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WP9 - D9.4 Additional additives for independent assessment

JOINT ACTION ON TOBACCO CONTROL

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1. Introduction

The original aim of WP 9 task 4 was to develop a new list with additional additives that could be subject to enhanced reporting obligations. The development should be performed in collaboration with WP 6 (Tobacco Product Evaluation) and WP 7 (E-cigarette Product Evaluation). This aim was set before the review panel started the evaluation of the reports presented by the tobacco industry according to Article 6, paragraph 4 of TPD. The approach and outcomes of this evaluation are described in *D 9.3 Report on the peer review of the enhanced reporting information on priority additives.* In brief, the review panel concluded that placing the responsibility for assessing priority additives on the tobacco industry is not suitable. The industry has a clear motivation to keep their products on the market, and also to maintain sales numbers, and therefore cannot be considered an unbiased part. Instead, assessment of additives in tobacco products should be based on independent sources and be performed by independent experts.

Based on these outcomes, it was also concluded that no new priority list according to article 6 of TPD should be established. Therefore the adjusted aim of task 4 is to provide member states and researchers with a list of selected additives that should be considered for further assessment using independent literature.

The selection of additives was performed in four parts:

Part 1 based on the SCENIHR evaluation from 2016.

Part 2 based on an evaluation of EU-CEG data from cigarettes, provided by WP 6. Due to limited resources, the evaluation of EU-CEG data was focused on cigarettes in the Netherlands. Using this data set, a list of additives of interest was extracted. This part should encourage member states to use national EU-CEG data for the development of their own priority additive lists in a similar way.

Part 3 is as well based on the evaluation of EU-CEG data from cigarettes, provided by WP6. This evaluation covered Netherlands, France, Belgium, Denmark, and Czech Republic and focused on CMR properties explicitly mentioned in the EU-CEG data set.

Part 4 is an overview of substances which are already prohibited for the use in tobacco products in Germany and Hungary. The compilation should encourage other member states to ban these additives in tobacco products or e-liquids as well.

Part 1: Additional additives in SCENIHR guidance document (2016 Tobacco additives)

SCENIHR evaluated a large number of tobacco additives (SCENIHR, 2016). For the priority list, 15 compounds from this evaluation have been selected already. The remaining compounds have been subjected to further selection. The selection criterion was a quota of 0.01% and higher of the additive on the tobacco weight. Assuming an average tobacco weight of 500mg, 0.01% would be 0.05mg. SCENIHR had assessed all these additives and no apparently high toxicity was discovered yet that would immediately led to a ban of the additive. However, several open questions remained as explained in some details in the annex 1 and so we selected compound from the SCENIHR evaluation, that are added in quantities of at least 0.01 %: 22 compounds or compound groups (ammonium compounds, potassium salts and sugars are grouped) qualify for this selection.

Overview of the 22 compounds with ≥0.01%:

Compound	CAS-No	Weight %	Comments
Acetanisole	100-06-1	0.013	
Acetic acid	64-19-7	0.05	
Ammonium compounds	several	0.056	
Benzaldehyde	100-52-7	0.13	
Benzoic acid	65-85-0	0.3	Top priority, see Annex 1
Benzyl alcohol		100-51-6	0.025
Butyric acid	107-92-6	0.01	
Caramel colours	8028-89-5	0.01	
Cellulose	several		
Ethyl butyrate	105-54-4	0.21	
Ethyl maltol	4940-11-8	0.01	
4-hydroxy-2,5-dimethyl-3(2H)-furanone	3658-77-3	0.01	
Lactic acid	50-21-5	0.05	
Piperonal	120-57-0	0.096	
Potassium citrate	866-84-2	Around 5	With other potassium salts
Potassium sorbate	590-00-1	0.05	
Prune juice extract	90082-87-4	0.95	
Rum	91450-09-8	0.01	
Sodium benzoate	532-32-1	0.3	
Sugars	several	3.99	Several sugars
gamma-valerolactone	108-29-2	0.026	
Vanillin	121-33-5	0.266	

Argumentation for inclusion in this list and possible concerns to be clarified regarding these additives are summarized in **Annex 1 to part 1** at the end of this document. This can be used as a starting point for further research.

Part 2: Additives that are applied at above 0.05mg/cigarette

To expand the list of additives that need further research, a search within EU-CEG data was performed with predefined criteria. In order to identify substances that are added to tobacco in amounts that might affect smoke chemistry or toxicity, an arbitrary threshold of 0.05mg (0.01% of 500mg tobacco) was set. This threshold was applied to one exemplary EU-CEG data set, in this case from the Netherlands. The curated dataset was obtained from JATC WP 6.

Substances (most of which have not been identified previously by SCENIHR or SCHEER) that were reported to be added above 0.05mg and inherit a potential concern are listed below. In some cases, a short initial assessment is provided, but further evaluation based on independent literature is required. The list should be considered as first guidance in an assessment process. Member states are encouraged to apply this procedure to their EU-CEG data and perform further assessments of the properties of the additives.

- **Acacia gum** (CAS-No 9000-01-5) (binder, combustion modifier, flavor and/or taste enhancer)
  - o Acacia gum is a complex mixture of non-volatile compounds, including sugars. Thus, pyrolysis of acacia gum can potentially lead to the formation of MAO inhibitors and other substances with toxicological concern. Further, an alteration of smoke pH is possible. Acacia gum itself is classified as an eye irritant.
  - o Acacia gum is used as a flavor and/or taste enhancer.
- **Acetoin** (CAS-No 513-86-0) (Flavour and/or taste enhancer, other)
  - o Acetoin is used as a flavor and/or taste enhancer. Taste is described by www.

thegoodscentcompany.com as "creamy, dairy, sweet, oily, milky, and buttery".

- **Acetone** (CAS-No 67-64-1) (Solvent – processing aid, filter component)
- **Acetyl tributyl Citrate** (CAS-No 77-90-7) (plasticiser)
- **Alkyl resin** (CAS-No 115-77-5) (carrier, binder)
- **Alkyl ketene dimer** (CAS-No 10126-68-8 and 84989-41-3) (sizing agent)
- **Alpha methyl styrene resin** (CAS-No 9011-11-4) (Adhesive)
- **Aluminium hydroxide** (CAS-No 21645-51-2) (filler, combustion modifier)
- **Aluminium sulphate** (CAS-No 10043-01-3) (sizing agent, combustion modifier)
- **Aluminium sulphate tetradecahydrate** (CAS-No 16828-12-9) (sizing agent, combustion modifier)
- **Apple juice/concentrate** (CAS-No 85251-63-4) (Flavour and/or taste enhancer)
    - o Apple juice/concentrate is a complex mixture of volatile and non-volatile compounds, including sugars. Thus, pyrolysis of apple juice can potentially lead to the formation of MAO inhibitors which are of concern for addictiveness, and other substances with toxicological concern.
- **Butyl acrylate-tert-butyl acrylate-styrene copolymer** (CAS-No 29497-08-3) (Binder)
- **Calcium carbonate** (CAS-No 471-34-1, 1317-65-3) (filler, colour, binder etc)
- **Carboxymethyl cellulose and its sodium salt** (CAS-No 9004-32-4) (binder)
- **Cardamom seed oil** (CAS-No 8000-66-6) (flavour and/or taste enhancer)
    - o Cardamom seed oil is used as a flavor and/or taste enhancer.
- **Carvone** (CAS-No 99-49-0) (flavour and/or taste enhancer)
    - o The compound is an activator of TRPM8 receptor that leads to a cooling sensation and can facilitate inhalation (Paschke et al., 2017). L-Carvon (see part 4) is therefore prohibited in Germany.
    - o Carvone is used as a flavor and/or taste enhancer.
- **Cationic starch** (CAS-No 56780-58-6) (solvent – processing aid, binder)
- **Chamomile extract and/or oil** (CAS-No 8015-92-7) (flavour and/or taste enhancer)
    - o Chamomile extract and oil are used as a flavors and/or taste enhancers.
- **Colophony, rosin** (CAS-No 8050-09-7) (filler, binder, sizing agent)
- **Coriander seed oil** (CAS-No 8008-52-4, 84775-50-8) (flavour and/or taste enhancer, filtration material)
    - o Coriander seed oil is used as a flavor and/or taste enhancer.
- **Corn mint oil** (CAS-No 68917-18-0) (flavour and/or taste enhancer)
    - o Compounds in corn mint oil are activators of TRPM8 receptor that leads to a cooling sensation and can facilitate inhalation (Paschke et al., 2017). Mint oils (see part 4) are therefore prohibited in Germany.
    - o Corn mint oil is used as a flavor and/or taste enhancer.
- **Cycloaliphatic hydrocarbon resin** (CAS-No 68132-00-3) (filtration material, adhesive)
- **Dextrose** (CAS-No 5996-10-1) (flavour and/or taste enhancer, other)
    - o Pyrolysis of dextrose (glycose) leads to the formation of substances of toxicological concern. Further, some pyrolysis products are precursors of MAO inhibitors, thus potentially enhancing addictiveness. (Talhout et al., 2006)
    - o Dextrose is used as a flavor and/or taste enhancer.
    - o For further detail, see below under **Sugars** in Annex 1.
- **Epichlorhydrin resin** (CAS-No 25212-19-5) (sizing agent)
- **Ethyl alcohol** (CAS-No 64-17-5) (solvent – processing aid)
- **Ethyl vanillin** (CAS-No 121-32-4) (flavour and/or taste enhancer)
    - o Ethyl vanillin is used as a flavor and/or taste enhancer. For further detail, see below under **Vanillin** in Annex 1.
- **Glyoxal** (CAS-No 107-22-2) (solvent – processing aid)
    - o According to CLP-database at ECHA, glyoxal has been classified as **Muta 2, H341.** Therefore, the use of glyoxal as additive is prohibited.
- **Hexanedioc acid** (CAS-No 25212-19-5) (sizing agent)
- **Lemon oils** (CAS-No 8008-56-8) (flavour and/or taste enhancer)

    - Lemon oil is used as a flavor and/or taste enhancer.
- **Lovage extract** (CAS-No 8016-31-7) (flavour and/or taste enhancer)
    - Lovage extract is used as a flavor and/or taste enhancer.
- **Lubricant white mineral oil** (CAS-No 8042-47-5)
- **Menthone** (CAS-No 89-80-5) (flavour and/or taste enhancer)
    - The compound is an activator of TRPM8 receptor that leads to a cooling sensation and can facilitate inhalation (Paschke et al., 2017). Menthone (see part 4) is therefore prohibited in Germany.
    - Menthone is used as a flavor and/or taste enhancer. Taste is described by www.thegoodscentcompany.com as "cooling, mentholic, minty, and woody".
- **Modified rosin** (CAS-No 65997-13-9, 8050-28-0, 91081-22-0) (adhesive, sizing agent)
- **Petroleum wax** (CAS-No 63231-60-7, 8002-74-2) (adhesive)
- **Phenyl carbinol** (CAS-No 100-51-6) (flavour and/or taste enhancer)
    - Phenyl carbinol (benzyl alcohol) is considered harmful by inhalation.
    - Phenyl carbinol (benzyl alcohol) is used as a flavor and/or taste enhancer. Taste is described by www.thegoodscentcompany.com as "chemical, fruity, cherry, almond, balsamic, and bitter".
    - For further detail, see below under **Benzyl alcohol** in Annex 1.
- **Polycyclopentadiene** (CAS-No 68132-00-3) (binder, adhesive)
- **Polyvinol/polyvinylalcohol** (CAS-No 25213-24-5, 9002-89-5, 54626-91-4) (adhesive, binder)
- **Raisin extract** (CAS-No 68915-86-6) (flavour and/or taste enhancer, other)
    - Raisin extract is used as a flavor and/or taste enhancer.
- **Tall oil rosin** (CAS-No 8052-10-6) (filler, binder, sizing agent)
- **Tamarind extract** (CAS-No 84961-62-6) (flavour and/or taste enhancer, other)
    - Tamarind extract is used as a flavor and/or taste enhancer.
- **Urea** (CAS-No 57-13-6) (combustion modifier)

Part 3: Additives from EU-CEG with CMR properties (harmonized classification)

According to TPD, the use of additives with CMR properties is prohibited (Article 7.6 e). Manufacturers are required to indicate whether additives in their products have CMR properties, when submitting their product in EU-CEG. WP 6 performed an evaluation of EU-CEG data on cigarettes additives that were indicated by manufacturers to have CMR properties. This resulting list of 75 additives in five countries was evaluated by WP 9 to determine whether they are actually harmonized classified CMR substances. The following two compounds are found to be harmonized classified in either CARC 1B or CARC 2; therefore action is already possible and required. Both compounds have been notified via EU-CEG in Belgium, France, Denmark, Czech Republic and the Netherlands. It is not known, whether these compounds have been notified in other countries (assessment was not performed for additional countries, due to limited resources available).

- Vinyl acetate (CAS-No 108-05-4), Carc 2, H351
- Petroleum distillate (CAS-No 64742-13-8), Carc 1B, H350

Additionally, the evaluation of additives in cigarettes from the Netherlands (see part 2) revealed glyoxal (CAS-No 107-22-2) used as solvent or processing aid. According to CLP-database at ECHA, glyoxal has been harmonized classified as Muta 2, H341. Therefore, the use of glyoxal as additive is prohibited.

Part 4: Additives already banned in two member states for the use in tobacco

Since some member states already ban particular additives, WP 9 task 4 partners aimed to collect information on such national bans on tobacco additives within the EU. Ultimately, information about banned additives was obtained from two countries; Germany and Hungary. Translations from German and Hungarian are non-official. This overview could inspire other member states to consider national bans of selected tobacco additives as well, and encourage them to cooperate with the aim to ban further substances. At least, the overview is an example for regulatory action.

The **German** Tobacco Product Ordinance banned several compounds in tobacco products (annex 1 for §4) and in liquids for e-cigarettes (annex 2 for § 28) (https://www.gesetze-im-internet.de/tabakerzv/index.html#BJNR098010016BJNE003601116). Reasons for selection were given in the individual paragraphs:

Prohibited Additives in Tobacco products (Annex 1 (for §4))

1. Vitamins or the following other additives, which are suggestive of health benefits or less health risks of the tobacco product:
   a) Amino acids or modified amino acids, which are authorized according §7, paragraph 1 sentence 1 No 1 in connection with annex 2 category 3 of the diet ordinance in the version which is in force for dietary food as well as S-adenosylmethionin and L-5-hydroxytrypthophan
   b) Carnitin
      L-Carnitin
      L-Carnitin hydrochloride
      L-Carnitin-L-tartrate
   c) Flavonoids as well as antioxidative active phospholipids
   d) Sodium selenite
2. Caffeine, taurine or the following other additives and stimulating additives and stimulating mixtures, associated with energy and vitality:
   a) Maltodextrin
   b) Ingredients including processed ingredients, extracts and oils of the coffee plant and coffee bean
   c) Ingredients including processed ingredients, extracts and oils of the tea plant Camelia sinensis L. Kuntze
   d) Ingredients including processed ingredients, extracts and oils of the guarana plant
   e) Ingredients including processed ingredients, extracts and oils of the Yerba mate plant
   f) Thujone
3. Additives with coloring properties for the emissions
4. Following additives in smoking tobacco which facilitate inhalation or nicotine uptake:
   a) p-Menthan 3-substituted and modified compounds, including
      p-menthan 3-carboxamide, including p-menthan 3-N-alkylcarboxamide
      p-menthan 3-ester
      p-menthan 3-ether
      p-menthan 3-carboxylic acids and associated esters
      menthon 1,2-glycerol ketal (CAS-No 63187-91-7)
   b) p-Menthan alcohols and associated esters
   c) Following compounds:
      Icilin (CAS-No 36945-98-9)
      Trimethyl isopropyl butanamide (CAS-No 51115-67-4)
      Isopulegol (CAS-No 7786-67-6 or 89-79-2)
      1-(di-sec-butyl-phosphoinoyl)-heptane
   d) Following compounds:
      aa) Menthol (CAS-No 1490-04-6)
      (-)-Menthol (CAS-No 2216-51-5)
      (+)-Menthol (CAS-No 15356-60-2)

bb) Menthon (CAS-No 89-80-5)
 (-)-Menthon (CAS-No 14073-97-3)
 (+)-Menthon (CAS-No 3391-87-5)
 L-Carvon (CAS-No 6485-40-1)
 Geraniol (CAS-No 106-24-1)
 Linalool (CAS-No 78-70-6)
 1,8-Cineol (CAS-No 470-82-6)
 Hydroxycitronellal (CAS-No 107-75-5)

e) Following compounds prepared from plants: Oils and ingredients prepared from plants of the following genera, Mentha, Eucalyptus, Ocimum, Thymus and Salvia

5. Following additives with CMR properties in unburned form:
   a) Compounds classified according to part 3 of annex VI of regulation (EC) 1272/2008 as CMR category 1A, 1B or 2
   b) Following other compounds:
      Birch tar oil (CAS-No 8001-88-5 and CAS-No 85940-29-0)
      Juniper tar (CAS-No 8013-10-3)
      Sassafras oil
      Sassafras wood
      Sassafras leaves
      Sassafras bark
      Methyleugenol (CAS-No 93-15-2)
      Estragole (CAS-No 140-67-0)
      Propylparaben (CAS-No 94-13-3)

Prohibited Additives in Electronic Cigarettes and Refill Container (Annex 2 (for §28))

1. Vitamins or the following other additives, which are suggestive of health benefits or less health risks of the consumption of electronic cigarettes of refill container:
   a) Amino acids or modified amino acids, which are authorized according §7, paragraph 1 sentence 1 No 1 in connection with annex 2 category 3 of the diet ordinance in the version which is in force for dietary food as well as S-adenosylmethionin and L-5-hydroxytrypthophan
   b) Carnitin
   L-Carnitin
   L-Carnitin hydrochloride
   L-Carnitin-L-tartrate
   c) Flavonoids as well as antioxidative active phosho lipids
   d) Sodium selenite
2. Caffeine, taurine or the following other additives and stimulating additives and stimulating mixtures, associated with energy and vitality:
   a) Maltodextrin
   b) Glucose, fructose and galactose
   c) Ingredients including processed ingredients, extracts and oils of the coffee plant and coffee bean
   d) Ingredients including processed ingredients, extracts and oils of the tea plant Camelia sinensis L. Kuntze
   e) Ingredients including processed ingredients, extracts and oils of the guarana plant
   f) Ingredients including processed ingredients, extracts and oils of the Yerba mate plant
   g) Thujone
3. Additives with coloring properties for the emissions
4. Following additives with CMR properties in unburned form:
   a) Compounds classified according to part 3 of annex VI of regulation (EC) 1272/2008 as CMR category 1A, 1B or 2
   b) Following other compounds:
      Birch tar oil (CAS-No 8001-88-5 and CAS-No 85940-29-0)

Continued

Juniper tar (CAS-No 8013-10-3)
Sassafras oil
Sassafras wood
Sassafras leaves
Sassafras bark
Methyleugenol (CAS-No 93-15-2)
Estragole (CAS-No 140-67-0)
Propylparaben (CAS-No 94-13-3)

5. Following ingredients except nicotine in the liquid which constitute in heated or non-heated form a risk to human health:
   a) Following flavorings:
      Diacetyl (CAS-No 431-03-8)
      2,3-Pentandione (CAS-No 600-14-6)
      2,3-Hexandione (CAS-No 3848-24-6)
      2,3-Heptandione (CAS-No 96-04-8)
      Coumarin
   b) Following compounds extracted from plants:
      Bitter almond oil
      Processed ingredients and extracts of the rhizome of Polypodium vulgare
      Processed ingredients, extracts and oils of the plant Mentha pulegium
      Agaric acid

Hungary banned several additives in e-cigarettes and tobacco products:

1 Material
2 2-Methyl-3- (para-isopropyl-phenyl) -propionaldehyde
3 Agar-agar
4 Alumina
5 Ammonium acetate
6 Ammonium citrate
7 Ammonium formate
8 Ammonium bicarbonate
9 Ammonium hydrogen malate
10 Ammonium hydroxide
11 Ammonium carbamate
12 Ammonium chloride
13 Ammonium lactate
14 Ammonium malt
15 Ammonium succinate
16 Ammonium sulfamate
17 Ammonium tartrate
18 Anthraquinone blue
19 Basic blue 26
20 Succinic acid (E 363)
21 Dehydro-menthofurolactone
22 Di-2-ethylhexyl adipate
23 Diammonium hydrogen phosphate
24 Diammonium carbonate
25 Diammonium malate
26 Diammonium succinate
27 Dibutyl phthalate
28 Phenol-formaldehyde-modified rosin
29 Galactose

30 Formic acid (E 236)
31 Urea (E 927b)
32 Carmine red
33 Caffeine
34 Krizein S
35 Coumarin-free tonka beans
36 Lactose
37 Maltose
38 Mannose
39 Methyl violet
40 Honey
41 Monoammonium phosphate
42 Sodium silicate
43 Solvent red 1
44 Pectins
45 Polyethylene glycol (E 1251)
46 Riboflavin-5-phosphate
47 Sucrose octaacetate
48 Saccharin (E 954)
49 Sudanese blue 11
50 Taurin
51 Tea
52 Theobromin

1 Material
2 2,6-Dertert-butyl-4-methylphenol
3 2-Phenyl-propionaldehyde
4 2-Methyl-3- (para-isopropyl-phenyl) -propionaldehyde
5 Acetyl tributyl citrate
6 Agar-agar
7 Alumina
8 Ammonium acetate
9 Ammonium citrate
10 Ammonium formate
11 Ammonium bicarbonate
12 Ammonium hydrogen malate
13 Ammonium hydroxide
14 Ammonium carbamate
15 Ammonium chloride
16 Ammonium lactate
17 Ammonium malt
18 Ammonium succinate
19 Ammonium sulfamate
20 Ammonium tartrate
21 Anthraquinone blue
22 Ginger (E 414)
23 Gold bronze (copper)
24 Basic blue 26
25 Succinic acid (E 363)
26 Brilliant blue
27 Dehydro-menthofurolactone
28 Di-2-ethylhexyl adipate
29 Diammonium hydrogen phosphate
30 Diammonium carbonate

31 Diammonium malate
32 Diammonium succinate
33 Dibutyl phthalate
34 Ethyl citrates (triethyl citrate E 1505)
35 Phenol-formaldehyde-modified rosin
36 Galactose
37 Formic acid (E 236)
38 Isopropyl alcohol
39 Maple syrup
40 Cocoa and cocoa products
41 Urea (E 927b)
42 Carmine red
43 Carrageenan (Irish lichen extract) (E 407)
44 Coffee
45 Caffeine
46 Krizein S
47 Decouminated tonka beans
48 Lactose
49 Maltose
50 Mannans, modified mannans
51 Mannose
52 Molasses
53 Methyl violet
54 Honey
55 Monoammonium phosphate
56 Sodium silicate
57 Solvent red 1
58 Pectins
59 Polyethylene glycol (E 1251)
60 Ponszo 4R
61 Riboflavin-5-phosphate
62 Sucrose octaacetate
63 Saccharin (E 954)
64 Silica gel (E 551)
65 Sudanese blue 11
66 Talc (E 553b)
67 Tartrazine
68 Taurin
69 Tea
70 Theobromine
71 Titanium dioxide (E 171)
72 Triethyl citrate (E 1505)

Annex 1 to part 1

JATC WP 9 follows the SCENIHR reasoning for the selected compounds, as cited below. Due to limited time, most of the argumentation by SCENIHR was not updated with recent literature. However, a short discussion on addictiveness enhancement by sugars is provided by WP9 experts.

Acetanisole (CAS-No 100-06-1), evaluation by SCENIHR (2016).

> "Acetanisole is a known flavouring agent for food and is added to tobacco products for flavouring. More data are needed on the amount of acetanisole that imparts a noticeable flavour other than

tobacco.

In order to make a toxicity risk evaluation, it is necessary to know the exposure level of acetanisole through cigarette smoking. Therefore, research is needed to determine the amount of acetanisole in mainstream cigarette smoke.

In human intermittent inhalation studies at concentrations relevant for tobacco smoke, increased pulse rate and blood pressure were observed. Because many toxicological inhalation data on acetanisole are missing, expected health effects after exposure to acetanisole from cigarette smoke remains unknown. Experiments, particularly on the effects on the cardiovascular system, respiratory tract, and CNS should be carried out. It is unclear if toxic combustion products of acetanisole are formed upon smoking a cigarette. From a pyrolysis experiment, it was concluded that intact acetanisole is likely transferred to the smoke (Purkis et al., 2011)."

Acetic acid (CAS-No 64-19-7), evaluation by SCENIHR (2016).

"Toxicity

Acetic acid was investigated for the respiratory tract irritation properties. The respiratory response and sensory irritation potential of acetic acid in Swiss Webster mice were investigated. Groups of eight mice were exposed for 30 minutes to eight acetic acid vapor concentrations ranging from 89 to 1730 ppm. Periocular wetness was observed in all animals following acetic acid exposures at 560, 572, 1694, and 1730 ppm. Other clinical signs noted immediately following exposure to 1694 and 1730 ppm were respiratory difficulty, decreased motor activity, and opacities of the eye. The concentration of acetic acid which produced a 50% decrease in respiratory rate (RD50) was determined to be 577 ppm. (http://industrydocuments.library.ucsf.edu/tobacco/docs/trdd0100).

It was found that most of the acetic acid (95.9%) is in mainstream smoke in the intact form. Maximum level in smoke may reach 2160 µg. Two other compounds have been identified as being formed during pyrolysis: acetic acid anhydride (4%; max level in smoke- 90 µg and ethanol (0.1%; max level in smoke 2 µg) (Baker and Bishop, 2004). In another study, 100% of acetic acid was transferred to the mainstream smoke (Purkis et al. 2011). Thus, it does not form substances that may have CMR properties in the concentrations found in any of the products concerned (cigarettes/RYO).

Characterising flavor

It is added to tobacco during the manufacturing of cigarettes in order to give cigarettes a distinct taste and smell and thus may contribute to attractiveness."

Ammonium compounds (several CAS-No), evaluation by SCENIHR (2016).

"In the Netherlands, ammonium compounds are rarely added. Ammonium Phosphate is used in the highest concentrations, with 13 counts in NL ingredient lists, 5 in NTM, total number of brands 4265, average (weight %) 0.068 (0.056). Nevertheless, ammonia is transferred to smoke from the ammonium compounds naturally present in tobacco.

Regarding characterising flavour, ammonium compounds react with sugars during tobacco processing and smoking to form flavour compounds that have flavour-enhancing effects, such as deoxyfructosazine compounds, e.g. pyrazines, pyridines and pyrroles. Furthermore, DAP reacts with carbonyl compounds, such as formaldehyde and acetaldehyde in smoke, to reduce the harshness and irritation of cigarette smoking. More data are needed on the amount of ammonium compound that impart a noticeable flavour.

Regarding characterising flavour, there are some studies indicating that ammonium compounds increase the pH of the smoke which would consequently increase the amount of uncharged, or free, nicotine. Because the free base form is better absorbed, it has been hypothesised that it may result in faster and increased absorption of nicotine. However, results are inconclusive, and more research is needed to better understand the role that ammonium compounds play in nicotine transfer to tobacco smoke.

Regarding toxicity, ammonia is the major pyrolysis product generated from ammonium compounds during cigarette smoking. The critical effect of ammonia is irritation of the eyes, skin and upper respiratory tract. A risk assessment procedure using a Margin of Exposure (MOE) analysis concluded that a risk of effects on the respiratory tract epithelium due to ammonia could not be excluded. No thorough assessment on systemic effects was done. These conclusions were, however, based on ammonia levels in smoke that might also result from precursors in natural tobacco. More research in this area is needed."

Benzaldehyde (CAS-No 100-52-7), evaluation by SCENIHR (2016).

"Regarding characterising flavour, benzaldehyde is one of several other aldehydes present in cigarette tobacco and cigarette smoke. Benzaldehyde is a known flavouring agent for food and is added to tobacco products for flavouring. More data are needed on the amount of benzaldehyde that imparts a noticeable flavour.

To perform a risk evaluation, it is necessary to know the exposure level of benzaldehyde through cigarette smoking. Therefore, research is needed to determine the amount of benzaldehyde in mainstream cigarette smoke. Because only limited toxicological inhalation data on benzaldehyde are available, it is unclear what health effects to expect after exposure to benzaldehyde from cigarette smoke. Such experiments should be carried out, with a particular focus on the effects on the respiratory tract and CNS.

It is unclear if toxic combustion products of benzaldehyde are formed upon smoking a cigarette. Pyrolysis experiments performed by the tobacco industry indicate that benzaldehyde transfers largely intact into the smoke, with some formation of benzoic acid. Additional pyrolysis experiments are recommended."

Benzoic acid (CAS-No 65-85-0) and **sodium benzoate** (CAS-No 532-32-1), evaluation by SCENIHR (2016).

"Benzoic acid and sodium benzoate should be considered as one group, using benzoic acid as the representative one. They pose no safety concerns per se, but it was reported that benzene, phenol and styrene can be formed following thermal decomposition. Because these are CMR compounds, data on pyrolysis related to benzoic acid as representative of the two are needed to carry out a proper evaluation."

Addendum by WP9: Benzoic acid has been classified according to CLP 1272/2008 EC as STOT RE 1 with target organ lung. This compound should be assessed with priority.

Benzyl alcohol (CAS-No 100-51-6), evaluation by SCENIHR (2016).

"Benzyl alcohol is on the list of fragrance allergens designated by the EU. It is considered harmful by inhalation: vapors may cause drowsiness, dizziness, respiratory irritation and irritation to eyes, nose and throat. Moreover, it is a local anaesthetic and could facilitate tobacco smoke inhalation. When heated to decomposition, it emits acrid smoke and fumes."

Butyric acid (CAS-No 107-92-6), evaluation by SCENIHR (2016).

"It does not lead to the formation of compounds, which may have CMR properties in any of the products (cigarettes/RYO) to a significant or measurable degree. During combustion, most of the compound (97.5 %) is not transformed. The maximum level in smoke is 54 µg. Two other unidentified substances were found at 2.5 % (maximum level in smoke 1.4 µg) (Baker and Bishop, 2004)."

"It is added to tobacco during the manufacturing of cigarettes in order to give cigarettes a distinct taste and smell and thus may contribute to attractiveness. Its minimum detectable threshold level (flavour potency) was established as 240 ppb (Kalianos, 1976)."

Caramel colours (CAS-No 8028-89-5), evaluation by SCENIHR (2016).

"The rational for inclusion is similar to the one related to natural extracts being a poorly characterised mixture of several to hundreds of chemicals; the composition is further dependent upon variable factors such as preparation methods. Although generally recognised as safe as food additives and flavours, this classification is not valid for their inhalation effects and pyrolysis products in tobacco smoke. The combustion/pyrolysis chemistry of caramel colours is still not well known in terms of their physiological, toxicological and synergistic additive effects to potentiate the harmful effects of tobacco smoke.

However, the pyrolysis of sugars (major component of caramel colours), was well reported. Upon combustion/pyrolysis at temperatures (up to 900°C) attained during smoking, these compounds, especially the carbohydrates, will give rise to a complex mixture of toxic, carcinogenic, mutagenic compounds, besides aroma/flavour compounds. Compounds formed include smoothing agents (e.g. organic acids), flavours (e.g. caramel), facilitating nicotine delivery (e.g. aldehydes) and with CMR properties (e.g. PAHs, formaldehyde). The complex mixtures used as additives are a cause of concern and could contribute to CMR properties, addictiveness and characterising flavour of tobacco smoke. Therefore, it is important to acquire more data on the exact composition of each of the undefined complex additives in unburnt and burnt forms."

Cellulose (several CAS-No), evaluation by SCENIHR (2016).

"Cellulose is used to prepare both the cigarette paper that wraps the tobacco and the filter (both the inner and outer layers). The cigarette paper is an important part of a cigarette. It controls how the tobacco burns and the amount of smoke. Generally, the more cellulose used, the greater the amount of smoke that is produced.

Reconstituted tobacco is made up of mashed tobacco stems and other parts of the tobacco leaf that would otherwise be discarded. Cellulose fibres are added to help bind and fill this reconstituted tobacco in cigarettes.

Cellulose does not transfer intact to the mainstream smoke, but undergoes extensive pyrolysis. Nearly 100 volatile products were reported from pyrolysis of cellulose. A complex mixture of toxic and carcinogenic compounds such as polycyclic aromatic hydrocarbons including benzo[a]pyrene, phenols, benzene, toluene, naphthalene, catechol, furan and furan derivatives, volatile aldehydes and levoglucosan, formaldehyde, acetaldehyde, acetone and acrolein were identified.

Formaldehyde, acetaldehyde, and acrolein are well-known upper respiratory tract and eye irritants. Aldehydes such as acetaldehyde, besides being toxic, are also reported to potentiate the effect of nicotine addiction. The generation of harman as a condensation product of acetaldehyde and biogenic amines may be responsible for the observed reinforcing effect of acetaldehyde.

In conclusion, the generation of carcinogenic and toxic compounds upon pyrolysis is well established. Further research to ascertain the composition of flavour compounds and pro-addictive compounds (e.g. aldehydes) formed and their interaction with tobacco/smoke chemicals and their effect on MAO would be useful to ascertain the level of influence of this additive alone or in synergy on the addictiveness and palatability of the product."

Ethyl butyrate (CAS-No 105-54-4), evaluation by SCENIHR (2016).

"Typically used as fragrance in amounts of 0.005-0.01 weight % (Monographs on Fragrance Raw Materials, 2013). Even more than this amount of ethylbutyrate is generally added to tobacco products. Ethylbutyrate may impart a noticeable flavour other than tobacco."

Ethyl maltol (CAS-No 4940-11-8), evaluation by SCENIHR (2016).

"Ethyl maltol was evaluated by the JECFA (1974). Given the use as a food additive, the focus was on oral exposure. Short-term studies in rat and dog indicated no abnormalities upon repeated oral exposure (90 days). A long-term exposure study in rat also did not indicate any treatment-related effect reference. Results of a one-generation study did not reveal effects on parental animals or offspring (JECFA (1974)."

"Tobacco smoke from test cigarettes containing ethyl maltol and additive-free reference cigarettes were tested in 90-day nose only inhalation studies with rats. In these studies, the biological activity of the smoke was not altered by adding ethyl maltol (Vanscheeuwijck et al., 2002; Renne et al., 2006).

No other information was found regarding relevant studies on inhalation exposure. Intact transfer rates of close to 100 % have been reported from pyrolysis studies (Baker and Bishop, 2004)."

4-hydroxy-2,5-dimethyl-3(2H)-furanone (CAS-No 3658-77-3), evaluation by SCENIHR (2016).

"4-hydroxy-2,5-dimethyl-3(2H)-furanone was evaluated by the JECFA (2005). Given the use as a food additive, the focus was on oral exposure: Genotoxicity was observed for this furan, though this was considered to be an effect caused by high dose and related to a mechanism involving reactive oxygen species, rather than the generation of a reactive metabolite, such as an epoxide. 4-Hydroxy-2,5-dimethyl-3(2H)-furanone (No 1446) showed no carcinogenicity in a 2-year study in which rats were given a dose of up to 400 mg/kg bw per day. For 4-hydroxy-2,5-dimethyl-3(2H)-furanone, the NOEL of 200 mg/kg bw/d from a 2-year dietary study in rats is >2300 times the estimated daily per capita intake of this agent from its use as a flavouring agent in Europe or the USA. The Committee, therefore, concluded that the safety of this agent would not be a concern at the estimated current intake. This was recently confirmed by EFSA (2015).

No other international reviews were found (i.e., IPSC, US EPA, HC, etc.), including studies on inhalation exposure.

Tobacco smoke from test cigarettes containing 4-hydroxy-2,5-dimethyl-3(2H)-furanone I and additive-free reference cigarettes were tested in 90-day nose-only inhalation studies with rats. In these studies, the biological activity of the smoke was not altered by adding ethyl maltol (Vanschreeuwijck et al., 2002; Renne et al. 2006).

A pyrolysis study investigated the composition of the pyrolysate and reported 70.1 % acetic acid, 25.4 % acetic anhydride, 1.8 % acetol acetate, and 0.4 % benzaldehyde (Baker and Bishop, 2004)."

Lactic acid (CAS-No 50-21-5), evaluation by SCENIHR (2016).

"Lactic acid is a natural, functional metabolite in mammals and serves as mammalian fuel. According to the "lactate shuttle" concept, it represents a major means of distributing carbohydrate potential energy for oxidation and gluconeogenesis.

According to OECD Report and JEFCA Report on lactic acid, it does not present a hazard for human health based on its low hazard profile (https://hpvchemicals.oecd.org/UI/handler.axd?id=fd79fce6-c7e2-48ed-aead-8728c961980c)

After combustion, lactic acid is found in mainstream smoke mostly in the intact form (83.2 %; maximum level in smoke – 5200 µg); other products of its pyrolysis that were found are: methylmaleic anhydride (3.7 %; maximum level in smoke 230 µg) and 2 lactides (13.1 %-810 µg) (Baker and Bishop, 2004; Baker et al., 2004). Thus, it does not form substances that may have CMR properties in the concentrations found in any of the products concerned (cigarettes/RYO)."

Piperonal (CAS-No 120-57-0), evaluation by SCENIHR (2016).

"Regarding attractiveness, piperonal is one of several aldehydes present in cigarette tobacco and cigarette smoke. Piperonal is a known flavouring agent for food and beverages and is added to tobacco products for flavouring. More data are needed on the amount of piperonal that imparts a noticeable flavour.

Regarding addictiveness, there are some studies indicating that piperonal has psychoactive effects, such as anxiety reduction. It is, therefore, suggested to perform fMRI studies on smokers and non-smokers, including adolescents who are exposed to piperonal, to study its effects on the brain.

To perform a toxicity risk evaluation, it is necessary to know the exposure level of piperonal through cigarette smoking. Therefore, research is needed to determine the amount of piperonal in mainstream cigarette smoke.

Because toxicological inhalation data on piperonal are missing, it is unclear what health effects are expected after exposure to piperonal from cigarette smoke. Such experiments should be carried out, particularly on the effects on CNS, irritation and sensitisation, as such effects were reported to occur.

It is unclear if toxic combustion products of piperonal are formed upon smoking a cigarette. Pyrolysis experiments performed by the tobacco industry indicate that piperonal transfers almost intact into the smoke, with some formation of methoxybenzoic acid. More studies on the combustion process of piperonal during smoking are needed."

Potassium citrate (CAS-No 866-84-2), evaluation by SCENIHR (2016).

"Toxicity

From information published on Toxnet Hazardous Substance Data Bank (http://toxnet.nlm.nih.gov), it is concluded the following for potassium citrate:

Inhalation: May cause mild – or no - irritation to the respiratory tract.

Ingestion: No adverse effects expected.

Skin Contact: May cause mild – or no - irritation and redness.

Eye Contact: Potassium citrate may cause mild irritation, possible reddening.

Chronic Exposure: No adverse health effects expected.

Aggravation of Pre-existing Conditions: No adverse health effects expected."

"Characterising flavour

Potassium citrate is added to the wrapper of the tobacco column to control puff number and ash appearance, and thus may contribute to attractiveness."

Potassium sorbate (CAS-No 590-00-1), evaluation by SCENIHR (2016).

"In all in vitro and in vivo tests, no signs of genotoxicity were detected (Münzner et al., 1990, Mpountoukas et al., 2008).

As reported in Toxnet (May 2015): Can cause eye irritation.

At simulated tobacco burning temperatures up to 1000°C, neat potassium sorbate completely pyrolyzed to form aromatic ring materials including benzene, toluene, propyltoluene, xylene, methylxylene, styrene, phenol and butanone. Biological studies indicated that there were no relevant differences in the genotoxic or cytotoxic potential of either mainstream smoke from cigarettes with or without added potassium sorbate. Rats exposed to mainstream cigarette smoke developed respiratory tract changes consistent with those seen in previous smoke inhalation studies, with no relevant histopathological differences between the control and the potassium sorbate test cigarette groups. These studies demonstrated that high levels of potassium sorbate could alter the burning rate of the tobacco leading to alteration in the smoke chemistry profile. Yet, based on the panel of biological endpoints monitored, it appeared that added potassium sorbate produced little relevant change in the overall toxicity profile of smoke (Gaworski et al., 2008)."

Prune juice extract (CAS-No 90082-87-4), evaluation by SCENIHR (2016).

Pyrolysis of sugars leads to formation of a number of CMR substances.

Rum (CAS-No 91450-09-8), evaluation by SCENIHR (2016).

"Natural/botanical concentrates/extracts/resins (e.g. from several fruits - fig, plum, raisins, fenugreek, carob, cocoa, caramel, **rum**, etc.) form a large number of tobacco additives. They are poorly characterised complexes of several to hundreds of chemicals; the composition further depends upon variable factors influencing botanical source and preparation methods. Although generally recognised as safe as food additives and flavours, this classification is not valid for their inhalation effects and pyrolysis products in tobacco smoke. The combustion/pyrolysis chemistry of each of these additives is not well known in terms of their physiological, toxicological and synergistic additive effects to potentiate the harmful effects of tobacco smoke.

However, many of the botanical extracts have a rich carbohydrate/sugar content together with varying amounts of proteins, amino acids and other flavour compounds. The pyrolysis of this class of compounds has been well reported Upon combustion/pyrolysis at temperatures (up to 900°C) attained during smoking, these compounds, especially the carbohydrates, give rise to a complex mixture of toxic, carcinogenic and mutagenic compounds, as well as aroma/flavour compounds. Compounds formed include smoothing agents (e.g. organic acids), flavours (e.g. caramel), facilitating nicotine delivery (e.g. aldehydes) and with CMR properties (e.g. PAHs, formaldehyde). Moreover, pyrazines are important flavour impact compounds that are formed under pyrolytic conditions via reactions between amines and carbonyl compounds, generally sugars. Several pyrazines are also added as additives to cigarettes to impart flavour to low tar cigarette (Alpert et al., 2016). For more details, see plum extract, fenugreek, sugars and cellulose.

The complex mixtures used as additives cause tremendous harm and contribute to CMR properties, addictiveness and attractiveness of tobacco smoke. Therefore, it is important to collect more data on the exact composition of every undefined complex additive in unburnt and burnt forms.

It was not possible to prioritise among the natural extracts, because the information available for each of them is scant, and hampered by their unknown and complex composition."

Sugars (several CAS-No), evaluation by SCENIHR (2016).

Update provided by WP9 experts regarding addictiveness:

Recent studies have reported that sugar content is positively correlated with increase of aldehydes (Talhout et al., 2006). The link between inhibition of monoamine oxidase (MAO) by aldehydes and an increase in addictiveness of nicotine has been demonstrated clearly in previous studies (Guilhem et al., 2006; Villegier et al., 2006). Although sugar additives do not necessarily lead to a production of acetaldehyde, other aldehydes could be produced that might be even more active inhibitors of MAO. As demonstrated in Deliverable WP9-D9.3 (Report on the peer review of the enhanced reporting information on priority additives), sorbitol leads to a significant increase of formaldehyde.

Original information from SCENIHR:

"Many types of sugars are added, rather frequently and in relatively high amounts. Sugars are added as flavour or casing to tobacco (invert sugar is used most abundantly, with 767 counts in NL ingredient lists, none in NTM, total number of brands 4265), average (weight %) 2.734 (3.990).

Regarding attractiveness, the addition of sugars to tobacco was suggested to increase attractiveness by reducing the harshness of tobacco smoke caused by volatile basic components, such as ammonia, nicotine and other tobacco alkaloids. This is because upon cigarette smoking, sugars produce acids that reduce the pH of the inhaled smoke. In addition, 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. More data are needed on the amount of sugars that impart a noticeable characterising flavour.

Regarding addictiveness data are inconclusive. Sugars in tobacco may act proaddictively, because their combustion products such as acetaldehyde and formaldehyde have been suspected of increasing the addictive effect of nicotine. There are some studies indicating that sugars do not contribute to the production of acetaldehyde in mainstream smoke, on a weight-by-weight basis, greater than the overall formation of acetaldehyde from natural tobacco polysaccharides, including cellulose, which are the primary precursor of acetaldehyde in mainstream smoke (Cahours et al., 2012). However, other studies performed in cigarettes with one type of tobacco showed that sugar content is positively correlated with the quantity of aldehydes produced. More research into the pro-addictive effects of sugars is warranted.

Regarding toxicity, 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. Many pyrolysis products including organic acids, acetaldehyde (irritant and possible carcinogen), acrolein (irritant), 2-furfural see section on furfural), acrylamide, and (carcinogenic) polyaromatic hydrocarbons (PAHs) were reported. Mainstream cigarette smoke with and without various levels of sugars was investigated in in vitro cytotoxicity and genotoxicity assays, in vivo inhalation toxicity studies with primary emphasis on irritative changes in the respiratory tract, and in dermal tumorigenicity studies. They did not show a significant increase of the parameters studied as marker of toxicity, but all of those studies had severe methodological and interpretation limitations (Roemer et al., 2012).

Further research is needed to confirm the effects of combustion products of sugars, especially because they are possible or known carcinogenic compounds.

Finally and importantly, sugars and/or their combustion products are among the thousands of compounds contained in cigarette smoke, thus additive effects or reactions with other compounds are likely to occur."

Gamma-Valerolactone (CAS-No 108-29-2), evaluation by SCENIHR (2016).

"It is a weak-flavoured chemical found in products such as Virginia tobacco, cocoa, coffee, honey, peaches and wheat bread. The odour is often described as sweet, hay-like, coumarinic and coconut."

Vanillin (CAS-No 121-33-5), evaluation by SCENIHR (2016).

"Cigarette companies report using vanilla bean extract, vanillin and ethyl vanillin. Natural vanilla is a complex extract and expensive. Thus, synthetic vanilla flavour substances, vanillin and ethyl vanillin are used to reduce costs. Vanillin is one of the most universally accepted popular aromatic chemicals. Thermal decomposition or burning may release carbon monoxide or other hazardous gases, acrid smoke and irritating fumes. Vanilla flavour is one of the most popular flavours worldwide and is used to enhance the organoleptic properties (pertaining to taste, colour, odour, and touch, involving use of the sense organs) of tobacco smoke, to make the product more attractive to consumers, thereby, promoting and sustaining tobacco use, especially by young people and firsttime users.

At low application levels, vanilla, the synthetic vanillin and ethyl vanillin are known to interact with other flavours and potentiate their effect, for example chocolate. Therefore, additional data is required to ascertain the effect of low vanillin levels and its interaction with other flavours on palatability and inhalation of smoke/nicotine.”

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