that have sweet/vanillin type aromas have been developed and patented by the industry¹⁰. In the USA, vanillin is banned as a characterizing flavour but not at non-characterizing levels. In France, vanillin or ethyl vanillin > 0.05 % of tobacco mass is prohibited in cigarettes. In Canada, vanillin is totally banned in cigarettes, little cigars and blunt wraps and recently Brazil has a similar ban.

Conclusions

Vanilla flavour, natural or synthetic, is reported to be used as flavouring. Vanillin contributes to the increase in attractiveness of smoking by chemosensory stimulation of neural receptors that improve nicotine delivery by masking its bitter taste and reducing harshness of smoking. Flavour additives, like vanilla, play an important role in enhancing smoking behaviour and abuse potential¹¹. Vanilla flavour is used to improve the organoleptic properties of tobacco smoke, making the harsh cigarette smoke palatable, thereby enhancing the attractiveness of smoking to naïve users by facilitating and increasing use and exposure to toxic and addictive compounds. According to the industry documents, vanillin increases mildness of harsh blends without altering smoke toxins. It also masks sidestream and addresses some smoker's concerns about exposing others to toxic smoke. Sensory cues are important determinants of smoking satisfaction, reward and craving reduction. The unique sensory effects of vanillin contribute to the reinforcing effects of smoking, thereby contributing substantially to morbidity and mortality. Thus banning of flavours at both characterizing and non-characterizing levels is very important to reduce the burden of harm caused by tobacco products.

- European Chemical Substances Information System (ESIS) IUCLID Chemical Data Sheet: Vanillin. Institute for Health and Consumer Protection (IHCP), Joint Research Centre, European Commission, http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/121335.pdf (accessed on 28 July 2012)
- Organisation for Economic Co-operation and Development (OECD) Vanillin. Screening Information Data Sets (SIDs), United Nations Environment Programme (UNEP) Publications, http://www.inchem. org/documents/sids/sids/121335.pdf (accessed on 28 July 2012)
- United States National Library of Medicine (NLM) Hazardous Substances Data Bank (HSDB). 3 TOXNET, search term: vanillin, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (accessed on 28 July 2012)
- Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) Tabakerzeugnisse (website). Germany, http://service.ble.de/tabakerzeugnisse/index2.php?site_key=153&site_key=153 (accessed on 28 July 2012)

- 5 Higman HC, Higman EB & Chortyk OT (1974) Pyrolysis of Selected Tobacco Flavouring Additives. Tob Sci 18: 140-142
- 6 Stotesbury SJ, Willoughby LJ & Couch A (2000) Pyrolysis of Cigarette Ingredients Labelled with Stable Isotopes. Beiträge zur Tabakforschung 19: 55-64
- 7 Lemus R, Carmines EL, Van Miert E, Coggins CR, Anskeit E, Gerstenberg B, Meisgen TJ, Schramke H, Stabbert R, Völkel H & Terpstra PM (2007) Toxicological Comparisons of Cigarettes Containing Different Amounts of Vanillin. Inhal Toxicol 19: 683-699
- Wertz MS, Kyriss T, Paranjape S & Glantz SA (2011) The Toxic Effects of Cigarette Additives. Philip Morris' Project Mix Reconsidered: An Analysis of Documents Released through Litigation. PLoS Med 8: e1001145
- Tobacco Products Scientific Advisory Committee (TPSAC) (2011) Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations. Submitted to FDA: March 23, 2011, Final edits from the July 21, 2011 meeting are included, http://www.fda.gov/downloads/ AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ UCM269697.pdf (accessed on 28 July 2012)
- HouminerY (1989) Potential Flavouring of Sidestream by Using Flavour-Release Technology. Philip Morris, Bates: 2051567894/7895, http://legacy.library.ucsf.edu/tid/jxo42d00 (accessed on 28 July 2012)
- 11 Megerdichian CL, Rees VW, Wayne GF & Connolly GN (2007) Internal Tobacco Industry Research on Olfactory and Trigeminal Nerve Response to Nicotine and Other Smoke Components. Nicotine Tob Res 9: 1119-1129

Further Reading

- 12 Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR (2010)

 Addictiveness and Attractiveness of Tobacco Additives. Pre-consultation opinion, http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf (accessed on 28 July 2012)
- Conference of the Parties of the WHO Framework Convention on Tobacco Control (FCTC) (2010)
 Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention
 on Tobacco Control (Regulation of the Contents of Tobacco Products and Regulation of Tobacco
 Product Disclosures). FCTC/COP4(10), http://www.who.int/fctc/guidelines/Decisions9and10.pdf
 (accessed on 28 July 2012)
- Bates C, Connolly GN & Jarvis M (1999) **Tobacco Additives**: **Cigarette Engineering and Nicotine Addiction**. Action on Smoking and Health, London, U.K.
- Wigand JS (2006) Additives, Cigarette Design and Tobacco Product Regulation. A Report to: World Health Organization, Tobacco Free Initiative, Tobacco Product Regulation Group, 28 June-2 July 2006, Kobe, Japan

