



Tobacco additives

Information for Professionals

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This report on seven tobacco additives. sugars, sorbitol, propylene glycol, glycerol, ammonium compounds, cocoa, furfural and the smoke components acetaldehyde, formaldehyde and acrolein, has been created by the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. The electronic version of this report can be found on the RIVM website www.tabakinfo.nl. A report on seven other tobacco additives, menthol, carob bean, cellulose fibre, prune juice, vanillin, guar and licorice, has been created by the German Cancer Research Center, (DKFZ), Heidelberg, Germany. The introduction is a common product. The electronic version of that report can be found on the DKFZ website <http://www.dkfz.de/de/tabakkontrolle>.

The reports have been written in the context of the EU project Public Information Tobacco Control (PITOC). The reports aim to inform professionals on the general uses, tobacco industry uses and harmful health effects of selected tobacco additives. A version for the lay public has been based on the fact sheets in the current report. The originals of the laymen fact sheets can be found on the RIVM website www.tabakinfo.nl and the DKFZ website <http://www.dkfz.de/de/tabakkontrolle> (in English).

These fact sheets aim to inform the public on the general uses, tobacco industry uses and harmful health effects of the selected tobacco additives. They have been translated by all 16 partners of the project to their national languages and will be disseminated through their websites.

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National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport



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Introduction

In the EU, smoking accounts for 695000 preventable deaths per year. In addition, almost 80,000 non-smokers 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 describes facts on the attractive, addictive and hazardous effects associated with seven tobacco additives used by the tobacco industry most often and in highest quantities: sugars, sorbitol, propylene glycol, glycerol, ammonium compounds, cocoa, furfural. In addition, information is given on the combustion products acetaldehyde, formaldehyde and acrolein that are relevant for many of these additives. As such, it provides 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 experts in the field of tobacco product composition. The German Cancer Research Center, (DKFZ), Heidelberg, Germany, published a similar report on seven other additives: smoke components acetaldehyde, formaldehyde and acrolein.

These fact sheets are 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 10 (WHO-FCTC, 2010). The World Health Organization Framework Convention on Tobacco Control (FCTC) is a reaction to the world-wide tobacco epidemic and aims to contribute to the reduction of smoking-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 respectively. 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 stage.

General information on tobacco additives

The tobacco industry uses many additives in the manufacturing of tobacco products.

In literature it is generally stated that over 600 ingredients are added to tobacco products. The modern American blend cigarette contains about 10 percent additives by weight, mostly in the form of sugars, humectants, ammonia compounds, cocoa, and licorice (Rabinoff, 2007).



Reasons for adding additives to cigarettes

Additives are intentionally added to cigarettes by the tobacco industry to modify the flavour, regulate combustion, moisturise the smoke, preserve the cigarettes, and in some instances to act as solvents for other additives (Rabinoff, 2007). 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, 2010) 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 others (SCENIHR, 2010). Specific additives can mask the bitter taste, improve the flavour and reduce the irritation of inhaled smoke. Examples of flavouring substances include sugars, sweeteners, 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 capsule (DKFZ, 2012). 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 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 increase the addictiveness to tobacco smoke (Talhout *et al.*, 2007).

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 applied (Wigand, 2006). 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 to 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.

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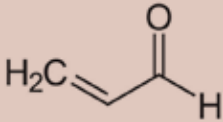
Acrolein

Acrolein: overview

Acrolein (2-propenal) can be formed from diverse sources through the incomplete combustion or pyrolysis of organic materials, including tobacco. Smoking of cigarettes constitutes a significant source that is equivalent to or exceeds the total human exposure to acrolein from all other sources. As an example, the maximum concentration in areas with a high traffic density is about $10 \mu\text{g}/\text{m}^3$, whereas exposure of smokers (and non-smokers) in poorly ventilated rooms may be as high as several hundred $\mu\text{g}/\text{m}^3$ of acrolein (Stevens and Maier, 2008). The primary source of acrolein in cigarette smoke is the either naturally occurring or from (poly) sugars, such as glucose, added to tobacco or tobacco products. However, there is a possibility that a small percentage of the acrolein in smoke comes from glycerol, it being one of its major combustion products. A portion of the acrolein found in smoke could also be formed by the aldol condensation of formaldehyde and acetaldehyde, produced as part of the pyrolysis process, which occurs during cigarette smoking during the pyrolysis process (Stevens and Maier, 2008).

Chemical and physical information

Chemical name Acrolein
Molecular formula C_3H_4O
Structure formula



Synonyms Acraldehyde; acrylaldehyde; acrylic aldehyde; allylaldehyde; propenal; 2-propenal; prop-2-enal; prop-2-en-1-al
Odour description Almond cherry (odour strength: high) (www.thegoodscentscompany.com)
CAS number 107-02-8
Molecular weight 56.06 g/mol
Volatility vapour pressure, 210 mm Hg at 20°C
Boiling point 52 °C
Octanol water partition coefficient, log P, log K_{ow}: 1.2, 0.101

Acrolein is not an additive but a smoke component primarily produced upon combustion of tobacco additives. The effects/possible effects of acrolein, which occur during cigarette smoking are illustrated herein. Acrolein is a highly reactive compound which primarily reacts in the respiratory tract, as demonstrated in non-lethal animal studies conducted in experimental animals. These studies showed acrolein to be a potent irritant at relatively low concentrations and short exposure durations. To date, there is no consistent evidence to conclude that acrolein has a specific role of acrolein in the etiology of cancer for smokers. In addition, there is no data available on the contribution of acrolein to altering the addictiveness or attractiveness of cigarettes.

Function of smoke component

Acrolein is a smoke component and it is not used by tobacco manufacturers as an additive. Acrolein is generated during the combustion of the many (poly)sugars added to tobacco such as glucose.

Amount of acrolein in cigarette smoke

Studies have reported a sales-weighted mean for 74 tested brands of 0.11 mg acrolein per cigarette (Phillips and Waller, 1991), with the sales weighted mean being the mean amount of acrolein in the smoke produced per cigarette adjusted to the difference in composition of the brands most commonly sold. A study in which the average acrolein smoke content of 48 different brands of filtered cigarettes from various international markets (Philip Morris commercial brands) was analysed by a smoking machine using the Canadian Intense method, the amount of acrolein in mainstream smoke was found to be 0.122 mg per cigarette (Counts *et al.*, 2005). This study was used for the exposure assessment.

Pyrolysis and reaction products in cigarette smoke

Acrolein is the pyrolysis product of the combustion of most of the (poly) sugars contained in tobacco (this is not the case with just tobacco) and is a highly reactive compound that will interact with numerous smoke components thereby forming several secondary pyrolysis products. However, there is insufficient information on these reaction products to make a meaningful conclusion on the contribution of acrolein. Acrolein is also a toxic pyrolysis product of glycerol, which is added to cigarettes as a humectant.

Harmful health effects of acrolein

Hazard assessment of toxic effects

The direct toxicity of acrolein, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to acrolein is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

Although acrolein has been shown to form DNA adducts in oral tissue, there is no evidence either in humans or experimental animals that acrolein is carcinogenic.

Non-carcinogenic effects: Local respiratory effects and systemic effects

Owing to the high reactivity of acrolein, it binds primarily to the respiratory tract (the application site) of smokers during smoking. This has been observed in non-lethal studies in experimental animals; an indication that the respiratory system is a target for acrolein toxicity. It has also been

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demonstrated that acrolein is a potent irritant at relatively low concentrations and short exposure durations. The main source of exposure of the general population to acrolein is through tobacco smoke. The main effects reported following acrolein exposure occurred in the respiratory tract and this included changes in the olfactory epithelium of rats exposed to 0.9, 3.2 and 11 mg/m³, 6 hours per day, 5 days per week for 13 weeks (Feron et al., 1978). This study for acrolein gave the lowest value to be used in the risk assessment (e.g. point of departure (PoD)) with a LOAEL of 0.9 mg/m³. No systemic effects were reported in this study. A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives (RIVM, 2012) was applied to draw the following conclusions:

Risk for local effects:

A risk of effects on the respiratory tract epithelium due to acrolein exists.

Risk for systemic effects:

No thorough assessment on systemic effects was made. No systemic effects were reported in the inhalation study, which is expected given that acrolein is very reactive and will therefore exert its effect at the first site of exposure.

Potential effects on addictiveness and attractiveness of acrolein

Addictiveness

No data have been reported to suggest that acrolein plays a role in smokers' addictiveness to cigarettes.

Attractiveness

No data have been reported to suggest that acrolein plays a role in smokers' attractiveness to cigarettes.

Conclusions

Acrolein, an aldehyde and a combustion product of many of the (poly) sugars added to tobacco, is a very reactive compound, which exerts its primary effects on the respiratory tract; its main target site. Margin of exposure (MOE) analysis demonstrates that the risk of effects on the respiratory tract epithelium due to acrolein does exist. Higher levels of acrolein may occur due to the combustion of other additives such as glycerol. In terms of carcinogenicity, there is not reported evidence to suggest that acrolein produced as a result of smoking poses a carcinogenic risk. Similarly, no data on the addictiveness and/or attractiveness of cigarettes, due to acrolein exposure during smoking have been reported.

Finally, it must be borne in mind that acrolein is only one component out of the thousands of compounds contained in cigarette smoke, thus the additive effects of acrolein or its reactivity with other compounds cannot be excluded.

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Acetaldehyde

Acetaldehyde: overview

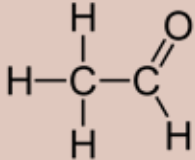
Acetaldehyde is a natural reaction product of metabolic processes in many organisms and can be generated from a range of sources. Cigarette smoke constitutes one of the significant sources of exposure to acetaldehyde.

Acetaldehyde itself is not used as an additive but it generated from the combustion of tobacco additives, such as (poly)sugars and glycerol/glycerine. Exposure to acetaldehyde through cigarette smoking occurs via inhalation, making the respiratory tract the first site of exposure. Acetaldehyde is a highly reactive compound that forms several systemically active adducts already outside (e.g. in tobacco) or inside the body (IPCS, 1994).

Acetaldehyde is not an additive but a smoke component primarily produced upon combustion of tobacco additives. The effects/possible effects of acetaldehyde, which occur as a result of exposure during cigarette smoking are illustrated herein. Inhalation exposure to acetaldehyde causes mild irritation of the upper respiratory tract. Acetaldehyde is classified as possibly carcinogenic to humans by the

Chemical and physical information

Chemical name Acetaldehyde
Molecular formula C_2H_4O
Molecular structure



Synonyms Ethanal; acetic aldehyde; aldehyde; ethylaldehyde; acetylaldehyde; diethylacetal, 1,1-diethoxy ethane
FEMA number 2003
Odour description Pungent, ethereal, fresh, lifting, penetrating, fruity and musty (odour strength: high) (www.thegoodscentcompany.com)
Taste description Pungent, fresh, aldehydic, refreshing and green (at 10 ppm) (www.thegoodscentcompany.com)
CAS number 75-07-0
Molecular weight 44.1 g/mol
Volatility vapour pressure, 755 mm Hg at 20 °C
Boiling point 20-21°C
Octanol water partition coefficient, log P, log K_{ow} : 0.4-0.5, 0.06-0.53

International Agency for Research on Cancer. Importantly, acetaldehyde has been hypothesized to indirectly influence the addictiveness of cigarette smoking through the generation of harman. Harman is a condensation product of acetaldehyde which has been shown to inhibit monoamine oxidase (MAO). Acetaldehyde induces reinforcing effects and acts synergistically with nicotine in self-administration studies. The MAO inhibitory properties of acetaldehyde are presumed to be responsible for the increase in nicotine self-administration and maintenance of behavioural sensitization to nicotine. There is no reported data on the effects of acetaldehyde and attractiveness of cigarettes.

Function of smoke component

Acetaldehyde is a smoke component and it is not used by tobacco manufacturers as an additive. Acetaldehyde is generated during the combustion of the many (poly)sugars added to tobacco.

Amount of acetaldehyde in cigarette smoke

The mainstream smoke from an average cigarette contains 1.448 mg of acetaldehyde when the cigarette is smoked on a smoking machine using the Canadian Intense method (Counts *et al.*, 2005); maximum levels of acetaldehyde reported to be present in inhaled smoke can reach up to 2.1 mg per cigarette, depending on the puff profile intensity, method of detection and/or tar level (Seeman *et al.*, 2002; Talhout *et al.*, 2007). These values were used for the exposure assessment.

Pyrolysis and reaction products in cigarette smoke

Acetaldehyde can condense with small molecules such as amino acids (e.g. tryptophan and tryptamine), which are present in tobacco as well as other with other molecules present throughout the body. Harman is formed from the reaction of acetaldehyde with tryptophan and tryptamine at levels of ranging from 0.1-5.8 µg of harman per cigarette (Talhout *et al.*, 2007). Although produced in lower amounts than other acetaldehyde metabolites, combustion products and possible degradation products, harman, together with these other by-products are hypothesised to have important biological effects in the brain stimulating addictiveness to cigarette smoking (Talhout *et al.*, 2007).

Harmful health effects of acetaldehyde

Hazard assessment of toxic effects

The direct toxicity of acetaldehyde, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to acetaldehyde is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

A study conducted in experimental animals exposed via inhalation to acetaldehyde over their lifetime demonstrated a 1 in 100,000 excess lifetime cancer risk (lower 95% confidence limits) at a concentration of 11-65 µg/m³. Tumour incidence has been shown in experimental animals at acetaldehyde concentrations that caused irritancy. For humans, the irritancy threshold has been determined at 2 mg/m³, assuming an exposure of 40 cigarettes per day. Based on data in animal studies, IARC has classified acetaldehyde as possibly carcinogenic to humans (IARC, 1999).

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Non-carcinogenic effects: Local respiratory effects and systemic effects

The main effects reported following acetaldehyde exposure occurred in the respiratory tract which included mild to severe changes in the olfactory epithelium of rats exposed to 1365 mg/m³, 6 hours per day, 5 days per week for 112 weeks (Woutersen *et al.*, 1986). A similar study investigating changes in the olfactory epithelium of rats exposed for 6 hours per day, 5 days per week for 4 weeks, reported a NOAEL of 273 mg/m³ (Appelman *et al.*, 1986). No systemic effects were reported in these studies. A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives (RIVM, 2012) was applied to draw the following conclusions:

Risk for local effects:

Considering the 28-month study, risk of effects on the respiratory tract epithelium from acetaldehyde cannot be excluded. Considering the 4-week study, a risk of effects on the respiratory tract epithelium due to acetaldehyde exists. Combining both evaluations it is concluded that a risk of effects on the respiratory tract epithelium due to acetaldehyde exists.

Risk for systemic effects:

No thorough assessment on systemic effects was made. Nevertheless, no systemic effects were reported in the inhalation studies described here, which is expected given that acetaldehyde is very reactive and will therefore exert its effect at the first site of exposure.

Potential effects on addictiveness and attractiveness of acetaldehyde

Addictiveness

Self-administration is increased in juvenile rats exposed intravenously following exposure to a combination of acetaldehyde and nicotine in concentrations similar to those found in tobacco smoke, whereas exposure to acetaldehyde or nicotine alone did not result in increases in self-administration. These results suggest that acetaldehyde may have a pro-addictiveness effect in the presence of nicotine (Talhout *et al.*, 2007). However, to date, no relevant increases and persistent blood levels of acetaldehyde have been reported upon inhalation of the compound in tobacco smoke. These uncertainties have led to questions being asked as to whether acetaldehyde inhaled from tobacco smoke will reach the brain through the blood-brain barrier to induce an addictive effect in concert with nicotine (Seeman *et al.*, 2002). Therefore, increase in addictiveness due to the smoking of cigarettes may not necessarily be directly associated with acetaldehyde production in smoke. The production of harman is proposed as an indirect route through which acetaldehyde increases addictiveness. Harman is known to inhibit MAO, which is an enzyme responsible for the degradation of neurotransmitters including dopamine, serotonin, and noradrenalin and is therefore a target enzyme for inhibition by antidepressant drugs. Upon MAO inhibition, brain levels of these neurotransmitters will increase, stimulating the reward system in the brain. As nicotine already tends to stimulate the release of neurotransmitters, both mechanisms could synergistically act together thereby contributing to tobacco addiction.

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Attractiveness

No data have been reported to suggest that acetaldehyde plays a role in smokers' attractiveness to cigarettes.

Conclusions

Acetaldehyde is not an additive but a smoke component produced upon combustion of the many poly(sugars) added to tobacco. As acetaldehyde is highly reactive and rapidly metabolized in the respiratory tract, systemic bioavailability of acetaldehyde is expected to be low. Margin of exposure (MOE) analysis demonstrated that a risk of effects on the respiratory tract epithelium due to acetaldehyde exists. In addition, the carcinogenic effects observed in animal studies have led to the IARC classification of acetaldehyde to possibly carcinogenic in humans (IARC, 1999). In general, the systemic pathophysiologic role of acetaldehyde from cigarette smoke is poorly understood and warrants further investigation. Formation of several systemically active protein adducts, however, cannot be excluded. It is hypothesized that these adducts (such as acetaldehyde biogenic amine adducts), rather than acetaldehyde from cigarette smoke, play a role in the addictiveness of tobacco. Additives that enhance the addictiveness of smoking pose an indirect health hazard, as they increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke. An important condensation product of acetaldehyde is harman, an inhibitor of the MAO and presumed to be responsible for the reinforcing effects with nicotine self-administration studies. Further research on condensation products and active acetaldehyde adducts is needed to investigate this hypothesis. No data have been reported to suggest that acetaldehyde plays a role in smokers' attractiveness to cigarettes.

Finally, it must be borne in mind that acetaldehyde is only one component of the thousands of compounds contained in cigarette smoke, thus the additive effects of acetaldehyde or its reactivity with other compounds cannot be excluded.

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Formaldehyde

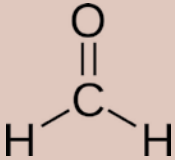
Formaldehyde: overview

Formaldehyde occurs naturally in the environment and it is formed in water by the irradiation of humic substances by sunlight and is present in low levels in most living organisms as a metabolic intermediate. Other sources include fuel combustion, cooking of food and cigarette smoke. Cigarette constitutes a significant source of formaldehyde and reports have shown that its levels are higher in sidestream smoke than in mainstream smoke (SIDS, 2002).

Formaldehyde is not an additive but a smoke component primarily produced upon combustion of tobacco additives. The effects/possible effects of formaldehyde, which occur during cigarette smoking are illustrated herein. Formaldehyde is a group 1 carcinogen as designated by the International Agency for Research on Cancer; therefore regarded as a known human carcinogen. Importantly, formaldehyde has been hypothesized to indirectly influence addictiveness of cigarette smoking through the generation of monoamine oxidase (MAO) inhibitors such as norharman. Norharman is a condensation product of formaldehyde and

Chemical and physical information

Chemical name Formaldehyde
Molecular formula CH₂O
Molecular structure



Synonyms Methanal, oxomethane, oxymethylene, methylene-oxide, methylaldehyde, formic aldehyde, methyl oxide
CAS number 50-00-0
Molecular weight 30 g/mol
Melting point -92 °C
Boiling point -19,5 °C
Volatility vapour pressure, 3886 mm Hg at 25 °C
 Octanol water partition coefficient, log P: 0,35

tryptophan speculated to contribute to the addictive properties of formaldehyde. No data have been reported to suggest that formaldehyde plays a role in smokers' attractiveness to cigarettes.

Function of smoke component

Formaldehyde is not used by tobacco manufacturers as an additive. It is a smoke component produced upon combustion of many of the (poly) sugars added to tobacco.

Amount of formaldehyde in cigarette smoke

A study in which the average formaldehyde smoke content of 48 different brands of filtered cigarettes from various international markets (Philip Morris commercial brands) was analysed by a smoking machine using the Canadian Intense method, the amount of formaldehyde in mainstream smoke was found to be 0.0605 mg per cigarette (Counts *et al.*, 2005). This study was used for the exposure assessment.

Pyrolysis and reaction products in cigarette smoke

Formaldehyde breaks down into methanol and carbon monoxide at temperatures above 150°C. However, uncatalysed decomposition of formaldehyde is slow at temperatures below 300°C (SIDS, 2002). A study showed that norharman was formed in high levels in mainstream cigarette smoke as a result of the pyrolysis of tryptophan and subsequent reaction with formaldehyde (Herraiz, 2004). In total, approximately 0.1-5.8 µg of norharman was found to be present in one cigarette (Talhout *et al.*, 2007).

Harmful health effects of formaldehyde

Hazard assessment of toxic effects

The direct toxicity of formaldehyde, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to formaldehyde is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

Formaldehyde is classified as a group 1 carcinogen, which indicates that it is carcinogenic to humans, based on sufficient evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals (IARC, 2006).

Non-carcinogenic effects: Local respiratory effects and systemic effects

Inhalation is the principal route of exposure to formaldehyde. The main effects reported following formaldehyde exposure occurred in the respiratory tract. Personal breathing zone air concentrations ranged from 0.05 to 0.5 mg/m³ (median 0.3 ± 0.16 mg/m³) for the chemical workers in a mean durations of employment of 10.4 years (SD 7.3, range 1–36 years) (Holmstrom *et al.*, 1989). Clinical symptoms of mild irritation of the eyes

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and upper respiratory tract and mild damage to the nasal epithelium were observed in workers exposed for 10.4 years (range 1-36 years) to a median 8-hour-time-weighted median concentration of 0.3 mg/m³ (range: 0.05 to 0.5 mg/m³) (Holmstrom *et al.*, 1989). This concentration is of 0.3 mg/m³ is considered the lowest LOAEL by the Agency for Toxic Substances and Disease Registry (ATSDR) (<http://www.atsdr.cdc.gov/toxprofiles/tp111-a.pdf>). Studies showed that only a very small proportion of the population experienced symptoms of irritation following exposure to less than 0.12 mg/m³ formaldehyde (<http://www.atsdr.cdc.gov/toxprofiles/tp111-a.pdf>). Mucociliary clearance in the anterior portion of the nasal cavity and histopathological effects in the nasal epithelium were observed at 0.30 mg/m³ both in clinical studies in human volunteers and in cross-sectional studies of formaldehyde -exposed workers (Holmstrom *et al.*, 1989). No systemic effects were reported in these studies. A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives (RIVM, 2012) was applied to draw the following conclusions:

Risk for local effects:

Risk of effects on the respiratory tract epithelium due to formaldehyde exists.

Risk for systemic effects:

No thorough assessment on systemic effects was made.

Potential effects on addictiveness and attractiveness of formaldehyde

Addictiveness

Formaldehyde can indirectly influence addictiveness, since condensation of tryptophan with formaldehyde is reported to produce norharman (Herraiz, 2004). Norharman has been shown to inhibit monoamine oxidase (MAO), an enzyme responsible for the degradation of neurotransmitters including dopamine, serotonin, and noradrenalin and is therefore a target enzyme for inhibition by antidepressant drugs. Upon MAO inhibition, levels of these neurotransmitters in the brain increases, stimulating the reward system. As nicotine stimulates the release of neurotransmitters in the brain, both mechanisms could act synergistically, thereby contributing to the addictive properties of tobacco (Belluzzi *et al.*, 2005; Talhout *et al.*, 2007).

Attractiveness

No data have been reported to suggest that formaldehyde plays a role in smokers' attractiveness to cigarettes.

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Role of acetaldehyde in tobacco smoke addiction.

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Conclusions

Formaldehyde is a very reactive compound that is generated from the combustion of many of the (poly)sugars added to tobacco. The reactivity of formaldehyde after inhalation causes it to exert effects such as irritation and tissue damage at the primary site of exposure, particularly the upper respiratory tract. Margin of exposure (MOE) analysis demonstrates that the risk of effects on the respiratory tract epithelium due to formaldehyde exists. It is further noted that formaldehyde is classified by IARC as a group 1 carcinogen, which means that it is a known human carcinogen. Formaldehyde has been hypothesized to indirectly influence addictiveness of cigarette smoking through the generation of monoamine oxidase (MAO) inhibitors such as norharman (a condensation product of formaldehyde and tryptophan). More research is warranted to substantiate this hypothesis. Additives that enhance the addictiveness of smoking pose an indirect health hazard, as they increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke. No data have been reported to suggest that formaldehyde plays a role in smokers' attractiveness to cigarettes.

Finally, it must be borne in mind that formaldehyde is only one component out of the thousands of compounds contained in cigarette smoke, thus the additive effects of formaldehyde or its reactivity with other compounds cannot be excluded.

Further reading

Reports

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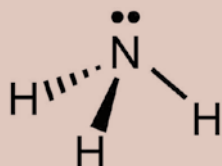
Ammonium compounds

Ammonium compounds: overview

Ammonia is one of the most extensively used industrial chemicals for the production of fertilizers, fibres and plastics, and explosives. Daily exposure occurs following ingestion of a range of food and drinks to which ammonia is added as an ingredient and through the production of endogenous ammonia in the body from the nitrogenous matter in nutrition, including urea (IPCS, 1990). Cigarette smoke is a significant source of exposure to ammonia through the addition of ammonium compounds and generation from natural components of tobacco (Willems et al., 2006). These components are converted to ammonia by the relatively high temperatures encountered during cigarette smoking. Examples of these compounds include ammonium acetate, carbonate, chloride, citrate, hydroxide, sulfate, tartrate, diammonium phosphate (DAP), and urea. The addition of some of these ingredients to reconstituted tobacco has been reported (Callicutt et al., 2006) to generate a type of cigarette blend component made up of waste parts of the tobacco plant, including stems or mid-ribs of tobacco leaves. Ammonium compounds assist in the production of reconstituted tobacco sheets, making these waste parts smokable and

Chemical and physical information

Chemical name Ammonia
Molecular formula NH_3
Molecular structure



Synonyms Ammonia gas; nitro-sil; ammonia; R 717; spirit of hartshorn;
STCC 4904210; OHS01050
FEMA number 4494
Odour description ammoniacal (odour strength: very high) (www.thegoodscentscompany.com)
CAS number 7664-41-7
Molecular weight 17.03 g/mol
Volatility vapour pressure, 6460 mm Hg at 20°C
Boiling point -33.35 °C
Octanol water partition coefficient, log Kow: 0.23 (estimated)

therefore suitable for blending with tobacco (Callicutt et al., 2006; Stevenson and Proctor, 2008).

The effects/possible effects of ammonia, which occur during cigarette smoking are illustrated herein. Ammonium compounds undergo pyrolysis during cigarette smoking to produce ammonia; this fact sheet therefore focuses on the health effects of ammonia instead of ammonium compounds. Ammonia causes irritation of the eyes, skin and upper respiratory tract. Ammonium compounds are presumed to be added by the tobacco industry to increase addictiveness of tobacco by modifying and improving the flavour of tobacco through reaction with sugars (Stevenson and Proctor, 2008). The flavour-modifying and flavour-enhancing properties of ammonia may play a role in smokers' attractiveness to cigarettes.

Table 1. Some ammonium compounds added to tobacco.

Ammonium compound	Function in tobacco	Molecular formula	CAS number	Decomposition temperature
Ammonium acetate	Acidity regulator ^a	CH ₃ COONH ₄	631-61-8	114°C ^b
Ammonium carbonate	Acidity regulator ^a	(NH ₄) ₂ CO ₃	10361-29-2 / 506-87-6	58°C ^b
Ammonium chloride	Acidity regulator ^a	NH ₄ Cl	12125-02-9	340°C (sublimes)
Ammonium citrate	Acidity regulator ^a ; reconstituted tobacco process (Larson et al., 1978)	(NH ₄) ₂ C ₆ H ₆ O ₇	3012-65-5	no data available
Ammonium hydroxide	acidity regulator (Fowles, 2001); aid in cigarette production process (Ames et al., 1986)	NH ₄ OH	1336-21-6	-77°C ^c
Ammonium sulfate	Acidity regulator ^a ; fire retardant (Slaven, 1984)	(NH ₄) ₂ SO ₄	7783-20-2	280°C ^d
Ammonium tartrate	Acidity regulator ^a ; ammonia delivery compound	(NH ₄) ₂ C ₄ H ₄ O ₆	3164-29-2	no data available
Diammonium phosphate	Reconstituted tobacco process (Callicutt et al., 2006; Stevenson and Proctor, 2008)	(NH ₄) ₂ HPO ₄	7783-28-0	70°C
Urea	Acidity regulator ^a ; ammonia delivery compound	CO(NH ₂) ₂	57-13-6	132.7°C ^b

^afunction reported in food

^bmelting point; decomposes to ammonia when heated above this temperature

^cmelting point; is an aqueous solution, heating leads to evaporation of ammonia

^dpoint at which ammonium sulfate decomposes, it cannot be melted at atmospheric pressure without decomposition

Function of additive

Ammonium compounds are added to tobacco to aid in the formation of reconstituted tobacco, to enhance flavour, and to reduce the harshness and irritation of tobacco (Callicutt *et al.*, 2006). In the Netherlands, tobacco manufacturers reported the addition of ammonium compounds to filters of cigarettes as burn rate modifiers to help control how quickly the cigarette burns (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)).

Amount of ammonium compounds added to cigarettes

Assuming an average tobacco weight of 700 mg per cigarette (Counts *et al.*, 2004), a commercial cigarette may contain a total amount (naturally present and added) of ammonium compounds in the range of 0.6 to 2.4 mg per cigarette (Willems *et al.*, 2006). In the Netherlands, tobacco manufacturers rarely report ammonium compound addition (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)), nevertheless ammonium compounds are still naturally present in tobacco.

Pyrolysis and reaction products in cigarette smoke

Ammonium compounds undergo pyrolysis during cigarette smoking to produce ammonia. The average ammonia content from 48 brands of filtered cigarettes obtained from

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various international markets (Philip Morris commercial brands) was analysed by a smoking machine using the Canadian Intense method and the amount in mainstream smoke was found to be 0.0311 mg per cigarette (Counts et al., 2005). This study was used for the exposure assessment.

Harmful health effects of ammonia

Hazard assessment of toxic effects

The direct toxicity of ammonia, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to ammonia is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

No carcinogenic effects have been reported.

Non-carcinogenic effects: Local respiratory effects and systemic effects

Ammonia is the major pyrolysis product generated from ammonium compounds during cigarette smoking. The European Union Scientific Committee on Occupational Exposure Limits (SCOEL) derived an Indicative Occupational Limit Value for ammonia in 1992 based on human data (SCOEL, 1992). They concluded that the critical effect of ammonia is irritation of the eyes, skin and upper respiratory tract. Human volunteer studies indicated that subjective symptoms start to occur at approximately 36 mg/m³ for exposures up to 6 hours, which was considered to be a LOAEL. No systemic effects were reported. A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives (RIVM, 2012) was applied to draw the following conclusions:

Risk for local effects:

A risk of effects on the respiratory tract epithelium due to ammonia cannot be excluded.

Risk for systemic effects:

No thorough assessment on systemic effects was made. Nevertheless, no systemic effects were reported in the inhalation studies described here.

Potential effects on addictiveness and attractiveness of ammonia

Addictiveness

Various researchers have reported that ammonium compounds are added to tobacco to facilitate the conversion of nicotine from its salt form in tobacco to its more volatile, non-protonated, "free base" form (Callicutt et al., 2006). This "free base form" is more easily absorbable by the smoker (Stevenson and Proctor, 2008; van Amsterdam et al., 2011) and it has been hypothesized that diammonium phosphate (DAP), one of the major additives used in reconstituting tobacco, increases the pH and the amount of uncharged, or free, nicotine in smoke, thereby providing a more powerful nicotine kick than the milder, low pH tobaccos (Stevenson and Proctor, 2008).

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The effect of ammonia on smoke pH, however, is highly controversial. In a study conducted by the tobacco industry, different amounts of ammonium compounds were used as additives in standard cigarettes including ammonium hydroxide, DAP, and urea (total soluble ammonia in tobacco maximum 2.26 mg/cigarette and minimum 1.02 mg/cigarette) with no changes observed in the (relative) transfer of nicotine from tobacco to tobacco smoke, or increases in tobacco pH or smoke pH (Callicutt *et al.*, 2006). If changes were observed in smoke pH, these effects were questionable due to the buffer capacity of the lining fluid of the lungs (SCENIHR, 2010; van Amsterdam *et al.*, 2011). No effects in the absorption of nicotine was detected in peripheral blood of smokers after smoking different brands of cigarettes with varying ammonia content (van Amsterdam *et al.*, 2011) or in arterial blood of smokers after smoking specifically manufactured test cigarettes varying only in ammonia content (McKinney *et al.*, 2012). More research is needed to better understand the role that ammonium compounds play in nicotine transfer to tobacco smoke.

Attractiveness

Ammonium compounds, which are added primarily in US style cigarettes, react with sugars during tobacco processing and smoking to form flavour compounds that have flavour-enhancing effects (BAT, 2000). The flavour-modifying and flavour-enhancing properties of ammonia may play a role in smokers' attractiveness to cigarettes. The mechanisms by which flavour enhancement is achieved are complex and not well understood, but are thought to involve reactions of reducing sugars with ammonia and its compounds. Internal tobacco industry documents revealed that the reaction between endogenous or added sugars and ammonium compounds are used for modifying and/or improving the flavour of the smoke of tobacco. In the case of DAP, deoxyfructosazine compounds (pyrazines, pyridines and pyrroles) are formed; many of which have established flavouring properties. Furthermore, DAP reacts with carbonyl compounds, such as formaldehyde and acetaldehyde in smoke, to reduce the harshness and irritation of cigarette smoking (Green and Rodgman, 1976; BAT, Year loaded: 2003).

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Conclusions

Ammonium compounds are added by the tobacco industry in the production of reconstituted tobacco sheets and enhance the flavour of cigarette smoke. Ammonium compounds undergo pyrolysis during cigarette smoking to produce ammonia. Ammonia causes irritation of the eyes, skin and upper respiratory tract. Margin of exposure (MOE) analysis for ammonia demonstrates that the risk of effects on the respiratory tract epithelium due to ammonia cannot be excluded. In the Netherlands, ammonium compounds are rarely added to cigarettes and only to filters as burn modifiers. Nevertheless, ammonia is transferred to smoke from the ammonium compounds naturally present in tobacco. Ammonium compounds are presumed to be added by the tobacco industry to increase addictiveness of tobacco by modifying and improving the flavour of tobacco. There are indications from tobacco industry documents that reactions between (added) sugars and ammonium compounds result in products that enhance the flavour and thereby influencing smokers' attractiveness to cigarettes. Increasing addictiveness and/or attractiveness can have a major impact on smoking consumption and increased risk.

Finally, it must be borne in mind that ammonia is only one component out of the thousands of compounds contained in cigarette smoke, thus the additive effects of ammonia or its reactivity with other compounds cannot be excluded.

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Cocoa

Cocoa: overview

Cocoa is produced from the seed of the tropical tree *Theobroma cacao* and its products, such as shells, extract, distillate, and powder, are used in a number of applications, including the processing of tobacco in cigarettes. It is used to smooth and enhance tobacco flavour, to sweeten tobacco and to add its own characteristic flavour (tobacco documents). Cocoa is one of the main additives in tobacco in amounts of 0.2% (w/w) tobacco per cigarette. Cocoa consists of numerous compounds, some of which are psychoactive compounds (i.e. theobromine, caffeine, serotonin, and a host of others). With the exception of theobromine and caffeine, all other psychoactive compounds from cocoa occur naturally in the human body. The amount of each individual psychoactive ingredient present in cigarettes due to addition of cocoa is low in comparison to daily intake through food (much less than 10% for most compounds). Nevertheless, exposure through smoking should not be neglected as it represents two different types of exposure through inhalation of (1) cocoa itself and (2) combustion products of cocoa and its ingredients (RIVM, 2002).

Chemical and physical information

Tobacco manufacturers in the Netherlands report various CAS numbers for cocoa, among which 84649-99-0 (cocoa extract), 95009-22-6 (cocoa powder), and 84649-99-3 (cocoa extract). For detailed chemical and physical information on cocoa-derived ingredients present in tobacco, please refer to the RIVM report 650270002 (on cocoa) (RIVM, 2002).

The effects/possible effects of cocoa, which occur during cigarette smoking are illustrated herein. The amount of cocoa added to tobacco is low and it is unlikely that cocoa contributes directly to the toxicity already caused by the major tobacco components. Mechanisms of enhancing addictiveness of smoking have been proposed, however, it is unclear whether sufficient amounts of psychoactive compounds are produced to exert psychopharmacological effects that would increase addictiveness. Although cocoa is reported to be added as a flavour enhancer by manufacturers, it is unclear how and to what extent it influences the taste of inhaled smoke or attractiveness to cigarettes.

Function of additive

Reports from tobacco manufacturers indicate that cocoa is used in the casing of tobacco products as a flavour enhancer (Baker *et al.*, 2004).

Amount of cocoa added to cigarettes

The total amount of cocoa in cigarettes manufactured for sale in Germany has been reported to maximal use levels of 0.2% (w/w) in tobacco, equivalent to 1.4 mg per 700 mg cigarette (SCENIHR, 2010). In the Netherlands, the tobacco manufacturers report an average total amount of 0.34% (w/w) in tobacco, with a maximum reported amount of 1.14%, which corresponds to a maximum of 0.8 mg (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)). In Table 1, the amount of all psychoactive ingredients of cocoa in 1 cigarette (w/w) is shown.

Table 1: Potential exposure levels of psychoactive compounds through cigarette smoking or food intake, adapted from RIVM report 650270002 (on cocoa) (RIVM, 2002)

Compound originating from cocoa	Amount in 1 cigarette (w/w) ^a
Theobromine	0.03%
Caffeine	0.003%
Serotonin	<0.001%
Histamine	<0.001%
Tryptophan*	0.004% total in cigarettes
Tryptamine ^b	0.001% total in cigarettes, <0.001% attributed to cocoa addition
Tyramine ^b	0.06% total in cigarettes, <0.001% attributed to cocoa addition
Phenylethylamine ^b	0.07% total in cigarettes, <0.001% attributed to cocoa addition
Octopamine	unknown
Anandamide	<0.001%

^a Based on a cocoa level of 1% (w/w) in cigarettes

^b Naturally occurring in tobacco plants

Some of the psychoactive compounds have been detected in mainstream or sidestream smoke, e.g., caffeine, theobromine (Rodgman, 1992), and phenylethylamine (Smith *et al.*, 2004). Precise amounts have not been reported.

Pyrolysis and reaction products in cigarette smoke

Pyrolysis of cocoa results in the generation of minor amounts of phenol, *o*-, *m*-, *p*-cresol, xylenols, catechol, palmitic acid and stearic acid (<0.001% (w/w) in tobacco) and nitrous gasses, carbon monoxide and dioxide.

Tryptophan combustion can generate 3-amino-1,4-dimethyl-5H-pyrido(4,3-b)indole (Trp-P-1) and 3-amino-1-methyl-5H-pyrido-(4,3-b)indole (Trp-P-2). Furthermore, tryptophan contains reactive groups and forms reaction products with other compounds during combustion, such as beta-carbolines, including harman (see acetaldehyde fact sheet) (RIVM, 2002).

Harmful health effects of cocoa and cocoa-derived ingredients

Hazard assessment of toxic effects

The direct toxicity of cocoa, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to cocoa is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

No carcinogenic effects have been reported.

Non-carcinogenic effects: Local respiratory effects and systemic effects

The exposure to cocoa and cocoa-derived ingredients transferred to cigarette smoke in their pure forms is negligible compared with the exposure to these compounds through food and drinks or compared with the endogenous production of these compounds (RIVM, 2002). However, the consequences of the exposure route, which is inhalation through smoking and oral intake through food, have not been studied.

In a 90-day rat inhalation study with a 6-week recovery period performed by the tobacco industry, it was observed that even when added in high amounts to cigarettes, cocoa did not induce a toxicological response different from the response in control cigarettes (without cocoa) (Coggins *et al.*, 2011). Nevertheless, the risk associated with the generation of combustion products produced upon cocoa pyrolysis has not been thoroughly studied and thus an adequate risk assessment for cocoa or its pyrolysis products is currently not possible.

Potential effects on addictiveness and attractiveness of cocoa and cocoa-derived ingredients

Addictiveness

Several pharmacological effects of cocoa-derived ingredients have been reported to influence the addictiveness of smoking. These include the bronchodilatory effect of theobromine and caffeine, which result in improved bioavailability of nicotine. Furthermore, reaction products of tryptophan, phenylethylamine, tryptamine and tyramine, which are formed during combustion, are thought to exert monoamine oxidase inhibiting properties. For example, tryptophan and tryptamine react with acetaldehyde in tobacco to form the beta carboline harman (see the acetaldehyde fact sheet. The resulting anti-depressive effects of harman have been suggested to contribute to addiction caused by cigarette smoking (RIVM, fact sheet acetaldehyde (RIVM, 2002)).

In general, the pharmacologically active substances present in cocoa do not exert a psychopharmacological effect in man owing to their extremely low exposure concentrations and/or the inability of these substances to cross or reach the blood-brain barrier (Smit, 2011). Due to a lack of studies

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Addictiveness and Attractiveness of

specifically directed to the psychoactive effects of cocoa compounds added to tobacco on addiction, there is insufficient evidence that the addition of cocoa to tobacco contributes to the addictive properties of cigarette smoking.

Attractiveness

The addition of cocoa to tobacco is intended to enhance flavour and therefore is suggested to contribute to the attractiveness of smoking. However, although a considerable percentage of cigarette weight could be cocoa and chocolate extracts (up to 0.56%), it is not known to what degree this influences the flavour of inhaled mainstream or side stream smoke, and especially how this might influence smoking initiation in youths (Fowles, 2001).

Conclusions

Cocoa is added to tobacco in relatively high amounts, resulting in the enrichment of tobacco with numerous cocoa derivatives. Due to lack of relevant toxicity data for cocoa, no quantitative risk assessment can be performed. Effects attributed to cocoa derivatives include bronchodilatory effects exerted by the methylxanthines theobromine and caffeine. MAO inhibitory effects are also exerted by combustion products which are presumed to have an effect in addictiveness. Further research on condensation products is needed to investigate these effects further. The addition of cocoa to tobacco is intended to enhance flavour and therefore is suggested to contribute to the attractiveness of smoking. Additives that enhance the attractiveness of smoking pose an indirect health hazard, as they increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Finally, it must be borne in mind that cocoa derivatives represent only several components out of the thousands of compounds contained in cigarette smoke, thus the additive effects of cocoa derivatives or their reactivity with other compounds cannot be excluded.

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2-furfural

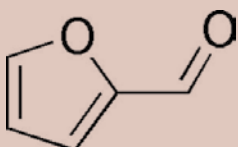
2-furfural: overview

2-Furfural and many of its derivatives occur widely as natural constituents of food and is used as a flavour ingredient in a variety of food products and beverages. It is present in tobacco leaves as well as produced during the acid hydrolysis or heating of mono-, di- and polysaccharides containing hexose or pentose fragments (JECFA, 1999).

2-Furfural is not an additive but is a smoke component produced upon combustion of tobacco and tobacco additives. The effects/possible effects of 2-furfural, which occur as a result of cigarette smoking are illustrated herein. 2-furfural occurs in cigarette smoke as a pyrolysis product of many of the (poly) sugars added to tobacco, therefore its main source of exposure is during cigarette smoking. Consequently, a large part of the total amount of 2-furfural to which smokers are exposed in mainstream smoke is absorbed by the lungs. 2-Furfural is a reactive compound and can cause respiratory tract irritation as observed in workers exposed for 8 hours a day. There are some indications that 2-furfural is

Chemical and physical information

Chemical name 2-furfural
Molecular formula $C_5H_4O_2$
Structure formula



Synonyms furfural, furaldehyde, 2-furaldehyde, alpha-furaldehyde, furfuraldehyde, 2-furfuraldehyde, 2-furylaldehyde, furfurylaldehyde, 2-formylfuran, fural, furale, 2-furfurale (Italian), 2-furandaldehyde, furancarbondal, 2-furancarbondal, 2-furancarbaldehyde, 2-furancarboxaldehyde, 2-furylcarboxaldehyde, furol, furole, alpha-furole, furfurol, furfurole, furyl-methanal, 2-furyl-methanal, 2-furil-methanale (Italian), pyromucic-aldehyde, Quakeral, artificial-ant-oil, artificial-oil-of-ants, bran-oil.

FEMA number 2489

Odour description Sweet, brown, woody, bready, caramellic, with a slight phenolic nuance (odour strength: medium)
(www.thegoodscentscompany.com)

Taste description Brown, sweet, woody, bready, nutty, caramellic with a burnt astringent nuance (at 30 ppm) (www.thegoodscentscompany.com)

CAS number 98-01-1 (4;6;7)

Molecular weight 96.08 g/mol

Volatility vapour pressure, 0.98 mmHg, 1.08 mmHg at 20°C

Boiling point 162°C

Octanol water partition coefficient: log P, log K_{ow} : 0.41, 0.67

carcinogenic upon oral exposure in mice, however, this effect remains to be established in rodent inhalation studies. 2-furfural is not classified by regulatory and review agencies as carcinogenic (IARC, 1995). In addition, there is no data available on the contribution of 2-furfural to altering the addictiveness to cigarettes. 2-furfural has flavour-enhancing characteristics which may influence the attractiveness to cigarettes.

Function of smoke component

2-Furfural is primarily a smoke component, and rarely an additive produced upon combustion of many of the (poly)sugars added to tobacco. Only one cigarette manufacturer reported the use of 2-furfural as a flavouring agent in their products in cigarettes marketed in the Netherlands (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)).

Amount of 2-furfural in tobacco smoke

In the Netherlands, tobacco manufacturers report the addition 2-furfural in amounts of 0.03% (w/w) tobacco, which is 0.21 mg based on a cigarette containing 700 mg tobacco (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)). Mainstream cigarette smoke is reported to contain, on average, 12 (\pm 1) μ g of 2-furfural based on a study conducted using four commercial filter cigarettes differing in tar and nicotine content and measurements with a laboratory smoking machine and ISO puffing conditions) (Kataoka *et al.*, 1997). This study was used for the exposure assessment.

Pyrolysis and reaction products in cigarette smoke

2-Furfural is a pyrolysis product of many of the (poly)sugars added to tobacco, in particular fructose, sugar containing additives like liquorice, and other cigarette components. Sugars, being a major component of tobacco, lead to the generation of high levels of 2-furfural in cigarette smoke. However, there is insufficient information on the possible reaction products of 2-furfural.

Harmful health effects from 2-furfural

Hazard assessment of toxic effects

The direct toxicity of 2-furfural, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to 2-furfural is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

The toxic injury following oral exposure to 2-furfural may lead to carcinogenicity as evidenced in experimental animal studies (IARC, 1995). However, it has not been established if a similar effect occurs following inhalation exposure. Further, 2-furfural showed a co-carcinogenic effect upon incubation with the potent mutagen benzo[a]pyrene (IARC, 1995). This is of concern, since there are several mutagens in cigarette smoke and interaction with 2-furfural could lead to the generation of toxic compounds to which humans could potentially be exposed to. Based on currently available data from animal studies, IARC does not classify 2-furfural as carcinogenic to humans (IARC, 1995).

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Non-carcinogenic effects: Local respiratory effects and systemic effects

PubMed and the European Union Risk Assessment Report for 2-furfural (http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/SUMMARY/2furaldehydesumo50.pdf) were used to select a suitable study for the point of departure (PoD; the most relevant study/ies that most closely resemble the smoking exposure scenario in study design and duration) for 2-furfural after inhalation exposure. In hamsters exposed for 6 h per day, five days per week, over 13 weeks, a NOAEL was established at a level of 77 mg/m³ (Feron and Kruyssen, 1978). Rats, however, were more susceptible, showing histopathological nasal changes at the lowest concentration tested in a 28-day study (6 hours/day, 5 days/week), 20 mg/m³ (Arts *et al.*, 2004). This study also reported NOAELs of 640 mg/m³ (3 hours/day) or 320 mg/m³ (6 hour/day) for systemic effects. Arts *et al.* (2004) report the same systemic dose of 92 mg/kg for both exposures. Rats were found to be more susceptible than mice, suggesting that species specificity should be taken into account in human risk assessment, as this could have profound effects on results. Concentrations used in the animal study were equivalent to the concentrations to which workers were reported to be exposed. This exceeds 8 mg/m³, the established 8-h TWA¹ (SER, 1992) and these concentrations were reported to have caused respiratory tract irritation in these workers (Di Pede *et al.*, 1991). A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives (RIVM, 2012) was applied to draw the following conclusions:

Risk assessment for local effects:

Risks of effects on the respiratory tract epithelium from 2-furfural cannot be excluded.

Risk assessment for systemic effects:

The risk of systemic inhalation toxicity due to 2-furfural can be excluded.

Potential effects on addictiveness and attractiveness of 2-furfural

Addictiveness

No data have been reported to suggest that 2-furfural plays a role in smokers' addictiveness to cigarettes.

Attractiveness

In the food industry, 2-furfural is used as a flavour and fragrance as it has a sweet caramel-like, flavour. In spite of its flavour characteristics, there are no studies which report that 2-furfural makes cigarettes more palatable.

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¹ 8-h TWA, time-weighted average concentration to which a worker can be repeatedly exposed for 8 hours per day, 5 day per week for 40-years, without experiencing adverse effects.

Conclusions

2-furfural is found in cigarette smoke as a result of pyrolysis of many of the (poly)sugars added to tobacco. Addition of 2-furfural to tobacco has rarely been reported by manufacturers in the Netherlands. Nevertheless, exposure to 2-furfural via inhalation results in local effects near the sites of exposure including histopathological changes in the respiratory and olfactory epithelium. Margin of exposure (MOE) analysis demonstrates that the risk of effects on the respiratory tract epithelium due to 2-furfural cannot be excluded, while the risk of systemic inhalation toxicity can be excluded. Caution needs to be taken because mouse co-incubation studies with benzo[a]pyrene and 2-furfural showed that 2-furfural had co-carcinogenic effects and could enhance the carcinogenic potential of other mutagens present in tobacco smoke. More research is needed to further investigate this effect in inhalation studies. The International Agency for Research on Cancer has not classified 2-furfural as carcinogenic to humans. In addition, there is no data available on the contribution of 2-furfural to altering the addictiveness to cigarettes. On the other hand, 2-furfural has flavour characteristics which may influence the attractiveness of cigarettes. Additives that enhance the attractiveness of smoking pose an indirect health hazard, as they increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Finally, it must be borne in mind that 2-furfural is only one component out of the thousands of compounds contained in cigarette smoke, thus the additive effects of 2-furfural or its reactivity with other compounds cannot be excluded.

Further reading

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Glycerol

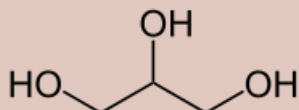
Glycerol: overview

Glycerol has widespread use and can be found in a wide array of industrial, and consumer products including soaps/detergents, pharmaceuticals, cosmetics, tobacco, food and drinks and a constituent of other products, such as paints, resins and paper (SIDS, 2002). Furthermore, glycerol is present in animal as well as vegetable fat, where it is bound to fatty acids to form triglycerides (DCS, 2007). Consumers may be exposed to glycerol by the oral and dermal routes of exposure. Smoking leads to an additional glycerol uptake by inhalation (SIDS, 2002).

The effects/possible effects of glycerol, which occur during cigarette smoking are illustrated herein. Glycerol found in tobacco can occur either naturally or added as an additive. Glycerol is added to cigarettes as a humectant to help retain moisture (DCS, 2007). The total content in tobacco is relatively high when compared to other ingredients used as additives in tobacco. Under smoking conditions, glycerol is transferred almost completely to the pyrolysate in its pure form, of which 12% is measured in mainstream smoke. The break down of glycerol causes the formation

Chemical and physical information

Chemical name	1,2,3-Propanetriol
Molecular formula	$C_3H_8O_3$
Molecular structure	



Synonyms	glycerine, trihydroxypropane, cristal, glyceol
FEMA number	2525
Odour description	odourless (www.thegoodscentscompany.com)
Taste description	sweet (www.thegoodscentscompany.com)
CAS number	56-81-5
Functional class	humectant, bodying agent, solvent, plasticizer, flavouring agent
Volatility	vapour pressure, 0.00248 mm Hg at 50 °C
Boiling point	290 °C

of acrolein, which is a highly reactive compound inducing mild to moderate irritation in the respiratory tract (see Acrolein fact sheet). No data have been reported to suggest that glycerol plays a role in smokers' addictiveness to cigarettes. Glycerol on the other hand has a positive influence on smokers' attractiveness to cigarette smoking given that humidification improves the palatability of cigarettes.

Function of additive

Reports from tobacco manufacturers in the Netherlands indicate that glycerol is added to tobacco as a humectant.

Amount of glycerol added to cigarettes

Glycerol is contained in casing materials, cigarette paper and the tobacco itself. Therefore, the amount of glycerol present in the final product depends on the materials used in the manufacturing process and varies greatly per brand. The amount present is relatively high in comparison to other constituents of cigarettes. In Scandinavia, the total amount of glycerol present in tobacco was reported to be 4.5% (w/w), which corresponds to 31.5 mg based on a cigarette containing 700 mg tobacco (DCS, 2007). In the Netherlands, the average amount added as reported by the manufacturers is 1.0% (w/w) tobacco, with a maximum of 4.4% (w/w), corresponding to an average of 7.1 mg and a maximum of 30.8 mg per cigarette based on the same weight of tobacco in a cigarette (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)). The transfer rate of glycerol to mainstream smoke in filtered cigarettes has been reported to be 12% (Paschke *et al.*, 2002). Thus, the estimated levels in mainstream smoke assuming a 12% transfer rate were 3.8 mg from average levels in Scandinavia, 0.9 mg from average levels in The Netherlands and 3.7 mg from maximum levels in The Netherlands. These values were used for the exposure assessment.

Pyrolysis and reaction products in cigarette smoke

It has been reported that almost all glycerol present in tobacco is transferred to the pyrolysate in its pure form (Baker and Bishop, 2004). Acrolein is a toxic pyrolysis product of glycerol, which is highly reactive and causes irritation in the respiratory tract. The relationship between added glycerol and acrolein formation is unclear and warrants investigation (Carmines and Gaworski, 2005).

Harmful health effects of glycerol

Hazard assessment of toxic effects

The direct toxicity of glycerol, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to glycerol is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

No carcinogenic effects have been reported.

Non-carcinogenic effects: Local respiratory effects and systemic effects

The addition of glycerol may result in increases in the total amount of acrolein present in cigarette smoke. This is of concern because acrolein is

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toxic and can induce mild to moderate irritation in the respiratory tract (refer to the Acrolein (3) and Sugars (12) fact sheet for more information). The main effects reported following glycerol exposure were local irritant effects to the upper respiratory tract observed when rats were exposed to 662 mg/m³, 6 hours per day, 5 days per week for 13 weeks, with no toxic effects observed at 165 mg/m³ (Renne, 1992). No systemic effects were reported in this study or in a study with rats exposed to concentrations of 1000, 1930 and 3910 mg/m³, 6 hours per day, 5 days per week for 14 days (Renne, 1992). A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives² (RIVM, 2012) was applied to draw the following conclusions:

Risk for local effects:

The risk of effects on the respiratory tract epithelium due to glycerol exists.

Risk for systemic effects:

No thorough assessment on systemic effects was made.

Potential effects on addictiveness and attractiveness of glycerol

Addictiveness

No data have been reported to suggest that glycerol plays a role in smokers' addictiveness to cigarettes.

Attractiveness

Humectants are added to trap water thereby keeping the moisture in the tobacco and preventing it from drying out. Glycerol is therefore considered to positive influence attractiveness of cigarette smoking given that humidification improves palatability of cigarettes.

Conclusion

Glycerol generates many pyrolysis products during smoking; one being acrolein which is a toxic and highly reactive substance that causes irritation in the respiratory tract. Margin of exposure (MOE) analysis demonstrates that the risk of effects on the respiratory tract epithelium due to glycerol exists. Increased exposure to glycerol and its toxic degradation products such as acrolein, could enhance the deleterious health effects associated with cigarette smoking. No data have been reported to suggest that glycerol plays a role in smokers' addictiveness to cigarettes. Glycerol, on the other hand, may play a role in smokers' attractiveness to cigarettes due to its humectant properties or moisturising effects. The relatively large amounts added in tobacco are considered to be contributory factors to the attractiveness of cigarettes which may result in increased smoking and therefore increased exposure to the toxic components in cigarette smoke.

Finally, it must be borne in mind that glycerol is only one component out of the thousands of compounds contained in cigarette smoke, thus the additive effects of glycerol or its reactivity with other compounds cannot be excluded.

² It is recognised that several assumptions have been made and that the risk assessment can be refined reconsidering these assumptions but such a refinement is beyond the scope of the present analysis.

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Propylene glycol

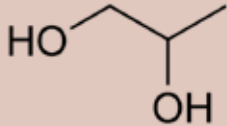
Propylene glycol: overview

Propylene glycol is used in several applications including the food industry as a food additive and as a humectant in tobacco. In addition, it is a solvent for food colours, flavours, pharmaceuticals, cosmetics, and in the paint and plastics industries. Propylene glycol is also used to create artificial smoke or mist during fire-fighting trainings, in discotheques, and in movie, television, and theatre productions (The Health Council of the Netherlands (2007)). There are several ways in which the general population can be exposed to propylene glycol, with inhalation and dermal contact being the main routes of exposure. Propylene glycol is added to cigarettes as a humectant to help retain moisture and ameliorate cigarette smoke. Effects of propylene glycol on smoke mildness in amounts resembling typical commercial addition rates of European cigarettes (not exceeding 3%), however, have not been reported.

The effects/possible effects of propylene glycol, which occur during cigarette smoking are illustrated herein. Cigarette smokers are exposed to propylene glycol

Chemical and physical information

Chemical name	1,2-Propanediol
Molecular formula	$C_3H_8O_2$
Molecular structure	



Synonyms	Propylene glycol; propane-1,2-diol; 1,2-dihydroxypropane; 1,2-propylene glycol; 2,3-propanediol; hydroxyl-propanol; alphapropylene glycol; methyl glycol; methylethyl(ene) glycol; monopropylene glycol; trimethyl glycol; Dowfrost; PG 12; propylene glycol USP; Sirlene; Solar winter BAN; Solagard P; Ucar 35CAS nr.
FEMA number	2940
Odour description	Odourless, very slight acloholic (www.thegoodscentscompany.com)
CAS number	57-55-6
Molecular weight	76.10 g/mol
Volatility	vapour pressure, 0.082 mm Hg at 20 °C
Boiling point	188 °C

in its pure form, which is transferred to cigarette smoke during pyrolysis. As propylene glycol is present in artificial mist used in theatres, etcetera, human data of respiratory and eye irritation relating to brief exposure is available for propylene glycol, although not for the pyrolysis products of propylene glycol or long term exposure to propylene glycol. Propylene oxide, which is formed from propylene glycol in small amounts, is regarded as possibly carcinogenic in humans by the International Agency for Research on Cancer humans (IARC, 1994). No data have been reported to suggest that propylene glycol plays a role in smokers' addictiveness to cigarettes. The effects of propylene glycol in the attractiveness to cigarettes at levels added to European cigarettes (0.2-2.4% (w/w) tobacco) have not been investigated.

Function of additive

Reports submitted by tobacco manufacturers indicate that propylene glycol is added to tobacco as a humectant.

Amount of propylene glycol added to cigarettes

The typical amount reported in European cigarettes is 0.2-2.4% (w/w) tobacco, corresponding with 1.4 to 14 mg considering a cigarette with 700 mg tobacco (DCS, 2007). In the Netherlands, the average amount is reported to be 1.3% (w/w) cigarette, with a maximum of 5% (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)). Less than 10% of the manufacturers report an amount exceeding 2.0% (w/w) cigarette. Dutch manufacturers report that propylene glycol is added to the filter material as well as tobacco. Assuming a 9.9% transfer rate of propylene glycol to mainstream smoke in cigarettes (Paschke *et al.*, 2002), the estimated levels in mainstream smoke were 0.14 to 1.4 mg from average levels in Europe (1.4-14 mg), 0.91 mg from average levels in The Netherlands (9.1 mg) and 3.5 mg from maximum levels in The Netherlands (35). These values were used for the exposure assessment.

Pyrolysis and reaction products in cigarette smoke

Propylene glycol gives rise to propylene oxide at levels ranging from 12-100 ng in the smoke of U.S. cigarettes smoked on a smoking machine (Hoffmann *et al.*, 2001). Additionally, pyrolysis of propylene glycol results in formation of small amounts (<10%) of 1,3-propylene glycol, acetol or acetic anhydride, and pyruvaldehyde (Baker and Bishop, 2004).

Harmful health effects of propylene glycol

Hazard assessment of toxic effects

The direct toxicity of propylene glycol, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to propylene glycol is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

There is no evidence that propylene glycol is carcinogenic to humans (The Health Council of the Netherlands (2007)). However, propylene glycol is produced from the hydrolysis of propylene oxide. Propylene oxide is regarded as possibly carcinogenic to humans (IARC, 1994) and trace amounts are always present with propylene glycol (Hoffmann *et al.*, 2001).

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Non-carcinogenic effects: Local respiratory effects and systemic effects

The main effects reported following propylene glycol exposure were an increased number of goblet cells in the respiratory tract and nasal hemorrhaging observed when rats were exposed to 160 mg/m³ (the lowest concentration tested), 6 hours per day, 5 days per week for 13 weeks (Suber *et al.*, 1989). Effects such as nasal burning, stinging and throat irritation were attributed to exposure to propylene glycol as part of a pharmaceutical formulation inhaled 2 times a week by patients suffering from allergic rhinitis for 1-4 weeks. However, these effects were significantly less following a change in the content of propylene glycol in the formulation from 20% to 5% (The Health Council of the Netherlands (2007)). Minor systemic effects were observed only in female rats which included body weight reduction and changes in leukocyte profile. These systemic effects on body weight and leukocyte profile have not been found consistently in other studies indicating that gender differences in susceptibility to propylene glycol's adverse effects in the rat, but other studies do not provide additional evidence for this. Short-term exposure levels to amounts of propylene glycol in artificial mist cause eye and throat irritation in healthy human subjects (The Health Council of the Netherlands (2007)). A risk assessment procedure using a Margin of exposure (MOE) analysis for tobacco additives (RIVM, 2012) was applied to draw the following conclusions:

Risk on local effects:

A risk of effects on the respiratory tract epithelium due to propylene glycol exists.

Risk on systemic effects:

No thorough assessment on systemic effects was made.

Potential effects on addictiveness and attractiveness of propylene glycol

Addictiveness

No data have been reported to suggest that propylene glycol plays a role in smokers' addictiveness to cigarettes.

Attractiveness

Humectants are added to cigarettes to trap water and retain the moisture and to prevent the tobacco from drying out. Attractiveness in terms of optimal moisture conditions is therefore maintained. In an early internal document of the tobacco industry it was stated that addition of propylene glycol in concentrations of 5%, 6%, and 7% increased the mildness of cigarette smoke (Danker, 1958). Propylene glycol was suggested as a 'promising plus factor' to be marketed as a 'mouth emollient', 'soothing agent', or 'ingredient X added for those who like a mild smoke'. A later document reported small reductions in irritation for cigarette smoke from tobacco treated with 3 and 6% propylene glycol; although this was accompanied by reductions in nicotine delivery from these cigarettes (Shepperd and Bevan, 1994). By adding propylene glycol, the tobacco industry aims to maintain nicotine impact and at the same time reduce irritation. The effects of propylene glycol on smoke mildness for additions less than 3% as found in European cigarettes (range 0.2-2.4%) have not been investigated.

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Conclusion

Propylene glycol was initially added to tobacco as a humectant but also has properties to ameliorate cigarette smoke as documented in internal tobacco documents. Margin of exposure (MOE) analysis demonstrates that a risk of effects on the respiratory tract epithelium due to propylene glycol exists. Propylene glycol has very low systemic toxicity in experimental animals and very high doses are used in most acute studies to determine a toxic level. There is no evidence that inhalation of propylene glycol is carcinogenic, however, the trace amount of propylene oxide present to industrially produce propylene glycol as well as the levels generated during cigarette smoking are regarded as possibly carcinogenic to humans. No data have been reported to suggest that propylene glycol plays a role in smokers' addictiveness to cigarettes. The effect of propylene glycol on attractiveness to cigarettes at levels found in European cigarettes (range 0.2-2.4%) warrants investigation.

Finally, it must be borne in mind that propylene glycol is only one component out of the thousands of compounds contained in cigarette smoke, thus the additive effects of propylene glycol or its reactivity with other compounds cannot be excluded.

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Sorbitol

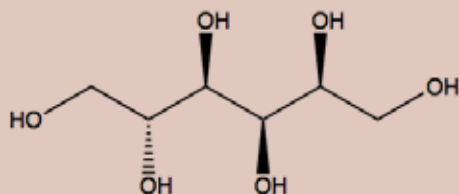
Sorbitol: overview

Sorbitol is a naturally occurring sugar alcohol and an endogenous product of glucose metabolism which is used in foods, cosmetics, pharmaceuticals and in industrial surfactants and stabilizers as a humectant and an artificial sweetener. For these applications, sorbitol is approved by the FDA as generally recognised as safe (GRAS), affirmed as a flavouring agent and an adjuvant (Bennett, 1998).

In the case of tobacco, sorbitol is present as a natural constituent of tobacco plants and it is also added to tobacco as a humectant. The effects/possible effects of sorbitol, which occur during cigarette smoking are illustrated herein. Sorbitol is converted into numerous pyrolysis products, including acrolein, acetaldehyde, formaldehyde and 2-furfural (DCS, 2007), some of which are classified as carcinogens. As smokers are exposed to these pyrolysis products rather than to the pure form of sorbitol via inhalation, the U.S. Food and Drug Administration (FDA) and the Flavour and Extract Manufacturers Association (FEMA) approval as a generally recognized as safe (GRAS) cannot be applied to tobacco due to the

Chemical and physical information

Chemical name Sorbitol
Molecular formula $C_6H_{14}O_6$
Molecular structure



Synonyms D-sorbitol, D-glucitol, hexahydric alcohol, glucitol
FEMA number 3029
Odour description odourless to sweet caramel (odour strength: low) (www.thegoodscentscompany.com)
Taste description sweet (www.thegoodscentscompany.com)
CAS number 50-70-4
Molecular weight 182.2 g/mol
Volatility vapour pressure, <0.1 mm Hg at 25 °C
Melting point 110-112 °C
Octanol water partition coefficient, $\log P_{ow}$: -2.2

potential effects of these pyrolysis products. Further details on the effects of these products on toxicity, addictiveness and attractiveness can be obtained from the individual fact sheets.

Function of additive

Sorbitol is added as a humectant to prevent crumbling of tobacco and to improve its burning and smoke characteristics (DCS, 2007).

Amount of sorbitol added to cigarettes

In the Netherlands, the average total amount of sorbitol in tobacco is reported by the manufacturers to be 0.044% (w/w), with a maximum of 0.313% (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)). This approximates a maximum total amount of sorbitol of 2.2 mg, considering a cigarette with 700 mg tobacco.

Pyrolysis and reaction products in cigarette smoke

There are two main regions in the burning zone of a cigarette: the combustion zone where oxygen reacts with carbonized tobacco to produce simple gases such as carbon dioxide, carbon monoxide and hydrogen, and the pyrolysis/distillation zone where most smoke products are generated (Baker, 2004). The temperature of a burning cigarette varies considerably, usually ranging between 700–950°C during a puff in the combustion region, between 200–600°C in the pyrolysis/distillation zone, and below 350°C as the generated vapors are drawn out of the pyrolysis/distillation region during the puff and cooled down in the presence of diluting air (Baker, 2004). Sorbitol is extensively pyrolysed at 900 °C and converted to compounds, such as acrolein, acetaldehyde, formaldehyde and 2-furfural. Other pyrolysis products of sorbitol include furan, 2-methyltetrahydrofuran, propionaldehyde, acetone, methanol, and carbon monoxide (DCS, 2007).

Harmful health effects of sorbitol

Hazard assessment of toxic effects

The direct toxicity of sorbitol, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to sorbitol is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

No carcinogenic effects have been reported.

Non-carcinogenic effects: Local respiratory effects and systemic effects

Sorbitol is readily converted into its pyrolysis products upon combustion; information on exposure to the pure compound is of less relevance given that inhalation of the pure form of sorbitol is negligible. The quantitative contributions of sorbitol pyrolysis products, some of which are also pyrolysis products of tobacco, are not known. As sorbitol is extensively pyrolysed to its combustion products, including acrolein, acetaldehyde,

formaldehyde and 2-furfural, it is of more relevance to report the potential toxic effects of these compounds. Further details on the potential effects of these products on attractiveness, addictiveness and toxicity can be obtained from the individual fact sheets. The risk associated with sorbitol combustion products such as 2-methyltetrahydrofuran, propionaldehyde, acetone, methanol, and carbon monoxide is not known. Given the lack of relevant data for sorbitol a risk assessment is currently not possible.

Potential effects on addictiveness and attractiveness of sorbitol

Addictiveness

No data have been reported to suggest that sorbitol plays a role in smokers' addictiveness to cigarettes. However, sorbitol in tobacco can act pro-addictively by generation of combustion products, such as acetaldehyde and formaldehyde which have been reported to increase the additive effect of nicotine (refer to the acetaldehyde (4) and formaldehyde (5) fact sheet).

Attractiveness

Sorbitol can have a positive effect on the attractiveness of cigarette smoking, since humectants are added to trap water thereby keeping the moisture in the tobacco and preventing it from drying out. Attractiveness in terms of optimal moisture conditions is therefore maintained. Sorbitol can have a negative effect on the attractiveness of cigarette smoking, since it gives tobacco smoke a slightly bitter taste and a vague odour of cellulose.

Conclusions

Sorbitol, naturally present in the tobacco plant or added, acts as a humectant. As a pure constituent, it is GRAS-approved by FEMA, however, this approval is not applicable to cigarette smoking, where exposure to (combustion products of) sorbitol occurs via inhalation, and not oral exposure. Due to lack of relevant toxicity data for sorbitol, no quantitative risk assessment can be performed. Nevertheless, upon smoking, sorbitol is extensively pyrolysed to acrolein, acetaldehyde, formaldehyde and 2-furfural; some of which are classified carcinogens and have the potential to induce effects on toxicity, addictiveness and attractiveness. Pyrolysis products that enhance the addictiveness and/or attractiveness of smoking pose an indirect health hazard, as they increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke. Specific fact sheets are available for these aldehydes (see fact sheets for acetaldehyde, acrolein, formaldehyde and 2-furfural).

It must be borne in mind that sorbitol combustion causes release of only several components out of thousands of compounds contained in cigarette smoke, thus the additive effects of these components or their reactivity with other compounds cannot be excluded.

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Refer to fact sheets

Acetaldehyde

Acrolein

2-Furfural

Formaldehyde

Sugars

Sugars: overview

Sugars are natural components of tobacco, in levels up to 20% by weight and are formed via enzymatic hydrolysis of starch after priming (harvesting) and in the early stages of the curing process. The sugar content is highly variable among the different tobacco types, but levels present are primarily dependent on the method of curing. Flue-cured (e.g. bright, Virginia) and sun-cured tobaccos contain higher sugar contents in comparison with air-cured tobacco (e.g. Burley), due to the sugars being largely metabolised during air-curing. Generally, the sugar content of dried tobacco is 20% by weight for flue-cured, 10% for sun-cured and negligible for air-cured tobacco.

During the manufacturing process of cigarettes, sugars (i.e. glucose, fructose, and sucrose) are intentionally added to tobacco. In addition, there are many other sugar-containing tobacco additives, such as fruit juices, honey, molasses extract, corn and maple syrups, and caramel. A typical American blend tobacco contains approximately 12% by weight of sugar, of which 4% is added, whereas flue-cured,

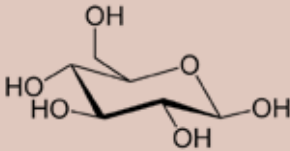
Chemical and physical information

Chemical name Sugars are organic molecules which belong to the group of carbohydrates and are contained in tobacco in mono-, di-, and polysaccharide forms. Sucrose (or table sugar as it is also known) is a disaccharide containing one unit of glucose and one unit of fructose, which are both monosaccharides. A typical example of a polysaccharide is cellulose.

Glucose as an example:

Molecular formula $C_6H_{12}O_6$

Molecular Structure



Synonyms D-(+)-Glucose monohydrate, Dextrose monohydrate

CAS number 50-99-7

Molecular weight 180,16 g/mol

Melting point 150°C

Virginia tobacco (used for British cigarettes) contains higher levels (approximately 20%).

The effects/possible effects of sugars, which occur during cigarette smoking are illustrated herein. Although sugars are generally recognised as safe (GRAS) in food, toxic properties have been attributed to the pyrolysis products of sugars during cigarette smoking. Pyrolysis products are generated in levels which can induce toxic, addictive and/or attractive effects (see fact sheets for acetaldehyde, acrolein, formaldehyde and 2-furfural). Sugars in tobacco may act pro-addictively to generate combustion products, such as acetaldehyde, which has been reported to increase the addictive effect of nicotine. Sugars are also known to improve the taste and smell of tobacco, thereby enhancing the attractiveness of smoking. As this could stimulate smoking behaviour, addition of sugars results in increases in exposure to toxic substances, including carcinogenic compounds.

Function of additive

Reports from tobacco manufacturers suggest that additives are used as flavours, casings, binders, formulation aids or humectants

Amount of sugars added to cigarettes

Amongst the sugars added to tobacco are glucose, fructose, invert sugar (fructose/glucose mixture), sucrose, and brown sugar. Honey, corn syrup, molasses (by-product of sugar cane), fig juice, and prune juice are examples of syrup containing sugars.

An American blend cigarette contains 10% additives per weight of tobacco, and sugars constitute the largest weight of tobacco additives, with monosaccharides being added to a maximum of 4% (w/w) (Talhout *et al.*, 2006). Assuming an average tobacco weight of 0.7 grams per cigarette, a commercial cigarette may therefore contain a maximum of 28 mg (4% w/w) of added sugar per cigarette. In The Netherlands, manufacturers report added sugar levels of on average 1.3% (w/w) tobacco with a maximum of 3.9% (analysis of data delivered to Dutch regulators in 2010 via the Electronic Model Tobacco Control (EMTOC, 2010)).

Pyrolysis and reaction products in cigarette smoke

Upon pyrolysis, sugars caramelize and break down into a mixture of mainly organic acids and a variety of aldehydes, such as acetaldehyde, acrolein, and 2-furfural. The reactions involved, varying from chemical degradation/polymerisation to condensation, are complex and the chemical identity of the final reaction products is largely unknown. Alternatively, sugars can be converted via the Maillard reaction to form amino-sugar complexes in percentages of 1.5-2.0% w/w tobacco. In this reaction, sugar reacts with amines (ammonium compounds, amino acids, proteins), which are naturally present or intentionally added to tobacco, thereby forming amino-sugar complexes. These complexes are thermally unstable and break down to obtain various compounds that can further react to generate other secondary substances and end products which could be toxic or carcinogenic, including, acrylamide and 2-furfural (Talhout *et al.*, 2006). There are two main regions in the burning zone of a cigarette: the combustion zone where oxygen reacts with carbonized tobacco to produce simple gases such as carbon dioxide, carbon monoxide and hydrogen, and the pyrolysis/distillation zone where most smoke products are generated (Baker, 2004). The temperature of a burning cigarette varies considerably, usually ranging between 700–950°C during a puff in the combustion region, between 200–600°C in the pyrolysis/distillation zone, and below 350°C as the generated vapors are drawn out of the pyrolysis/distillation region during the puff and cooled down in the presence of diluting air (Baker, 2004). Sugars typically combust to the carcinogenic polyaromatic hydrocarbons (PAHs) at high temperatures (> 650°C) and the significance of the generated pyrolysis products of sugar combustion is dependent on exposure.

Harmful health effects of sugars

Hazard assessment of toxic effects

The direct toxicity of sugars, toxicity due to its direct adverse effects or the toxicity it exerts as a result of its pyrolysis products entering the body, are described in this section. Indirect toxicity due to sugars is discussed in the section on attractiveness and addictiveness, as these features increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

Carcinogenic effects

No carcinogenic effects have been reported.

Non-carcinogenic effects: Local respiratory effects and systemic effects

As sugars enhance the attractiveness of smoking, they have the potential to stimulate smoking behaviour, thereby increasing the exposure to toxic substances, including carcinogenic compounds in cigarette smoke (i.e. aldehydes; see fact sheets on acetaldehyde, acrolein, formaldehyde, and 2-furfural). Only minor amounts of sugars (approximately 0.5% of glucose and sucrose) are transferred unchanged into mainstream smoke while the bulk of the sugar combusts, is pyrolysed or take part in pyrosynthesis. Further information on exposure to the resultant aldehydes can be found in the respective fact sheets. For these reasons a risk assessment of sugars cannot be performed nor is it considered relevant.

Acids produced by sugar combustion have been reported to reduce nicotine delivery and deeper inhalation of smoke thereby enabling a higher absorption of nicotine in the airways. This would result in higher exposure to toxic and/or carcinogenic substances (Talhout *et al.*, 2006) and hence possible deleterious health effects.

Potential effects on addictiveness and attractiveness of sugars

Addictiveness

Sugars in tobacco may act pro-addictively, since they generate combustion products, such as acetaldehyde, which has been reported to increase the addictive effect of nicotine (refer to the acetaldehyde fact sheet). Studies performed in cigarettes with one type of tobacco showed that sugar content is positively correlated with the amount of aldehydes, including acetaldehyde, produced. Thus, cigarettes with a high sugar content produce higher levels of acetaldehyde and other aldehydes (refer to the review by (Talhout *et al.*, 2006).

Attractiveness

The caramel flavours and the brown-coloured Maillard reaction products generated through the combustion of sugars in tobacco improve the taste and smell of tobacco products. Manufacturers exploit this property by selecting tobaccos naturally high in sugar and/or add sugars during cigarette production. Further, the sweet flavour of caramel is preferred by adolescents (Talhout *et al.*, 2006) and has a strong influence to smoking initiation.

Apart from masking the bitter taste of tobacco smoke as previously mentioned, the addition of sugars to tobacco has been suggested to

increase attractiveness by reducing the harshness of tobacco smoke caused by volatile basic components, such as ammonia, nicotine and other tobacco alkaloids. Upon cigarette smoking, sugars produce acids that reduce the pH of the inhaled smoke. These modifications to tobacco smoke in terms of “nicotine strength”, reduces harshness and smoke irritation making the taste milder, resulting in better palatability. Therefore, as reported by the tobacco industry, an ideal cigarette is one in which the impact of nicotine is maximised, while the mildness experienced by the smoker is increased (Bernasek *et al.*, 1992). Additionally, it has been reported that a maximum content of sugars should not be exceeded due to their potential to produce smoke carbonyls. This is in agreement with a report published by R.J. Reynolds Tobacco in which it was stated that “knowing that smoke carbonyls are irritating compounds and can transfer harshness from the throat to the nose, it would be advantageous not to add more sugar than is needed to optimise smoothness” (Bernasek *et al.*, 1992). Although it has not been proven in controlled experiments, reducing the harshness and irritation of tobacco smoke, especially attracts new smokers, as it may encourage the development of a smoking habit (Talhout *et al.*, 2006).

Conclusions

The presence of naturally contained as well as intentionally added sugars in cigarettes could lead to deleterious health effects through the generation of toxic combustion products and through the stimulation of smoking behaviour. Due to lack of relevant toxicity data for sugars, no quantitative risk assessment can be performed. Acetaldehyde, acrolein, formaldehyde and 2-furfural are generated from the combustion of the sugars contained in tobacco and are transferred to cigarette smoke in considerable amounts. Importantly, aldehydes are suspected to contribute to addictiveness, and exhibit toxic properties, which could be carcinogenic. In addition, sugars contribute to the increase in attractiveness of smoking by improving flavour, masking the bitter taste of cigarette smoke and reducing the harshness. Thus, sugar combustion products elicit toxic, addictive and attractive effects. Increase of addictiveness and attractiveness pose an indirect health hazard, as they increase the consumption of cigarettes in smokers and thus the exposure to the toxic components of tobacco smoke.

It must be borne in mind that sugars cause release of several components out of thousands of compounds contained in cigarette smoke, thus the additive effects or their reactivity with other compounds cannot be excluded.

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Refer to fact sheets

Acetaldehyde
Acrolein
2-Furfural
Formaldehyde

More information

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