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Increased Health Hazards due to Additives of Tobacco Products – Consequences for Product Regulation

Background

In Germany, tobacco smoking claims more lives than alcohol, illegal drugs, road accidents, AIDS, homicides and suicides taken together: Each year, about 110,000–140,000 deaths are caused by cigarette smoking. No other product, if used as intended, is as addictive and disease causing and reduces life expectancy as dramatically, namely by 10 years on average [14]. About 50 percent of smokers die prematurely from the consequences of smoking, with one half of these premature deaths occurring already in middle age (between 35 and 69 years). Those who die in early middle age lose more than 20 years of their average life expectancy [14]. Disease-related costs and productivity losses alone amount to about 40 billion euros in Germany each year [11].

To protect children and youth, effective measures are required to curtail smoking. Jointly with over 30 experts from the fields of medicine, health sciences and economics, the Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ) has produced action recommendations for effective protection of the public against smoking and passive smoking [11].

While medics and health scientists agree about the measures to be taken, such as raising tobacco tax, fighting illicit trafficking of tobacco products, prohibiting tobacco advertising and sponsoring, creating smokefree environments, and limiting the sale and distribution of tobacco products, there is no common position in matters of tobacco product regulation yet. However, it should be clear that the regulatory principles of health and safety at workplaces, which provide for health risk limits of carcinogens and toxic substances, are not applicable to tobacco smoke for a host of reasons.

A publication issued in 2004 by the European Commission, in which experts from all over Europe have presented their views on tobacco product regulation, also deals with fundamental questions of how to regulate tobacco products, particularly cigarettes [41].

Certainly, numerous problems relating to cigarette production still need to be solved by way of regulations. Surprisingly, however, the matter of additives does not receive adequate attention. This publication is intended to change this. In the following, we will discuss additives that are listed in the Tobacco Product Regulation of the German Food and Commodities Act (Lebensmittel- und Bedarfsgegenständegesetz, LMBG) as permitted tobacco additives in Germany. Germany was the first country in the European Union to permit addition of these substances to tobacco back in 1977; Belgium and the United Kingdom were the only ones to follow. According to EU Directive 2001/37/EC [8], a common European list of "ingredients" is required but has not yet been compiled. Therefore, there is a danger of further EU countries taking over the German list without further reviewing. The health hazards emanating from tobacco additives are outlined in the following.

1. Product Design of Cigarettes

For many decades, the tobacco industry has clearly grasped that cigarettes are basically nothing but a drug delivery device for nicotine. The industry is also aware of the fact that cigarettes contain a host of cytotoxic and carcinogenic substances that are generated, for the most part, in the cigarette smoke during the combustion process (pyrolysis) [13,23,26,29]. The health-damaging effects of cigarettes are determined by the total amount of all toxic substances contained in cigarettes and cigarette smoke [15]. Of the more than 4,800 different substances contained in the mainstream smoke of a cigarette, about 80 have been proven to be cancer causing or are suspected to cause cancer [23,30,34,48]. These include, in

Selected Carcinogens in Cigarette Smoke
(from: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 38, Tobacco Smoking (1985)[32] and vol. 83, Tobacco Smoke and Involuntary Smoking (2004)[34], Lyon, France; List of MAK and BAT Values, Deutsche Forschungsgemeinschaft (DFG), Report No. 40, 2004, Wiley-VCH[10]).
Classification of substances as carcinogenic by IARC based on available data:
Group 1: carcinogenic to humans; **Group 2A**: probably carcinogenic to humans; **Group 2B**: possibly carcinogenic to humans. Substances that have not yet been evaluated by IARC, but by the MAK Commission of the Deutsche Forschungsgemeinschaft (German Research Foundation, DFG), are listed with DFG's classification code: Number of carcinogenicity category and "(DFG)".
Category 1: "Substances that cause cancer in man .."; **Category 2**: "Substances that are considered to be carcinogenic for man .."; **Category 3**: "Substances that cause concern that they could be carcinogenic for man .."; **Category 4**: "Substances with carcinogenic potential for which genotoxicity plays no or at most a minor part. No significant contribution to human cancer risk is expected provided the MAK value is observed. .."; **Category 5**: "Substances with carcinogenic and genotoxic effects, the potency of which is considered to be so low that, provided the MAK and BAT values are observed, no significant contribution to human cancer risk is to be exprected. ..".
MAK: "Maximale Arbeitsplatz-Konzentration": maximum workplace concentration; BAT: "Biologischer Arbeitsstoff-Toleranz-Wert": biological tolerance value for occupational exposures.

Substance	Classification of carcinogens by IARC or DFG	Amount in mainstream smoke [ng or µg per cigarette]
Polycyclic aromatic hydrocarbons [a)]		
Benz[*a*]anthracene	2A	20–70 ng
Benzo[*b*]fluoranthene	2B	4–22 ng
Benzo[*j*]fluoranthene	2B	6–21 ng
Benzo[*k*]fluoranthene	2B	6–12 ng
Benzo[*a*]pyrene	2A	8.5–11.6 ng
Dibenz[*a,h*]anthracene	2A	4 ng
Dibenzo[*a,i*]pyrene	2B	1.7–3.2 ng
Dibenzo[*a,e*]pyrene	2B	present
Indeno[1,2,3-*cd*]pyrene	2B	4–20 ng
5-Methylchrysene	2B	up to 0.6 ng
Naphthalene	2 (DFG)	2–4 µg
Heterocyclic hydrocarbons		
Furan	2B	20–40 µg
Dibenz[*a,h*]acridine	2B	up to 0.1 ng
Dibenz[*a,j*]acridine	2B	up to 10 ng
Dibenzo[*c,g*]carbazole	2B	up to 0.7 ng
Benzo[*b*]furan	2B	present
***N*-Nitrosamines**[a)]		
N-Nitrosodimethylamine	2A	0.1–180 ng
N-Nitrosomethylethylamine	2B	up to 13 ng
N-Nitrosodiethylamine	2A	up to 25 ng
N-Nitrosodi-*n*-propylamine	2 (DFG)	approx. 1 ng
N-Nitrosodi-*n*-butylamine	2 (DFG)	up to 3 ng
N-Nitrosopyrrolidine	2B	1.5-110 ng
N-Nitrosopiperidine	2B	up to 9 ng
N-Nitrosodiethanolamine	2B	up to 36 ng
N-Nitrosonornicotine ("NNN")[b)]	1*	154–196 ng
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone ("NNK")[b)]	1*	110–133 ng
Nitrogen dioxide[c)]	3 (DFG)	up to 600 µg
Aromatic amines, volatile amines [a,d)]		
2-Toluidine	2A	30–200 ng
4-Toluidine	3 (DFG)	14–34 ng
2,6-Dimethylaniline	2B	4–50 ng
Aniline	3 (DFG)	102–364 ng
o-Anisidine	2B	present
2-Naphthylamine	1	1–22 ng

Substance	Classification of carcinogens by IARC or DFG	Amount in mainstream smoke [ng or µg per cigarette]
4-Aminobiphenyl	1	2–5 ng
***N*-Heterocyclic amines**		
2-Amino-9*H*-pyrido[2,3-*b*]indole ("AaC")	2B	25–260 ng
2-Amino-3-methyl-9*H*-pyrido[2,3-*b*]indole ("MeAaC")	2B	2–37 ng
2-Amino-3-methylimidazo[4,5-*b*]quinoline ("IQ")	2A	0.3 ng
3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole ("Trp-1")	2B	0.3–0.5 ng
3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]indole ("Trp-2")	2B	0.8–1.1 ng
2-Amino-6-methyl-dipyrido[1,2-*a*:3',2'-*d*]imidazole ("Glu-P-1")	2B	0.37–0.89 ng
2-Aminodipyrido[1,2-*a*:3',2'-*d*]imidazole ("Glu-P-2")	2B	0.25–0.88 ng
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine ("PhIP")	2B	11–23 ng
Aldehydes		
Formaldehyde	1	10–25 µg
Acetaldehyde	2B	770–864 µg
Glyoxal	3 (DFG)	present
Acrolein (2-propenal)	3 (DFG)	60–100 µg
Crotonaldehyde (*trans*-2-butenal)	3 (DFG)	10–20 µg
Furfural (2-furyl-methanal)	3 (DFG)	present
Phenols		
Phenol	3 (DFG)	10–64 µg
Catechol (1,2-dihydroxybenzene)	2B	59–81 µg
Hydroquinone (1,4-dihydroxybenzene)	2 (DFG)	110–300 µg
o-, m-, p-Cresol	3 (DFG)	50–110 µg
Caffeic acid	2B	up to 3 µg
Volatile hydrocarbons		
1,3-Butadiene	2A	20–40 µg
Isoprene	2B	450–1000 µg
Benzene	1	20–50 µg
Nitromethane[e)]	2B	0.5–0.6 µg
2-Nitropropane[e)]	2B	0.7–1.2 ng
Nitrobenzene[e)]	2B	25 µg
Various organic compounds		
Acetamide	2B	38–56 µg
Acrylamide	2A	present
Acrylonitrile	2B	3–15 µg
Vinylchloride	1	11–15 ng
Hydrazine	2B	24–43 ng
1,1-Dimethylhydrazine	2B	present
Ethylene oxide	1	7 µg
Propylene oxide	2B	up to 100 ng
Styrene	5 (DFG)	present
Butylhydroxytoluene	4 (DFG)	present
Safrole (4-allyl-1,2-methylenedioxybenzene)	2B	up to 40 µg
Urethane	2B	20–38 ng
Metals		
Arsenic	1	40–120 ng
Beryllium	1	0.5 ng
Nickel	1	up to 600 ng
Chromium (oxidation stage VI)	1	4–70 ng
Cadmium	1	41–62 ng
Cobalt	2B	0.13–0.20 ng
Lead (inorganic)	2A	34–85 ng
Selenium	3 (DFG)	< 12 ng
Radioactive substances		
Polonium-210	1	0.03–1.0 pCi

a) Polycyclic aromatic hydrocarbons, *N*-nitrosamines and aromatic amines are regarded as the principal lung carcinogens in tobacco smoke.
b) Elevated nitrate content of tobacco may lead to an increase in carcinogenic tobacco-specific *N*-nitrosamines, particularly *N*-nitrosopyrrolidine, in the smoke. Nicotine and nitrate are known to be precursors of *N*-nitrosonornicotine and NNK, with nitrate exerting a strong influence.
c) Nitrogen oxides resulting from decomposition of tobacco nitrate serve as precursors for ammonia; also, they are reactants in the formation of *N*-nitrosamines.
d) About 200 amines have been identified in tobacco smoke: approx. 40 aliphatic amines; 26 pyrroles, pyrrolines and pyrrolidines; approx. 70 pyridines; 11 piperidines and hydroxypyridines; a number of pyrazines, and about 30 aniline derivatives (IARC, vol. 38).
e) The formation of nitroalkanes increases with the nitrate content of the tobacco.
*) Cogliano V, Straif K, Baan R et al. (2004) Smokeless tobacco and tobacco-related nitrosamines. Lancet Oncology, 5, 708

particular, polycyclic aromatic hydrocarbons, aromatic amines, aldehydes, phenols, and tobacco-specific *N*-nitrosamines.
Other relevant toxic and harmful substances that need mentioning include: ammonia, hydrogen cyanide, carbon monoxide and quinoline, acetonitrile and mercury.

Cigarette manufacturers have known about the carcinogenic and disease causing properties of their products for at least five decades. The amount of knowledge and the unethical cover-up of all findings has become apparent in the testimonies of leading international experts in the ongoing US government lawsuit against Philip Morris (brand inter alia Marlboro) and other tobacco giants [37,44]. The cigarette manufacturers have not reduced the health risks of smoking, even though they have had technical possibilities to do so for years [1,44]. The toxic substances known to the manufacturers were never reduced for fear of thus indirectly admitting that cigarettes had so far not been "safe" – as claimed by the cigarette industry. Thus, consumer protection needs have been ignored for decades. Moreover, without any safety tests, further toxic additives were used in order to promote addiction in children and young adults and to mask the effects of smoking for consumers [44].

Cigarette manufacturers are using about 600 additives in their products. Additives can account for over ten percent of the total weight of a cigarette [2]. Internal documents of the tobacco industry and testimonies in the cigarette industry suit of the US government reveal the "technical strategies" of cigarette manufacturers: Manufacturers were aware of the fact that it is primarily the addictive potential of nicotine that keeps smokers smoking despite the sure prospect of most severe diseases and restrictions of life quality. When, despite all deception attempts by the industry since the 1950s, the public became increasingly concerned about the dangers of smoking, manufacturers developed new technologies allowing to reduce nicotine content according to ISO (International Standards Organisation) measurements while the bioavailability of nicotine for smokers was kept at a constant level or even increased. As a result of this useless measurement method, consumers have been systematically deceived about the actual amount of nicotine and the other toxins inhaled. This is because the ISO method measures only nicotine content of the particulate phase, not the total nicotine yield that is bioavailable, i.e. the addictive effect on the consumer. Cigarette manufacturers are reducing total nicotine content according to ISO measurements while keeping or even increasing the bioavailability of free nicotine by adding appropriate substances such as ammonia, urea or soda, thereby shifting the acid-base equilibrium towards more basic levels [12,38]. Thus, nicotine can change its form from a salt to "free" nicotine and be taken in – undetected by ISO measurements [12,38]. Alongside additives that serve such nicotine manipulation, cigarette manufacturers use a multitude of substances with a soothing, cooling or anesthesizing effect to facilitate much deeper smoke inhalation. The soothing effect, in particular, makes smoking more pleasant and enjoyable for beginning smokers, i.e. children and young adults [38]. This easier inhalation of the heath-damaging cigarette smoke is made possible only by additives.

Naturally, cigarette manufacturers have put great efforts into concealing, from the health and regulatory authorities, their knowledge, intentions, and practices concerning additive technologies. This becomes very clear in the charge by the US Ministry of Justice [37]. Besides the development of ammonia technologies, a major focus of the cigarette industry's internal organization since the 1950s has been to deceive health authorities, the public and the consumers [37,44]. In Germany, too, the responsible health authorities seem to be unaware of the effects and side effects of the multitude of additives to tobacco products that they have permitted like in a general clause. To change this is the goal of this publication.

2. "Permitted Additives": A Free Ticket to the World of Chemicals

The Regulation on Tobacco Products ("Tabakverordnung", Tobacco Regulation) of December 20, 1977, last amended by Article 21 of the Regulation on the Reform of Regulations Regarding Additives in Food of January 29, 1998, permits the use of a host of highly questiona-

ble additives in the manufacture of tobacco products. The list of substances reads like a stroll through the world of chemicals.

Permitted chemical substances include: all flavoring agents listed in the Flavoring Regulation ("Aromenverordnung"). It comprises over 130 individual substances and 30 chemically undefined mixtures including precursors to or reaction partners for the formation of carcinogenic substances such as amino acids, methyl β-naphthylketone, ammonium chloride, nitrates, glycols, and polysaccharides. In addition to the Flavoring Regulation, the Tobacco Regulation permits over 120 individual substances and 115 mixtures that are only vaguely chemically defined or completely undefined. In the following list, carcinogens are marked in bold type:

a chemically undefined mixtures such as fruits, fresh or dried, fruit juice and syrup, liquorice, maple syrup, molasses, spices, honey, wine, liqueur, spirits, coffee, tea, dextrins, sugars, starch, aromas, essences;
b moistening agents including glycerol, hydrated glucose syrup, hydrated saccharides, 1,2-propylene glycol, 1,3-butylene glycol, triethylene glycol, phosphoric acid, and their potassium and magnesium salts;
c adhesives and binders for cigars, pipe smoking tobacco, dark rolling tobacco, etc., such as: gelatine, shellac, collodion, cellulose acetate, ethyl and methyl cellulose, carboxymethyl cellulose, carboxymethyl starch, corn starch, acacia gum (gum Arabic), agar, alginic acid and salts, tragacanth, locust bean gum, guar gum, polyvinyl acetate, copolymers of vinyl acetate with ethylene;
d for tobacco foils: **glyoxal**, melamin-formaldehyde resin;
e as combustion modifiers: aluminum hydroxide, aluminum sulfate, aluminum oxide, magnesium oxide, **talc**, titanium dioxide, salts of nitric acid with alkali metals and alkaline-earth metals;
f substances for cigarette filters: glycerol acetate, triethyleneglycol diacetate, polyvinyl acetate;
g hot melt adhesives for glueing mouthpieces: e. g. paraffins, microcrystalline waxes; styrene, mixed and graft polymer resins; 2,6-di-*tert*-butyl-4-methylphenol, hydrated polycyclopentadiene resin;
h colours for cigarette papers, cigarette mouthpieces, and cigar wrappers including brilliant black, the **azo dyes** that are suspect carcinogens such as cochenille red, fast red, amaranth, orange GGN, sunset yellow, and **chromium complexes** of two further **azo** compounds (see Sect. 6 of this publication); indigotine (i. e. indigo);
i plasticizers for colours and paints used for printings on cigarette papers, filters, and holders: dibutylphthalate, glycerol acetate;
j substances for printings on cigarette papers and mouthpieces: anthraquinone blue, "black 7984", paraffin of low or high viscosity, linseed oil, copaiba wood oil, phenol-formaldehyde-modified colophony, colophony modified with acrylic acid, condensation products of phenols with formaldehyde, **salts** and **oxides of cobalt**, salts of 2-ethylhexanoic acid and others.

Result: The substances permitted according to the regulation cover vast chemical areas, giving manufacturers unlimited "creative freedom". Permitted additives are: undefined mixtures of flavorings, fruits, aromas, essences, juices, spirits, syrups, oils, woods, extracts, resins, flours, mucilages, metal oxide dusts, powders, cellulose in many modifications, and polymer resins. It is alarming that even a number of known carcinogens and substances that are suspected to cause cancer are permitted.
Whether or not the use of the actual amounts of these substances in the manufacture of cigarettes is legal according to the regulation, will not be discussed here. Scientific statements from a law perspective presume that, despite its general clause, the Tobacco Regulation does not permit manufacturing practices or levels of additives (or ingredients) that are harmful to health. This would mean that it would not be allowed to use the substances outlined in this article at such levels.

3. The Toxicological Fallacy of the Tobacco Regulation

The approval of tobacco additives in the Tobacco Regulation seems to be based on the notion that most of the listed additives are permitted for use in food and, consequently, cannot be harmful in tobacco products. This concept is totally absurd. As everybody knows, foodstuffs including additives are only exposed to the limited temperatures of food preparation, whereas the same additives in tobacco for smoking are subject to the high temperatures of the glowing cone (600–900 °C). As a result, they evaporate or sublimate, partly burn to carbon dioxide, nitrogen oxides, sulfur dioxide and water, but they are also converted into a multitude of pyrolysis products, dozens of which are carcinogenic.
It is not so much the additives in their original form that determine the toxic potential; much more relevant are their pyrolysis products. Another difference results from the fact that, after all, food additives approved for use in tobacco for smoking are not eaten; instead, after passing the glowing cone of the cigarette/cigar, they become effective primarily in the respiratory tract.
A smaller portion of the smoke condensate also gets swallowed, since it is deposited on the mucous membranes of the oral cavity. The condensate deposits in the

bronchial tree of the lungs that are carried out of the lungs by the bronchiolar transport system are usually swallowed, too. Basically, however, the toxic effects of smoking result from inhalation exposure.
It goes without saying that both factors, i.e. conversion of additives at high temperatures and inhalation, lead to toxic effects that do not play a role in foodstuffs.

Result: The basic approach of the Tobacco Regulation is wrong, because it permits the use – other than intended – of food additives for the manufacture of tobacco products; all of these food additives undergo pyrolytic changes in the glowing cone of a cigarette, cigar or pipe. As a result, these substances lose their intended harmlessness.
A Tobacco Regulation that contributes to health protection needs to take into account the toxic effects of pyrolysis products.

4. Many of the Additives Permitted in the Tobacco Regulation Increase Cancer Risk

General Principles:

The combustion products of raw tobacco alone are extremely damaging to health. Health risks are further increased substantially by a host of additives (underlined) [32,34]. In the following, a few general principles are outlined:

1) Combustion of tobacco produces carcinogenic polycyclic aromatic hydrocarbons. The amounts produced vary depending on the sort of tobacco. Addition of paraffins, waxes, oils and fats, shellac, collodion, cyclic isoprenoids, phytosterines, and organic compounds leads to an increased production of polycyclic aromatic hydrocarbons [19,35].
   Among the polycyclics regularly occurring as pyrolysis products are numerous substances that have been shown to induce cancer in animal experiments (see Tab. 1 with the classifications by IARC and DFG). The carcinogenic effect of the aromatics mixtures in lignite tar and coal tar has been proved by epidemiological methods for occupational exposure. Therefore, these were classified by IARC and the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft (DFG) in category 1 (carcinogenic to humans, DFG List of MAK and BAT Values, 2004 [10]).
   Particularly the local carcinogenic effect of these mixtures is attributed primarily to their content of polycyclics. Thus, it is anticipated that other mixtures containing polycyclics have the same effect. Please note that these substances easily penetrate human skin [9,35].
2) High quantities of nitrates in the tobacco plant promote the formation of carcinogenic *N*-nitrosamines [24]. This also applies to what is called "reconstituted tobacco", a by-product rich in nitrates, which is produced from tobacco dust, leaf scraps and tobacco stems. Reconstituted tobacco can account for up to 30 percent of the cigarette filling. The same effect results from added nitrate or ammonia compounds, which increase the yield of carcinogenic tobacco-specific *N*-nitrosamines and aromatic amines in the smoke [32f].
   Nitrates also promote the formation of nitroalkanes [20].
3) Added sugars, polysaccarides, pectins, syrups, starch, molasses, and related chemical additives produce aldehydes during pyrolysis; these are carcinogenic and highly irritating to mucous membranes [46]. The strong irritation of the mucous membranes of the respiratory tract is apt to enhance the effect of other carcinogens [18].
4) Tobacco humectants (moistening agents) glycerol, 1,2-propylene glycol, 1,3-butylene glycol, propylene glycol and sorbitol, which can constitute up to 5% of tobacco weight, cause formation of unsaturated aldehydes (such as acrolein) and alkylepoxides (such as propylene oxide) [28].
5) The protein fraction of the tobacco as well as added proteins or amino acids are the main precursors to volatile *N*-nitrosamines [32g].
6) Modified colophony (a resin from *Pinus* species) and fatty acid-modified phenol-formaldehyde resins have to be regarded as precursor substances of phenols, diphenols and phenol carbonic acids of tobacco smoke. The slightly acidic, phenolic fraction of cigarette smoke has tumor promoting properties, i.e., it induces so-called initiated ("dormant") tumor cells to grow into tumors [3,17].
7) Polyvinyl acetates and polyvinylacetate mixed polymer resins as additives may partly break down into carcinogenic vinyl acetate monomers by pyrolysis.
8) A chemical rule of thumb is: Starting materials containing structural elements of carcinogens (such as the β-naphthyl moiety in methyl β-naphthylketone, see above "a", or formaldehyde-derived bridges in mixed polymer resins, see above "j"), may break down into the respective carcinogens, e. g. β-naphthylamine (in the presence of nitrates) and formaldehyde, during pyrolysis. The same applies to the above-mentioned polymer resins, e.g. polyvinyl acetate, whose individual building blocks (vinyl acetate) are suspect to be carcinogenic [10].

Altogether, we can conclude that additives exacerbate the cancer causing effects of tobacco smoke in a variety of ways:

– as full-blown carcinogens
– as precursors of carcinogenic compounds that are formed by pyrolysis
– as modifiers of the absorption of carcinogens
– as modifiers of the enzymatic activation of proximate carcinogens and modifiers of the detoxification and elimination of active metabolites (ultimate carcinogens)
– as reaction partners, and by releasing reaction partners during the formation of carcinogens from several non-carcinogenic precursors in cigarette smoke
– by influencing the pyrolysis process, in particular the combustion temperature
– as tumor promoters or by promoting the formation of tumor promoters in cigarette smoke
– by influencing the smoking behavior in a way that leads to higher exposure of the smoker to carcinogens, whilst the carcinogen levels contained in the cigarette smoke are staying the same.

Result: Regulatory toxicology is justified in fighting against the inconsiderate use of additives whose individual pyrolysis products are largely uninvestigated, both chemically-analytically and toxicologically. Yet it is a fact that the mixtures of pyrolysis products have clearly been recognized as damaging to health.

5. Selected Carcinogens Generated from Additives During Pyrolysis

As mentioned above, pyrolysis leads to the formation of countless new chemical compounds, particularly carcinogens, from the organic material of tobacco products and additives. While the chemical structure of some of these compounds is known, their generation from precursor material is foreseeable in various cases. All in all, however, the chemistry of additive pyrolysis is largely unexplored. In the following, we have picked out some examples of carcinogens and their known or presumed precursor substances. Carcinogens are printed in bold type.

■ A foreseeable reaction is the cyclization of aliphatic chains of waxes, oils, paraffins and isoprenoids (the latter account for the flavor of tobacco) into **benzo[*a*]pyrene, benzanthracenes** and many other (carcinogenic) **aromatic polycyclics** [19]. Although a high nitrate content or nitrate additives in tobacco reduce the amount of polycyclics generated during pyrolysis [27], they also increase the yield of tobacco-specific ***N*-nitrosamines**.

■ The carcinogenic nitro compounds **nitromethane** and **nitropropane** are generated, among others, from added nitrates [32b]. Nitrate also promotes the formation of **nitrobenzene** (the nitro compounds mentioned are classified as carcinogens of category 2 and 3 according to the DFG List of MAK and BAT Values, 2004 [10]).

Nitrates are precursors of ammonia, which, in turn, promotes the formation of aliphatic and aromatic amines, pyrroles, piperidines, etc. About 200 amines have been identified. The most frequent primary, secondary, and tertiary acyclic and cyclic non-aromatic amines are: methylamine, ethylamine, dimethylamine, trimethylamine, 1-methylpyrrolidine, pyrrolidine. In the body, primary and secondary amines can be metabolized into cancer-inducing **hydroxylamine derivatives**. 4-Aminobiphenyl and 2-naphthylamine are notorious bladder carcinogens [24].

In addition, approximately 30 different **anilines** as well as **pyridine**, **naphthylamine** and **biphenyl** derivatives are known. Known for their strong cancer causing effect are also: several **anilines, *o*-, *m*- and *p*-toluidine, 1- and 2-naphthylamine, aminobiphenyls**. The aromatic amines of tobacco smoke increase with the nitrate content of the tobacco [20].

■ ***N*-nitrosonornicotine** and **4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone** ("NNK") and **five other *N*-nitrosamines** of tobacco smoke originate in the tobacco nicotine which can also be added in the form of tobacco extract or "reconstituted tobacco". During tobacco drying and during pyrolysis, various amines are generated from nicotine; these are nitrosated primarily by nitrite – which, in turn, comes from nitrate additives [28]. This accounts for the formation of 30–50% of NNK in tobacco smoke in the glowing cone, the remaining portion originates from preformed NNK of the tobacco. Alongside nitrite, nitrogen oxide is another nitrosating agent; it is formed by reduction of nitrate contained in or added to the tobacco. In general, the formation of aromatic amines during tobacco pyrolysis is substantially determined by available nitrogen donators and by the combustion temperature.

■ Nicotine is also the origin of the heterocyclic hydrocarbons, **dibenz[*a,h*]acridine** and **dibenz[*a,j*]acridine** [32d].

■ **Volatile *N*-nitrosamines**, in particular, ***N*-nitrosodimethylamine** and ***N*-nitrosopyrrolidine**, have their origin in tobacco proteins or added amino acids. Thus, the amino acid proline forms, on the one hand, *N*-nitrosoproline, but it also reacts, after nitrosation and decarboxylation, to *N*-nitrosopyrrolidine [32g].

■ **Nitrogen oxides (NO, NO_2)** are determined mainly by the nitrate concentration of the tobacco; part of these oxides originates from the combustion of amino acids and proteins [28]. **Nitrogen oxide** has been classified as a suspect human carcinogen [10]; since nitrogen monoxide forms DNA adducts, it also belongs to this category.

Nitrogen oxides react with secondary amines to form ***N*-nitrosamines** (see above) as well as with amino acids and other additives. The result is the formation of a vast

number of toxicologically unexplored *N*-nitrosamines. Nitrogen oxides contribute to the generation of tobacco-specific *N*-nitrosamines by nitrosation of nicotine and other alkaloids of the tobacco in the glowing cone [42].

■ Added sugars and starches lead to the formation of carcinogenic aldehydes such as **formaldehyde, acetaldehyde, acrolein** (2-propenal), **glyoxal, propionaldehyde, crotonaldehyde**, etc. [32a,45]. These aldehydes are genotoxic and, what is more, their strong local irritating effect in the respiratory tract and oral cavity contributes considerably to cancer development. Recent epidemiological research suggests that formaldehyde may cause not only tumors of the nasopharynx, but also leukemias [21,22].

■ *N*-heterocyclic amines such as **imidazoquinoline**, **-quinoxaline** and **-pyridine** have as their precursors amino acids permitted as additives [33]. Several dozens of these heterocyclics are known; eight cancer causing members of this substance class have been detected in tobacco smoke (see Tab. 1).

■ Volatile carcinogenic hydrocarbons such as **1,3-butadiene** and **benzene** are general products of burning organic material, with benzene forming preferably from precursor substances with aromatic rings or cyclohexane rings [32b].

■ Volatile **isoprene** (2-methyl-1,3-butadiene) is the pyrolysis product of isoprenoids (e.g. solanesol, phytone) [32c], which are the main constituents of tobacco flavor and are often added as tobacco extract; pyrolysis of tobacco extracts that are enriched by solanesol and its esters produces particularly high yields of **polycyclic aromatic hydrocarbons** [34a].

■ **Ethylene oxide**, like benzene, is a ubiquitous combustion product; in particular, it is produced from the tobacco humectant ethylene glycol [28]. Much the same applies to **propylene oxide**, which is a pyrolysis product of the humectant 1,2-propylene glycol.

■ **Vinyl acetate** can be a pyrolysis product of permitted polyvinyl acetates; **styrene** can be produced from polystyrenes and added cinnamyl derivatives.

■ Carcinogenic **amines** are produced – promoted by nitrate additives – during pyrolysis of tobacco [10]. Such amines can – directly or indirectly – also originate from colors, particularly from azo dyes, which are permitted according to the Tobacco Regulation.

■ Volatile phenols are generated from polysaccharides and polyphenols [32e]. Approximately 200 **phenols** are known. The chemical substance phenol itself is carcinogenic, as are the following: **cresols, diphenols (resorcine, hydroquinone, catechol)** [10,31,34]. Phenols are known for their irritant and tumor promoting properties. As to the magnitude of effect of phenols in tobacco smoke, the following ranking has been established experimentally: phenol, *o*-, *m*- and *p*-cresol, 2,4-, 2,6-, 3,4- and 3,5-dimethylphenol, *o*-chlorophenol, 2-ethylphenol [3,17].

Result: Additives that are known or expected, according to chemical plausibility, to lead to the formation of carcinogens during tobacco manufacturing or pyrolysis must not be used.

6. Carcinogens Used as Tobacco Additives That May Be Contained in Tobacco Smoke After Evaporation in the Glowing Cone

To date, 3,044 individual substances have been identified in tobacco, 4,800 in tobacco smoke [28,34]. About 1,200 of these are found both in tobacco and in tobacco smoke. This shows that the transition from the solid to an aerosol or the gaseous phase is easily possible [32,34].
The following is a selection of substances „permitted" according to the Tobacco Regulation which are carcinogenic from the start and may pass into tobacco smoke at the temperatures of the glowing cone.

1) **Glyoxal**; it is also a product of the combustion of cellulose and sugars.
   Glyoxal is suspected to cause cancer and has been classified as category 3B carcinogen according to the 2004 List of MAK and BAT Values of the Deutsche Forschungsgemeinschaft (DFG) [10].
2) 1 : 1 **Chromium** complex of α-(3-nitro-5-sulfo-6-hydroxyphenyl**azo**)-acetoacetic acid **anilide** and 1:1 **chromium** complex of 4-(3-nitro-5-sulfo-6-hydroxyphenyl-**azo**)-1-phenyl-3-methyl-pyrazolone-5.
   a) Azo dyes are characterized by the azo group –N=N–. They are formed by coupling of single and multiple diazotated arylamines. After inhalation of azo compounds there is a possibility of reductive cleavage of the azo group (by azoreductases of the liver and extrahepatic tissue), which leads to a release of the respective monocyclic amines. Numerous members of this substance group have been found to be carcinogenic in animal experiments. As a rule, monocyclic amines are excreted in urine. This is a reason to suspect that all azo dyes that contain a carcinogenic arylamine component may be split in the metabolism to release the arylamine component [10].
   b) Moreover, there is a possibility that the chromium portion of the 1:1 complex is present as chromium(VI) or is oxidized to yield chromium(VI) compounds in the glowing cone. Chromium(VI) compounds are classified as human carcinogens of category 1 (DFG) (e.g. zinc chromate) or category 2 (positive in long-term animal studies and therefore considered human carcinogens), see List of MAK and BAT Values of the DFG, 2004 [10]).

3) Salts and oxides of **cobalt**:
   these are carcinogens; cobalt and cobalt compounds are classified as category 2 carcinogens (reasonably anticipated to be carcinogenic in humans) (see DFG List of MAK and BAT Values [10]).
4) Dibutylphthalate, 2-ethylhexanoic acid:
   to be suspected as being carcinogens. These substances are called peroxisome proliferators. Prototype substances regularly induce a triad of liver, pancreatic and Leydig cell tumors in rats and mice. Dibutylphthalate is currently under review by the MAK Commission of the DFG.
5) **Talc**:
   suspected carcinogen, classified as category 3 of the DFG List of MAK and BAT Values, 2004 [10].

Result: Cigarette manufacturers add various "ingredients" to raw tobacco that are carcinogenic in the first place. Many of these may, partly unchanged, pass into tobacco smoke. Even though some ingredients are added in minute amounts, one has to take into account that a smoker may consume more than 350,000 cigarettes within a lifetime. Consequently, the elimination of ingredients is urgently required.

7. Additives That Make Tobacco Products More Addictive and Inhalation Easier

The bioavailability of nicotine, i.e. the chemical basis for addiction development, is coupled to the pH value. The more basic the tobacco smoke is, the faster nicotine is absorbed in the respiratory tract along with a more rapid delivery of nicotine to the brain and an increased intensity and duration of effect [12,25,36]. Ever since the invention of the technology in cigarette manufacturing by Philip Morris and the resulting worldwide success of the "Marlboro" brand, all tobacco giants have manipulated the bioavailability of nicotine by adding ammonia compounds, urea, soda, or other substances. These substances contribute considerably to nicotine addiction. They also serve to deceive and mislead consumers by producing low and seemingly harmless ISO measurement values.

Menthol is the only additive that is marketed actively and visibly for the consumer. The specific characteristics of menthol cause effects on the respiratory tract, pain relief, taste and cooling effects as well as effects on the central nervous system. As the US Department of Health and Human Services points out, menthol leads to increased respiratory frequency, higher respiratory volume as well as deeper smoke inhalation [43]. Tobacco companies use menthol primarily to "smooth" the smoke and as a local pain-reducing agent [4,38]. To cover the menthol taste if it is too strong, further additives such as peppermint, spearmint, cloves, camphor or wintergreen are used [5,38]. Although menthol is used primarily for its physiological and sensory effects, it also has effects on the central nervous system, has an addiction potential of its own and thus contributes to further increasing nicotine addiction. Menthol may also mask the early warning symptoms of respiratory distress such as chronic irritation of the respiratory tract [14b].

Further additives such as sugar, vanillin, cacao, liquorice, honey and others are designed to cover the normally harsh taste of tobacco and make smoking a more enjoyable and milder experience [2,38,48]. By adding the above-mentioned substances, cigarette manufacturers target primarily the youth market (children and young adults). This is clearly stated in internal tobacco industry documents:

"*People want mildness. [...] We also should win more young non-smokers with mildness.*" [7]

"*The beginning smoker and inhaler has a low tolerance for smoke irritation, hence the smoke should be as bland as possible.*" [39]

"Cigarettes should be low in irritation and possibly contain added flavors to make it easier for those who never smoked before to acquire the taste of it more quickly." [40]

"There is certainly nothing immoral or unethical about our Company attempting to attract those smokers [i.e. the twenty-one year old and under group] to our products." [39]

Result: The tobacco industry uses additives to increase the addictive potential of cigarettes. Numerous additives are used in order to make smoking easier for children and young adults. The added substances lead to additional health hazards. The enormous harm potential for children and young adults deserves particular emphasis. Children and young adults are not yet able to grasp the consequences of their consumption and are made addicts long before they reach adulthood. Additives that are designed to make smoking easier, in particular, to facilitate deeper smoke inhalation, as well as all additives that increase the bioavailability of nicotine are impermissible.

8. No Limit Values for Carcinogens in Tobacco Smoke Can Be Established

It is an internationally undisputed hypothesis that it is generally not possible to define limit values or effective thresholds for genotoxic carcinogens as a dose measure

below which there are no health hazards. This is because genotoxic carcinogens cause damage to the DNA of the genetic material. Although these do not yet lead to a tumor, they are irreversible because they are "codified" as a change in the DNA sequence (mutation) after the very first cell duplication and henceforth evade DNA repair. As a result, the mutation will be passed on to each generation of daughter cells. This type of DNA damage is called "initiation" and it means that the affected cells have reached the first of several stages leading to malignant transformation. Experiments have shown that such irreparable genetic damages add up as a result of repeated exposure to a genotoxic carcinogen. Based on the current state of knowledge, our understanding of genotoxic carcinogens is as follows:

– On the basis of today's scientific knowledge it is not possible to define either health-based limit values or "practical" effective thresholds for genotoxic carcinogens.
– Existing dose-effect curves do not simply break off below the lowest measuring points. Instead, they run – in all likelihood – towards zero in a more or less linear fashion in a dose-effect continuum. The effect decreases steadily with decreasing dosage. Consequently, there is also an increased risk in the lower exposure range, which is no longer experimentally accessible. However, although the risk declines proportionally with decreasing dose in this range, it does not abruptly become zero [47].

This understanding of the mode of action of genotoxic carcinogens shows that it is untenable to permit even the smallest amounts of tobacco additives if these or their pyrolysis products cause genetic damage.
The same applies to the numerous non-genotoxic carcinogens of tobacco smoke, such as the substances of the phenol fraction. In principle, it should be possible to derive limit values for non-genotoxic substances – as individual substances. However, this is not possible at present due to the incompleteness of available data. But even if it were possible to define limit values, these would be valid only for exposure to an individual substance, not a mixture of substances. This means that it would be unacceptable to apply these (yet to be established) limit values to tobacco smoke, since – toxicologically speaking – tobacco smoke is an extremely complex mix of gases and aerosols. Therefore, it is imperative to avoid non-genotoxic carcinogens, too. This requires fundamental changes in cigarette manufacturing.

9. Summary

The additives mentioned, like in a general clause, in the Tobacco Regulation give cigarette manufacturers almost unlimited freedom in designing the chemistry of their products. However, the goal of §§ 20 to 23 of the superior Food and Commodities Act (LMBG), which regulate trade and commerce in tobacco products, is to avoid **additional** risks beyond the unavoidable health risks of smoking. Consequently, the additives declared as generally permitted by the Tobacco Regulation would actually not be permissible. No legal assessment of this question is made here.

One reason for the freedom of designing tobacco productsgiven by the Tobacco Regulation ("Tabakverordnung") is the fact that it permits the addition of a multitude of undefined mixtures to tobacco. Examples are: mixtures of flavorings, fruits, aromas, juices, spirits, syrups, oils, woods, undefined extracts, resins, flours, mucilages, metal oxide dusts, undefined powders, cellulose in numerous modifications, and polymer resins.

The permission of proven carcinogens as additives is out of all reason. The same applies to substances that are suspected to cause cancer such as glyoxal, azo dyes and chromium complexes thereof, salts and oxides of cobalt, and others.
The Regulation also allows the use of additives which produce carcinogens in the pyrolysis process. These include:

a) waxes, oils, paraffins, isoprenoids, etc., which form the dreaded polycyclic aromatic hydrocarbons (indicator substances benzo[*a*]pyrene, benz[*a*]anthracene);
b) sugars and starches, from which – by pyrolysis – genotoxic and mucous-membrane irritating aldehydes are generated;
c) the Regulation permits the addition of amino acids, even though these produce carcinogenic heterocyclic amines.
d) It is allowed to use humectants, from which unsaturated aldehydes and aliphatic epoxides are generated by pyrolysis.
e) The use of nitrates is allowed, even though these promote – directly or indirectly – the formation of tobacco-specific *N*-nitrosamines and aromatic amines.
f) Phenol-formaldehyde resins are permitted; these may lead to the formation of various phenols and their derivatives, and formaldehyde.

The blanket approval of substances of the Flavoring Regulation ("Aromenverordnung") also opens the way to manipulation. Many of the preparations contained in this Regulation are not or only insufficiently chemically defined. Included are, for example, molasses, fatty acid salts of edible fats, agar, tragacanth, pectins, carrageen (polysaccharides from red seaweed), a large variety of oils, aromas and plant extracts. The list of flavorings

allows practically all amino acids as additives, even though it is known that amino acids turn into carcinogens at high temperatures (e. g. imidazoquinolines and imidazoquinoxalines). These dangerous compounds were identified and their carcinogenic potential analyzed back in the 1980s and 1990s.

Additives that are generally "permitted" according to the Tobacco Regulation include substances such as ammonia compounds, nitrates, vanillin, cocoa, liquorice and others, which increase tobacco addiction and influence inhalation depth, particularly in children and young adults.

The list of additives permitted for use in cigarettes by the Tobacco Regulation reads like a list of raw materials for manufacturing substances that cause cancer and increase addiction.

Therefore, we need testing procedures for additives which use advanced methods of analyzing carcinogens and take into account toxicological evaluations.

Only if it is evident that an additive is harmless it may be considered for use.

10. Action Recommendations for the Legal Regulation of Cigarette Manufacturing

The existing Tobacco Regulation needs to be completely revised: the list of additives permitted for foodstuffs is unsuitable for tobacco products. After all, the additives listed therein are not eaten; instead, after passing the glowing cone, they become effective basically in the respiratory tract. The conversion of additives to pyrolysis products at high temperatures, and the inhalative mode of intake lead to toxic effects that are irrelevant in edibles. Therefore, a health-oriented Tobacco Regulation needs to take into account the toxic effects of pyrolysis products.

Since cigarette manufacturers show no efforts of their own to produce less health-damaging products, even though they have the technologies and knowledge to do so, approval of the following additives should be annulled or their use be prohibited:

- All known and suspected carcinogens;
- all additives that lead to the formation of carcinogens by pyrolysis;
- all substances that contribute to increasing addiction;
- all substances that make it easier for children and young adults to start smoking, i.e. all "smoothing agents", bronchodilators, modifiers of inhalation, pain-relievers, antihistamines and others;
- all additives that may prompt a person to initiate smoking, cause relapse of tobacco use in former smokers, or prompt smokers to keep smoking when they might have otherwise quit.

All tobacco additives need to pass prior health safety testing and thorough toxicologic evaluation. Without this approval, none of these substances is allowed to be added to natural tobacco. Testing must meet the requirements of drug safety laws. For public health protection, a federal tobacco control authority needs to be established with the task of monitoring the tobacco industry and its products. Without government regulation, there is no way to be certain that any claims made by the tobacco industry are accurate and that consumers are not being mislead.

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