Tobacco Additives – A Study of the Available Literature

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This document is a review of a 424-page report, published only in Danish. This English version document is intended to bring the knowledge that we have gathered on the effects of the additives into focus.

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Introduction

Tobacco smoking is the most widespread non-preventable global cause of premature deaths developed by human beings. The harmless looking cigarette is a cocktail of specially tailored chemical additives, which causes immense addiction in the user, and eases the initial phase for the non-smoker to begin smoking.

No aspect of a cigarette is redundant of superfluous, every single added component has been scientifically designed, through many years of development, to refine and optimize the impact and the effect of the tobacco in the cigarette.

Smoking-related medical conditions, such as emphysema, heart disease, lung cancer and other cancers, are tragic consequences leading to suffering and death among users. These adverse effects regrettably only appear after a long time of repeated impacts, after the addiction to the cigarette has been established. Thus, unfortunately, these effects cannot be discovered and counteracted through early testing.

Benzyl benzoate (Xn: harmful), Allyl Hexanoate (T: toxic), Alpha Pinene (Xn: harmful and N: Dangerous for the environment), Menthol (Xi: Irritant), and Cocoa are just a few examples out of the massive number of additives that are frequently applied to cigarettes and tobacco products in general.

Aims

The primary aim of this work is to establish an international knowledge base about the additives that have been reported to the Danish Minister of Health, in order to provide the persons and decision-makers who work with these substances a secure source of exact information about them. We wish to provide insight into the various effects the additives can have on health. Additionally, this report discusses the toxic properties of additives, inform about the formation of countless new chemical compounds during the burning process of tobacco, *Pyrolysis*, and finally, the report also demonstrates how additives are contributing to tobacco addiction.

Existing legislation

In Denmark at the present moment there exists no legislation intended to govern and control which kinds of additives can be safely added to cigarettes. As this review indicates, a number of additives are hazardously toxic. The EU authorities frequently request from the tobacco companies information on what kind of additives they use, for what reasons, and if there exists some information about their toxic effects. However, such information is not often forthcoming. The lack of legislation on the use of additives in tobacco products have given the tobacco industry a free space here in Denmark,

as opposed to in a range of other countries such as the USA, France, and Germany, which at least have some general guidelines for which additives are permitted.

Finally in 2006, *House of Prince*, a subsidiary to *Scandinavian Tobacco Company*, reported to the Danish health authorities a list of 299 additives that they claim to use in their tobacco products. 249 of these reported additives seem to be added directly to the tobacco, while the final 50 are used in the production of filter, ink, glue and paper. In this project we have focused only on these 249 directly added substances.

Methods

The report builds on a literature study on the existing publicly available chemical, toxicological, medical science information on the topic. The literature search was conducted using different electronic databases. Initially, a search was performed on the online tobacco documents webpage (*www.tobaccodocuments.org*), which consist of documents that have been made publicly available from the tobacco industry's archives, as a part of the rearrangements between tobacco companies and 46 American states - the so-called Master Settlement Agreement from November 1998. In some instances particular searches were conducted directly in the individual tobacco companies' archives. An overview of these can be found on *www.tobaccoarchives.com*.

Our searches also covered the different databases that are made accessible by the National Library of Medicine. These include PubMed *(www.pubmed.*gov), which consist of references from medical journal articles; TOXNET *(www.toxnet.nlm.nih.gov)*, which is a collection of databases with articles that have a toxicological and environmental character; and PubChem *(www.pubchem.ncbi.nlm.nih.gov)*, that includes information on chemical compounds.

Furthermore, we have searched on e.g. IPCS INCHEM *(www.inchem.org)*, which is a database of peer-reviewed information on the chemical substances from international organizations including EU, JEFCA, OECD, and European Chemical Substances Information System *(ecb.jrc.it/esis)*.

We searched on the names, synonyms, and CAS numbers of the additives compounds. We also searched on words such as "smoking", "tobacco" and "toxicology". In addition to electronic databases, we have searched in the referred articles' reference lists. The articles are prioritized according to their treatment of: A) the toxicological effects of the additives caused by smoking; B) the toxicological effects of the additives caused by inhalation; and C) the toxicological effects of the additives caused by oral, dermatological, or similar exposure. We have prioritized human studies rather than studies performed on animals, and we have prioritized long-term over short-term studies. The outcome of our searches yielded few search results that matched points A and B. Hence, we deemed it necessary to include oral studies for some of the additives, because of the scarcity of information on these particular additives.

What's in a Cigarette?

As mentioned above, the majority of additives are added directly to the tobacco itself. For the sake of simplicity we have divided these into six main groups.

Aromatic compounds are definitely the biggest group of additives added to the tobacco. These compounds contribute to the specific flavor and taste of the individual cigarette brand. Although these same aromatic compounds are also used in the production of food, one must not forget that during pyrolysis in a burning cigarette these additives are subjected to heat up to 900 C. This kind of heat generates many new chemical compounds from every single one of the additives – resulting in the formation of thousands of newly produced compounds, which can be even more toxic and hazardous than the ones added during the production process. Some examples of aromatic additives used in tobacco production are *mentol*, *hexanoic acid*, and *isovaleric acid*.

Combustion regulating compounds are a group of additives that are added to cigarettes to modify the way and the rate in which the burning process proceeds, so that the cigarette burns neither too fast nor too slow. Some of these compounds influence the other particles in the smoke so that they become small and almost invisible, in order to make the smoke appear less irritating for both smokers and non-smokers. These types of additives are also found on the paper of the cigarette.

Moisturizing compounds, such as *glycerol*, is an additive type that is used to prevent the tobacco from drying out during the time lapse between harvest, production and consumption.

The main use of **filler** compounds is to increase the volume of the cigarette. *Cellulose* is an example from this group.

Preservatives are a group of additives that are used in tobacco to prevent it from **decomposing**. *Benzoic acid* is an example of this kind of additive.

Solvents, such as *ethanol*, are a group of additives used to dissolve the other additives, in order to distribute them evenly throughout the whole cigarette.

Additives - A Crafty Chemical Design with Several Applications

Flavor and engineering additives

Many additives are used in the design of the different kinds of cigarette brands to make them suitable for the tastes of a large group of people. In general, the tobacco that is used in the different cigarette brands is similar, and it is the additives that create the individual characteristics of the brand. This refers in particular to the aromatic compounds, which the tobacco industry uses to make the smoke more tempting with regard to smell and taste, and also to make the tobacco more gentle and soft, so that it becomes easier to smoke, as well as more appealing to beginning smokers.

Chemicals which make it easier for the smoke to penetrate the lungs

Additives have both direct and indirect negative repercussions. The direct negative effects are that some of additives are hazardously toxic for humans. The indirect negative effects are:

- An enhancement of the damaging effects of other harmful compounds by contributing to the formation of additional dangerous compounds during pyrolysis.
- An increase in the absorption of the other compounds that already exists in the smoke, generating greater addiction and entailing more destructive effects.

The indirect side effects of the additives are numerous and much more difficult to control, because it is complicated to get a complete overview of all the chemical processes that takes place during the burning of a cigarette.

The numerous functions of additives

As previously mentioned, additives contribute to make the smoking process more attractive, not only by altering the taste and odor of the tobacco, but also by smoothing out the harsh effects that is related to smoking tobacco in general. One additive that is added to ease the uptake of cigarette smoke is menthol. Menthol has a pain relieving effect through its stimulation of the temperature sensitive receptors on the skin and the mucous. Menthol makes the smoke feels less irritating when it enters the lungs. In the presence of menthol the smoker experiences more of a chilling and refreshing feeling while the smoke passes the respiratory passages. This chilling and refreshing effect is only experienced when the concentration of menthol remains low. When the concentration of menthol is increased, the effect increases strikingly from acting as chilling and refreshing towards acting as local anesthetic. At this stage menthol begins to act as an anesthetic drug providing a temporary improvement to symptoms such as cold, coughing and throat irritation This anesthetic effect will no doubt be experience as positive by smokers, even though the effect is not 'real' in physiological terms, but simply a nerve stimulating effect that is a manipulation of the senses. These effects also contribute to masking the early symptoms of tobacco induced respiratory illnesses such as coughing, irritation of the mucous and breathing difficulties, which are the results of chronic obstructive lung disease and cancer.

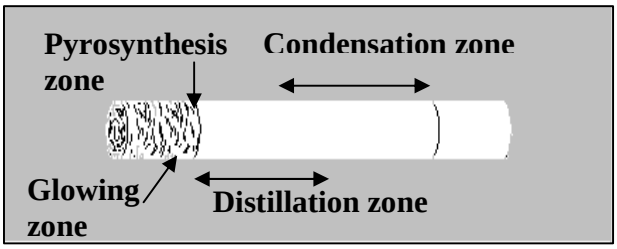
The burning cigarette

The smoke from a burning cigarette contains thousands of substances that are made up of millions of particles that are dispersed in a gas-vapor phase during the smoking process. Some of the compounds are present in amounts that are almost undetectable.

Pyrolysis of the tobacco additive, and the formation of over 4000 new chemical compounds

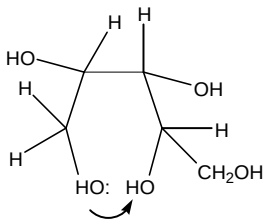
It is still very difficult to explain exactly what happens in a cigarette during pyrolysis. Tobacco products consist of numberless combinations of chemical substances, which can react independently or with each other, in reactions that are dependent on high temperatures.

The burning cigarette is sectionalized into four zones:
- Glowing zone
- Pyrosynthesis zone
- Distillation zone
- Condensation zone

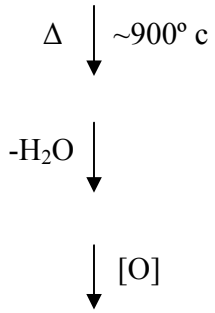


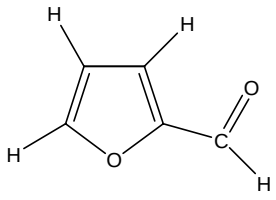
Additives in a cigarette are during pyrolysis exposed to temperatures up to 900° C, in zones both with and without access to oxygen. These extreme conditions give rise to a constant distillation and condensation of the additives, and in these environments many different chemical reactions between the additives and the 4000 compounds that also exist in the smoke will occur.

A series of studies and experiments trying to understand how the different additives affect tobacco during the exposure to high temperatures have been attempted. Some of these have also tried to simulate pyrolysis with a single compound or with a mix of matter. These studies have shown that during extreme pyrolysis conditions small organic compounds have greater tendencies to distillate directly into vapor (gas) form without undergoing any reactions, because of their high moisturizing nature, while the larger organic compounds with their higher boiling points have a better chance to react.



sorbitol





furaldehyde

Sorbitol, as illustrated above, is frequently used in tobacco products. A pyrolysis study of this compound has shown that sorbitol during pyrolysis convert to Furan, 2-methyl Furan, Furan-aldehyde etc. All of these are classified as being very toxic.

It's All about Competitive Strategy

In this chapter we present a short summary of the general results from our literature searches on all of the 249 additive compounds. The purpose of this was to describe the known toxicological impact, the process of decomposition in the body and the pyrolysis features of each compound.
Our research indicates that the main functions of the additives are not only to produce aroma, regulate the burning process, and provide the right moisture and preservation, but that every single one of the additives have as intended function an increase in the uptake of other compounds such as *nicotine*, and/or to make the smoke more pleasant and enjoyable. Additives apparently also have other unintended hidden impacts such as forming new combinations of chemical substances during pyrolysis which are even more damaging to the health of smokers and increases addiction.

Faster and Stronger addiction

Some additives create sweet taste, some softens the smoke, and others tone down the reaction of the nerves toward smoke with the aim to make it easier to smoke, and to hide the negative direct effects of smoking such as nausea, vomiting, shivering, and lung irritation.

Menthol, as previously mentioned, is a god example of a compound that masks the discussed unfortunate side effects, and it is actually one of the only additives that have been actively advertised by the tobacco producers(1). Menthol increases the permeability of chemical matter through the skin, the plasma membrane,

and raises the saliva production, the permeability of the mucosa in the mouth. Study on the topic has shown that menthol inhibits nicotine metabolism so that it is slowly converted and released into the smoke (1-8).

Liquorice is another additive compound that also make it easier to smoke (9). Tobacco with added liquorice is described as sweet, woody, round in taste and flavor (10). A third compound is *prolylen glycol*, which, according to a statement from the British-American Tobacco Company, reduces the release of nicotine while the amount tar is increased (11). This type of compounds is used to regulate tar-nicotine ration in the tobacco, which influence the sharpness of the smoke (12).

Experiments conducted on humans with *acetophenone* steam exposure, demonstrate that a concentration of more than 0,007 mg/m^3 of the compound gives rise to a disruption to the electronic activity of the brain. While a concentration of 0.01 mg/m^3 can affect lung sensors and the sensitivity to daylight. In comparison, the inhalation of a cigarette with 10 liter of air, will produce a concentration of acetophenone of 2.2 mg/m^3 - smaller than the concentrations mentioned above (13).

The additive *benzylalkohol* have proven to be local anaesthetic (14). The compound suppresses the central nervous system with effects such as paralysis, and respiratory deficiency (14;15). Even though the concentration of Benzylalkohol that induces these effects are higher those used in cigarettes, minor concentrations also effect on the nervous system (15-17).

The compound *cis-3-hexenol* reduces lung irritation, this was indicated during a test conducted by the American tobacco company Brown&Williamson (18). The test shows that the users preferred test cigarettes containing cis-3-hexenol over control cigarettes that did not contain the compound. The effect of cis-3-hexenol was described as *"a dramatic increase in smoke freshness and acceptability. Irritation is also markedly reduced*" (18-20).

Theobromin, which is found in chocolate, have been used in asthma treatments, because it can extend the bronchial tubes (21). When the bronchial tubes are extended the uptake of nicotine, alongside other compounds in tobacco smoke, is increased (22;23). The amount of the theobromin in cigarette smoke is probably not enough to cause the mentioned effects - further investigation into this is needed.

The added sugars, and the sugars that already exist in the tobacco plant, form a compound called *acetaldehyde*, when burned (24). It seems that acetaldehyd can interact with nicotine in the central nervous system, and influence the smoking behavior by generating an extensive addiction (25).

The Exact Effects of these Compounds Are Still Unknown

Chemical and physical irritation

All combustion products that are produced during pyrolysis of tobacco, such as smoke particles, when entering into the lungs will become chemically caustic, which will give rise to physical irritation of the lung tissue.

All the *carboxyl* acids that are used as additives in tobacco have a caustic effect on the lung tissue. Therefore, they are contributing to a reduction of the lung capacity throughout a smoker's lifetime. A study on the carboxyl acid

compound *cinnamyl acid* shows that it gives rise to serious membrane damage to the lungs' connective tissue, thus increasing the permeability of the tissue (26).

The *aldehydes* that are added to tobacco have been shown to have an irritating effect on the skin, eyes and mucosa (27). Some exsamples are *hexanal*, *2-methylbutylraldehyde*, *3-methylbutyradehyde*, and *veretaldehyde* (27;28;28-32).

Glycerol, which is an alcohol, raises the content of *acroleine*, *formaldehyde*, *acetaldehyde*, and *acetone* in cigarette smoke (33-35). *Acroleine* is a compound that is caustic and highly irritating for the skin, eyes, and respiratory passages (36). These groups of compounds are classified as being very toxic in case of inhalation, ingestion, and through skin contact (33-35).

Cocoa beans are also added to tobacco products to enhance aroma, but when the cocoa beans are roasted, they develop *pyraziner* (37). Pyraziner have an irritating effect on the respiratory passages (37).

Lung tissue damage

It seems that the majority of the aldehydes that are used as additives in cigarettes have direct effects on the membrane of cells, and possibly *cytotoxice*. These include 2-methylbutyraldehyde, hexanal, 3-methylbutraldehyde, and *salicylaldehyde* (26).

Guaiacol has shown to cause membrane damage on human lung fibroblast (38).

Linalool, an alcohol, has in an in vitro experiment on human lung fibroblast been shown to damage membranes (39).

The pyrolysis of cellulose produces a big amount of acetaldehyde (25;40). Acetaldehyde is very volatile, and can generate irritation and inhibition of the movements of the cilium in the respiratory passages. This decreases the transport of phlegm and dirt particles away from the respiratory passages (25;40).

Cancer and cells

Some of the additives we have been discussing very probably have a carcinogenic effect, even though there isn't sufficient documentation on the carcinogenic effects of the actual doses used in the manufacture of cigarettes. A few of the additives are suspected of creating carcinogenic pyrolysis by-products. There is a great need for further investigation into this topic, because our literature study suggest that several of the additives plays a major role in the carcinogenic consequences of tobacco, on top of the carcinogenic products that are produced by pyrolysis.

Compounds Which We Believe Need to Be Investigated Further

As mentioned earlier, glycerol produces acroleine under pyrolysis (41). Acroleine is very toxic, and an in vitro liver study indicate that acroleine is a central factor in the suppression of the immune system in the lungs, similarly to what has been observed among smoker lung cancer patients (42). Acroleine inhibit T-cell response for both macrophages and T-lymphocytes production of *interleucine*.

Interleucine is the compound that meditates the chemical communication between the cells of the immune system (43). Present in vitro studies have even shown that acroleine damages genomes and reduces reparation of broken DNA (42). This Acroleine-DNA interaction have almost the same pattern for mutation as the p53

gene, which is observed in lung cancer. Acroleine likewise take part in the inhibition of acetaldehyde reduction in the body. Acetaldehyde, which is a by-product from alcohol degradation in the lever, is classified as causing cancer on animals, but also expected to be carcinogenic for humans (42).

The pyrolysis of *saccharin*, invert sugar, and cellulose produces formaldehyde (44). Formaldehyde is classified by IARC as being group 1 carcinogenic, which means that it causes cancer in humans (45). The pyrolysis of cellulose also produces acroleine (44).

Pyrolysis studies indicate that the liquorice powder that is added to tobacco gives rise to an increase in the formaldehyde content of the smoke (46).

Linalool and other *tarpenic* compounds that are added to tobacco can be an precursor for the carcinogenic hydrocarbon compounds such as benzo(a)pyren (47), which are produced during smoking. Experiments on mice indicate that alpha-pinene have a similar carcinogenic effect when it is exposed to the skin for a period of time (53) Chronic contact can lead to skin tumors (54).

Yerba mate (Ilex paraguarensis) consists of tannins, and N-nitroso substances (55). These are suspected of being carcinogenic. A frequent intake produces a tendency to develop cancer in the respiratory passages(55;56).

Theobromine that is found in chocolate (48) can lead to chromosomal damage in human lymphocytes (49).

Hypersensitivity
Some of the additive can produce hypersensitivity, and are classified as allergenic according to the EU's cosmetic directive. These include compounds like Benzylalcohol, cinnamicalcohol, citronellol, geraniol, linalool, chamomile, benzaldehyde (50;51).

Other damage
A study done on rats illustrate that 1% solution of *salicylaldehyde* gives rise to a reduction in body mass, and increase in the total amount of febrile materials of micro bodies in the liver and kidneys. At 2% solution of salicylaldehyde the study registered distinct decrease in the size of the cytoplasm basophilic bodies in the liver (52).

An inhalation-based experiment on albino rats demonstrated that when rats are exposed to a closed atmosphere containing 0.07mg/m^3 *acetophenone,* for an uninterrupted period of 70 days, it induces changes in the rats' blood protein profiles, as well as pathological changes in their internal organs (13).

An experiment which tested the effects of *N-aromatic compounds* on egg leaders – their movement, contraction and ability to intercept egg cells, movement – concluded that N-aromatic compounds such as; 2,5-dimethylpyrazine, 2,6-dimethylpyrazine, 2-methylpyrazine, 2,3,5-trimethylpyrazine, and 2-methoxy-3-methylpyrazine reduces the functions of the reproductive organs among gold hamsters, even when exposed to low doses (57).

2,5-dimethylpyrzina has additionally been shown to inhibit the development of the sex hormones for both female and male rats (58-60).

Conclusion
Would you inhale Benzene? Expose yourself to corrosive substances?

Our goal was to uncover the physiological, chemical and toxic effects of the additives used in the production of cigarettes, as well as to discover the variety of pyrolysis products that are produced from every single additive. We have through a pertinacious literature search succeeded to an extent in finding information on the use, application, function and impact of these additives. The output of pyrolysis products and their physiological effects was partly described in the literature. Thus some of the additives have been shown to be outrageously hazardous to health. What we were able to find of scientific documentation on the additives' toxicity and how they decompose in the body have been limited. Most of the documentation that we have found comes from experiments that were either preformed by or directly supported by the tobacco industry. For this reason it is distinctly important to regulate which additives can be used in cigarette production. Of equal importance is more comprehensive research into this field.

To support our work with other information than what we found in the tobacco industry's archives, we included information from other types of articles that treat the issue from alternate points of view. We included, for instance, information based on experiments that measured the effects of the additives on the respiratory passages, digestion system, or upon direct contact with the skin, eye, mouth, and experiments with cells culture. However, here also we found *sadly* little documentation on the topic, even though a great part of these additives are even permitted in food products.

Nevertheless, we have managed to collect enough information to conclude that the main *functions* of these additives are to make it easier begin smoking and to create faster and greater addiction in smokers. The main *effect* of these additives is damage to the lungs. Furthermore, some of the additives are under suspicion of being carcinogenic, and others take part in increasing the effects of other carcinogenic compounds that are also found in tobacco.

As was pointed out in the report, there is a lack of knowledge on the exact effects of the additives, even though there is documentation that demonstrates that the additives have unfortunate effects. A further unfortunate fact is that there is lack of legislation in this area. There exists no legislation in Denmark or in the EU that can control what kinds of additives are permitted to be used in tobacco products. Although there have been initiative in EU directive, until now nothing has been accomplished.

There is great need for new knowledge on the function, reaction patterns, and toxicity effects of these additives when they are smoked. We believe that this knowledge needs to come from independent scientific experiments, because a great deal of the existing documentation has been produced by the tobacco industry. To produce the necessary documentation requires large resources. These resources could be used to set up a scientific unit who would be managed by the EU. The funding could be provided by the EU and the member states, or it could be required of the tobacco industry that they pay for the production of the documentation on the additives that they use. In this way the industry would be required to prove that their product is harmless to use.

There exists already a proposal in the EU-region about making a scientific unit, which would

develop methods to measure the effects of additives, create documentation on the compounds in the smoke, and in this way create a knowledge base for the political resolution which is sorely needed in this area. Even though such a proposal exists, and the EU has demanded a positive list over the additives in cigarettes since 2004, the work never has been implemented.

We, the Cancer Society, believe that the neglect of this area is the responsibility of the politicians. They should take the necessary steps to ensure that the work that is needed for delivering the positive list over the additives is set in motion. They should also formulate legislation which ensures that nothing is added to tobacco before is has been proven that it is safe to do so. It is not fair to expose the consumers to additives that are carcinogenic, damaging, caustic, which produce hypersensitivity and – potentially – lead to the death for the user. We hope that this rapport will contribute to inspire politicians in Denmark and in the EU to create a massive plan for further investigation into this area and the necessary regulation of the use of additives in tobacco products.

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