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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
Office of Science

## MEMORANDUM

Date: July 17, 2017

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Subject: Review of Saccharides as Tobacco Ingredients: Effects on Smoke Chemistry

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## 1. Background

Saccharides, particularly sugars, are natural tobacco constituents, and also are frequently added to tobacco during the manufacturing processes [1]. There are a number of publications that address the effects of sugars contained in cigarettes, however two opposing arguments exist. The tobacco industry funded studies found that added sugars do not increase the toxicity of the cigarettes [2, 3], whereas other studies have shown that sugars have a negative health impact on smokers [1, 4].

During the chemistry review of SE Reports for cigarettes, questions have been raised regarding the different levels of added sugars or sugar-containing ingredients found in the new and predicate products including the following:

- What are the possible effects of sugars on smoke chemistry?
- How do sugars mitigate the harshness of cigarette smoke?
- What smoke data should be required for SE determination of new products?

The Center for Tobacco Products, Division of Product Science has developed general SE review policies regarding these issues in the Chemistry Reviewer's Guide. This memo attempts to provide a comprehensive literature review and some additional recommendations related to certain specific scenarios. This memo only focuses on the chemical studies and does not address the toxicological studies in the literature.

## 2. Methods

We first conducted searches on literature databases using SciFinder and ScienceDirect. We used keywords such as "smoke chemistry" AND "sugar", "smoke chemistry" AND "saccharide", "sugar as tobacco ingredients" AND "effect", "pyrolysis of tobacco ingredients" AND "sugar", "pyrolysis of tobacco ingredients" AND "saccharide". These searches yielded a total of 145 results (after applying the English Language filter to the SciFinder search results). We also conducted a literature search in Google Scholar using keywords "smoke chemistry" AND "sugar" which yielded 212 results. We combined all the results, and then excluded the redundant articles, articles written in non-English languages, patents, and conference presentations. During the course of this review, more articles were discovered through the reference citations contained in the articles identified from the literature database searches. Eventually, 48 full-text articles contained relevant information and are reviewed in this memo (see the Reference List).

## 3. Results

### 3.1 Carbohydrates in tobacco products

#### 3.1.1 Carbohydrates as natural tobacco components

Tobacco contains a variety of carbohydrates which can account for more than 30% of tobacco weight [5] in the blended cigarettes. Carbohydrates exist in tobacco mainly in the forms of polysaccharides such as cellulose (~ 10%), pectin (6-12%), and starch as well as mono- or disaccharides (soluble sugars) such as fructose, glucose, and sucrose.[1]

Sugars in tobacco are formed via enzymatic hydrolysis of starch that begins in the early stage of the curing process. Air-curing of burley tobacco is performed by naturally drying the leaves at ambient temperature. The air-curing process is slow during which sugars are largely enzymatically metabolized resulting in very low sugar content. In contrast, during flue-curing and sun-curing, especially flue-curing, higher temperatures rapidly inactivate the sugar metabolism, but allow the degradation of starch to increase the sugar content. Sugar levels in flue-cured Virginia (8-30%), sun-cured Oriental (Turkish) (10-20%), and air-cured Burley (<0.2%) have been reported [5, 6]. Starch levels in flue-cured tobacco (5.5%) and air-cured tobacco (near zero) have been reported [5].

### 3.1.2 Carbohydrates as added ingredients

A typical American blended cigarette contains approximately 25-35% of both flue-cured and air-cured tobaccos, 3-15% of Oriental tobacco, and smaller amounts of other tobaccos [6]. Flue-cured and Oriental tobaccos yield mild smoke and have a low smoke pH (5.8-6.2), while burley tobacco yields strong, harsh smoke and have a high smoke pH (7.2-8.0) [7]. Tobacco manufacturers have been adding various mixtures of sugars, licorice, and cocoa, typically in the form of casings,[2] to burley tobacco to enhance the sensory quality of smoke for over 100 years [8]. Talhout et al. [1] reported that up to 13% (w/w) of sugars and sweeteners are intentionally added to tobacco. However, industry tobacco researchers [2, 9] reported that no more than 5% of sugars are applied to American-blend cigarettes. Although sucrose (table sugar) and invert sugar (the hydrolysis product of sucrose, mainly glucose/fructose mixture) are the most widely used casing materials [2], tobacco manufacturers have used a variety of other sugar-containing ingredients such as glucose, fructose, brown sugar, honey, corn syrup, molasses, and fruit juices or extracts [1].

Polysaccharides are also added to other components of a tobacco product. For example, cellulose and its derivatives have been used as binders in reconstituted tobacco, which is a common component in modern commercial cigarette [3, 10]. Cigarette paper contains cellulose fiber as the principal ingredient. The development of Fire Standard Compliant (FSC) cigarette paper has led to the use of various polysaccharides as banding materials (e.g., alginate, cellulose, starch, guar gum, carrageenan, pectin) in the manufacturing of banded cigarette paper [11]. The effect of banded paper is discussed in a separate review.[3]

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[1] Sugars can be divided into reducing sugars and non-reducing sugars. Reducing sugars are those that can tautomerize and isomerize upon dissolution in water. All monosaccharides (e.g., glucose and fructose) are reducing sugars, whereas sucrose is not.

[2] According to the tobacco manufacturers (see reference No. 8), casing flavors are applied early in the manufacturing process to the precut tobacco. Casing ingredients are substances used to enhance the tobacco product sensory quality by balancing sensory attributes and developing certain required taste and flavor characteristics. On the other hands, top flavors (or flavorings), are substances used to impart a specific taste and flavor in a tobacco product. They are applied to the cut and processed tobacco after the final drying and prior to cigarette manufacture, usually in parts per million (ppm) quantities in a complex mixture in solution. Top flavors (flavorings) give the tobacco brand its unique sensory characteristics.

[3] See DPS memo by John Gong and Thomas Eads. Summary of Literature on Fire Standard Compliant (FSC) Cigarette Paper. Dated 5/13/2016.

Recently, FDA's deeming rule expanded its regulatory authority over all tobacco products, including pipe tobacco, cigar tobacco, e-cigarettes, and waterpipe tobacco. Waterpipe tobacco has been reported to contain 30% tobacco and 70% honey or molasses [12]. Cigar tobacco is generally comprised of air-cured and fermented tobacco, containing very low natural sugars [13]. However, detailed information about the tobacco blend or ingredients used in these newly deemed products are limited.

### 3.2 Analytical-pyrolytic studies of individual saccharide ingredients

Two categories of experiments have been conducted to investigate the identity of the compounds formed during the combustion of a tobacco ingredient:

1. Pyrolysis of single saccharide ingredients and simple mixtures and subsequent analysis of the pyrolysis products
2. Cigarettes that contain a specific amount of saccharide ingredients and subsequent analysis of smoke constituents

Pyrolysis is the breakdown of larger molecules to smaller ones caused by heat, sometimes in the presence of reactive gases such as oxygen. Pyrolysis product profiles of saccharides depend on experimental conditions, particularly temperature, residence time and the presence of other substances. If the experimental conditions are reasonably similar to a burning cigarette, pyrolysis studies may provide information about the possible products formed during smoking, the thermal stability of the ingredients, and the temperature at which pyrolysis products are formed [14]. A number of pyrolysis products of various saccharides have been identified since the mid-1950s and has been the subject of several reviews [1, 15-18]. Below is a brief summary of the major findings from the studies conducted before the mid-2000s and reviewed by various authors.

- Pyrolysis products from glucose, fructose, and sucrose include, but are not limited to, furans (e.g., furfural and 5-hydroxymethylfurfural), acids (e.g., formic and acetic acid), levoglucosan, aliphatic aldehydes (e.g., formaldehyde, acrolein, and acetaldehyde), and aromatic hydrocarbons (e.g, benzene).
- Polysaccharides and simple sugars form similar pyrolysis products, but in different yields. Compared to cellulose, simple sugars seem to generate more formaldehyde, but less acetaldehyde, acetone, and acrolein [1, 18]. However, it is difficult to estimate the difference in total yields of pyrolysis products of simple sugars versus polysaccharides.
- The presence of oxygen in the pyrolysis atmosphere increases the formaldehyde from cellulose, and reduces the yield from sucrose and fructose [19].
- Polycyclic aromatic hydrocarbons (PAHs) are formed at temperatures higher than 650$^{o}$C from various carbohydrates, but not at lower than 460$^{o}$C [1].
- A large variety of products, including aldehydes, ketones, acids, pyrazines, and pyridines are formed from the Amadori reactions between sugars and amino acids [1].

In the 2000s, British American Tobacco (BAT) published a series of studies of single-substance ingredients to assess the pyrolysis products, particularly those having biological activities simulated from a burning cigarette [19-21]. These studies were not included in the aforementioned review articles; therefore, we will provide a brief summary below.

Baker & Bishop [20] studied 159 tobacco ingredients, including monosaccharides (fructose and glucose), disaccharides (brown, white, and invert sugars), caramel, honey, corn and maple syrups, molasses, fruit juices or extracts, and polysaccharides (cellulose fiber, gums, pectin, and starch). The pyrolysis conditions in this study included a flowing atmosphere of 9% oxygen in nitrogen, and heating programs (i.e., temperatures and durations) simulating both the inter-puff smolder period and cigarette-burning zone during a puff. The pyrolytic products were detected using a capillary GC-MS. Several examples of the commonly used carbohydrates are shown in Table 1. Furfural and low molecular weight acids (acetic acid or formic acid) are the most frequently detected and most abundant pyrolysis products. Benzene and toluene are formed from cellulose and white sugar. Based on several assumptions (e.g., unfiltered cigarette and 100% transfer of the pyrolysis products to mainstream smoke), the authors calculated the maximum amount[4] of each pyrolysis product in cigarette mainstream smoke when the ingredient was added to a cigarette at the maximum application level. Surprisingly, formaldehyde, acrolein, and acetaldehyde, were not reported as pyrolysis products in this particular study.

**Table 1**. Most abundant pyrolysis products of some carbohydrates found in tobacco products

| **Ingredient** | **Maximum application level* (ppm)** | **Composition of pyrolysate (Compound, %)** | **Relative Abundance (%)** | **Maximum smoke level from the ingredient (µg/cig)** |
|---|---|---|---|---|
| Cellulose fiber | 17000 | Hydroxymethylfurfural | 9.9 | 840 |
| | | Acetol | 7.6 | 650 |
| | | Methyl formate and/or hydroxyacetaldehyde | 6.3 | 540 |
| | | Furfural | 4.8 | 410 |
| | | Methyl pyruvate | 4.3 | 370 |
| | | Benzene | 3.1 | 260 |
| | | Acetic acid + 2-butenal | 2.6 | 220 |
| | | Phenol + methylfuranone + ethyltoluene | 2.1 | 180 |
| | | Toluene | 1.0 | 85 |
| | | Cresol | 0.9 | 77 |
| | | Styrene | 0.7 | 60 |
| Honey | 34000 | Hydroxymethylfurfural + | 28.7 | 4,900 |
| | | Furfural | 24.3 | 4,100 |
| | | Acetic acid | 6.3 | 1,100 |
| | | Methylfurfural | 5.6 | 950 |
| | | Methylbenzenediol | 4.1 | 700 |
| | | Toluene | 0.4 | 68 |
| | | Styrene | 0.2 | 34 |
| Starch | 19000 | Hydroxymethylpyranone and/or hydroxymethylfurfural | 52.6 | 5,000 |
| | | Unidentified product | 12.2 | 1,200 |
| | | Levoglucosan | 9.4 | 890 |
| | | Furfural | 3.2 | 300 |
| | | Linoleic acid | 2.9 | 280 |
| Sugar, invert | 62000 | Hydroxymethylfurfural | 40.1 | 12,000 |
| | | Furfural | 34.9 | 11,000 |

[4] The assumptions are not corrected for the water, carbon dioxide, carbon dioxide, or char generated during smoking, therefore, the calculated maximum levels of pyrolysis products in smoke are probably largely over-estimated.

| Ingredient | Maximum application level* (ppm) | Composition of pyrolysate (Compound, %) | Relative Abundance (%) | Maximum smoke level from the ingredient (µg/cig) |
|---|---|---|---|---|
| | | Glycoaldehyde and/or methyl formate | 4.0 | 1,200 |
| | | Acetic acid | 3.0 | 930 |
| | | Pyruvaldehyde | 2.3 | 710 |
| Sugar, white | 25000 | Hydroxymethylfurfurole | 40.0 | 5,000 |
| | | Furfural | 32.3 | 4,000 |
| | | Methylbenzenediol | 2.4 | 300 |
| | | Methyl furfural | 1.9 | 240 |
| | | Glycoaldehyde | 1.8 | 230 |
| | | Phenol | 0.3 | 38 |
| | | Benzene | 0.2 | 25 |
| | | Butanal? | 0.1 | 13 |
| | | 2-Butanone? | 0.1 | 13 |
| | | Cresol | 0.1 | 13 |
| | | Styrene | 0.1 | 13 |
| | | Toluene | 0.1 | 13 |

*Typical maximum level used on BAT products

In a separate study under the conditions of a smoldering cigarette between the puffs, Baker and colleagues [19] investigated 13 saccharides including simple sugars (fructose, glucose, brown sugar, white sugar, cane sugar, and invert sugar), molasses, cellulosic materials (cellulose fiber, hydroxylpropyl cellulose, and carboxymethyl cellulose), gums (acacia and xanthan gum), and starch. The common degradation products detected were $CO_2$, CO, water and methane. Acetic acid and formaldehyde were produced from almost all of the sugars and polysaccharides tested. Acrolein and acetaldehyde were more likely produced from polysaccharides than simple sugars.

Baker and colleagues also found that under smoldering conditions [21], pyrolytic formation of formaldehyde was influenced by other additives (e.g., amino compounds). For example, diammonium hydrogen phosphate (DAP) suppresses the formation of formaldehyde during the pyrolysis of glucose and fructose.

Finally, it is important to point out that pyrolysis of single ingredients does not reflect the complex interactions between ingredients, tobacco, smoke matrix effects under the actual smoking conditions. Furthermore, such studies do not take into consideration cigarette design features (e.g., filter ventilation and paper porosity) which can have a significant impact on smoke delivery. Therefore, caution must be taken when the results from the pyrolysis studies are used to quantitatively estimate the potential impact of changes in the quantities of saccharide ingredients on the yields of harful and potentially harmful constituents (HPHCs).

### 3.3 Effect of saccharide ingredients on mainstream HPHC smoke yields

While pyrolysis studies of individual ingredients under simulated smoking conditions can provide information about the potential compounds formed during cigarette smoking, the more relevant studies for a chemistry review is the cause-effect relationship between the ingredients and HPHC yields measured in mainstream smoke. We found the following five types of studies in the literature:

- Labelled studies

- Studies of experimental cigarettes containing only natural sugars
- Studies of experimental cigarettes containing single sugar additives
- Studies of experimental cigarettes containing casing mixtures
- Market survey studies

**3.3.1. Labelled studies**

Gager and colleagues reported that on average, only 0.5% of unchanged $^{14}$C-D-glucose or $^{14}$C-sucrose labelled-sugars were transferred from tobacco to mainstream smoke under FTC puffing regimen (35 mL puff volume, 2 seconds duration, and 60 second puff interval) due to very low vapor pressure and thermal and oxidative instability of sugars at the temperatures (600-900$^{o}$C) in a burning cigarette [22, 23]. The largest portion (51%-57%) of radioactivity was found in the sidestream smoke. In the gas phase of the mainstream smoke, the majority of radioactivity was in $CO_2$ (~ 3%) and CO (~ 2%), and only less than 0.5% of radioactivity was found in the organic compounds. Similar results were reported by other studies [24, 25].

Gager et al. also reported that acetone and acetaldehyde were among the products formed in highest radiochemical yields (0.05% to 0.1%) in mainstream smoke. The radiochemical yields of acrolein, crotonaldehyde, and benzene were less than 0.01%. However, the Gager et al. study did not report the yield of radioactive formaldehyde from the labelled-sugars.

A review article [26] briefly mentioned other work on the fate of $^{14}$C-labelled polysaccharides (starch, pectin, and cellulose) added to tobacco fillers, which was originally presented at the 1971 Tobacco Chemistry Research Conference. However the details of this study of $^{14}$C-labelled polysaccharides were not available, so we are not able to compare the effects of $^{14}$C-labelled polysaccharides on the composition of mainstream smoke with simple sugars.

**3.3.2 Studies on experimental cigarettes containing only natural sugars**

The second type of study investigates experimental cigarettes with no added sugars, but those that are endogenous or naturally occurring. We found two such studies [27, 28], which reported different results on the relationship between the natural sugar content and smoke aldehyde yields.

Cahours' study [27] investigated 65 experimental cigarettes made with a single tobacco type (either Sun-cured, or air-cured, or flue-cured), but each tobacco type came from several different countries. All cigarettes had the same design characteristics, but different in total natural sugar content (0% in most of the air-cured cigarettes to > 23% in some of the flue-cured cigarettes). The authors found no significant correlation between the total sugar content and acetaldehyde yields in smoke.

The Zilkey et al. study [28] included 25 experimental cigarettes that were blended from several types of bright and burley tobacco with natural reducing sugars in the blend ranging from 0% to 20%. The range of mainstream smoke levels in acetaldehyde, acrolein and total aldehydes was 163–1003 µg/cig, 14–75 µg/cig, and 303–1292 µg/cig, respectively. Analysis of the data from this study by Talhout and colleagues showed significant correlations between the reducing sugar content and the yields of acetaldehyde, acrolein, and total aldehydes with the $r^2$-value of 0.61, 0.59, and 0.64, respectively, in cigarettes without a charcoal filter [1]. Unlike the Cahours study, in which the experimental cigarettes were from different countries, each type of tobacco used in the Zilkey et al. study was grown in a small uniform field. Therefore, the data obtained in the

Zilkey et al. study may be less confounded by other factors that may impact the overall tobacco and smoke composition. This may be the reason why the data from the Zilkey et al. study showed significant associations between the sugar content and acetaldehyde yields, whereas those from the Cahours et al. study did not [1].

### 3.3.3 Studies of experimental cigarettes containing single sugar additives

The third type of study investigated the changes in smoke yields as a result of adding a certain amount of a single sugar additive to control cigarettes, typically containing no additives or ingredients. The test cigarette and control had the same tobacco blend and design features, and the only variable was the sugar or sugar-containing ingredient, found in seven different experimental studies [7, 29-34]. In addition, Roemer et al. [2] conducted a statistical analysis using the data contained in three of the experimental studies. A summary of each of the studies is described below in chronological order.

**Study 1**

In this BAT study [34], burley tobacco was sprayed with concentrated aqueous sugar solutions, dried, and the sprayed tobacco was manufactured into cigarettes with approximately the same weight. The added sugar levels consisted of 10.5% (glucose), 12.8% (fructose), 16.8% (glucose), and 17.8% (glucose + fructose). Control cigarettes were sprayed with equivalent volumes of water and the cigarettes were smoked under the 35 mL volume, 2-s duration, and 60-s interval regimen.

Compared to the control sample, the added sugars had the largest impact on 2-furfural levels, which increased by as much as 70% in cigarettes containing the highest sugar levels. Total carbonyls, volatile carbonyls, volatile acids, and total acids also increased by up to 15% whereas volatile aldehydes decreased by up to 17%. However, no information on the specific names of the analytes and details on the analytical methods were provided. Total nicotine alkaloids decreased by as much as 40%, which exceeds the amount of tobacco replaced by sugars, suggesting that the addition of sugars caused a reduction in nicotine transfer. According to the authors, a possible explanation for this may be that the increased formation of acids from the pyrolysis of sugars could enhance the filtration of nicotine along the tobacco rod. The levels in these measurements appeared to be dose-dependent for glucose. However, correlation between the sugar levels and smoke yields were not reported.

**Study 2**

In this R.J. Reynolds (RJR) study [7], either low-mid stalk burley tobacco (K1) or mid-upper stalk burley tobacco (K2) were cased with increasing amounts of 4%, 8%, 12%, and 16% of fructose, glucose, and sucrose. Non-filtered experimental cigarettes were manufactured using these tobaccos and then smoked under the FTC conditions (35 mL puff volume, 2 seconds duration, and 60 second puff interval). The smoke yields of four carbonyl compounds (formaldehyde, acetaldehyde, acetone, and acrolein) are shown in Table 2.

**Table 2.** Carbonyl (µg/cig) yields as a function of added sugars

| Sample | Formaldehyde | Acetaldehyde | Acetone | Acrolein |
|---|---|---|---|---|
| **CONTROL K1** | 16.0 | 506.7 | 268.9 | 117.5 |
| K1-4 Fructose | 18.2 | 590.7 | 333.0 | 135.4 |

| | | | | |
|---|---|---|---|---|
| K1-8 Fructose | 19.1 | 593.8 | 351.6 | 144.0 |
| K1-12 Fructose | 24.5 | 572.4 | 354.2 | 161.0 |
| K1-16 Fructose | 27.4 | 667.6 | 432.6 | 189.7 |
| K1-4 Glucose | 15.7 | 552.9 | 334.9 | 123.0 |
| K1-8 Glucose | 21.8 | 556.8 | 351.5 | 125.6 |
| K1-12 Glucose | 27.5 | 638.6 | 408.7 | 159.9 |
| K1-16 Glucose | 32.7 | 655.9 | 440.3 | 171.5 |
| K1-4 Sucrose | 20.4 | 574.2 | 364.3 | 138.7 |
| K1-8 Sucrose | 21.6 | 580.2 | 365.4 | 181.7 |
| K1-12 Sucrose | 23.3 | 554.6 | 352.8 | 202.8 |
| K1-16 Sucrose | 28.5 | 575.9 | 387.2 | 245.8 |
| **CONTROL K2** | 11.2 | 577.6 | 306.3 | 117.8 |
| K2-4 Fructose | 12.0 | 652.0 | 330.4 | 130.3 |
| K2-8 Fructose | 21.7 | 690.6 | 339.8 | 138.4 |
| K2-12 Fructose | 20.3 | 637.8 | 344.3 | 141.8 |
| K2-16 Fructose | 27.4 | 799.4 | 415.5 | 177.6 |
| K2-4 Glucose | 18.6 | 567.3 | 216.0 | 93.3 |
| K2-8 Glucose | 19.8 | 635.8 | 249.2 | 103.2 |
| K2-12 Glucose | 20.2 | 783.6 | 427.8 | 160.4 |
| K2-16 Glucose | 20.9 | 717.2 | 395.0 | 146.6 |
| K2-4 Sucrose | 18.2 | 561.0 | 270.2 | 108.6 |
| K2-8 Sucrose | 24.8 | 626.4 | 302.2 | 144.8 |
| K2-12 Sucrose | 27.8 | 612.8 | 339.6 | 179.3 |
| K2-16 Sucrose | 37.4 | 774.4 | 396.3 | 214.9 |

Talhout et al. [1] analyzed the data and found that there were clear correlations between the added sugars and smoke yields of the four carbonyls, especially for formaldehyde and acrolein, with the $r^2$-values for these 2 HPHCs typically greater than 0.9.

Talhout et al. also calculated the absolute increases (µg/cig) of each carbonyl compound in smoke as a function of weight percent of added sugar using the data from the Shelar study. For example, for K1 (low-mid stalk burley), increase per weight percent of added sugar was 0.8–1.2 µg/cig for formaldehyde, 3.3–10.5 µg/cig for acetaldehyde, and 3.8–9.1 µg/cig for acrolein. For K2 (mid-upper stalk burley), increase per weight percent of added sugar was 0.6–1.8 µg/cig for formaldehyde, 13.0–20.5 µg/cig for acetaldehyde, and 3.7–7.9 µg/cig for acrolein. In terms of the relative percent increases in smoke yield as a function of per weight percent of added sugar, formaldehyde had the largest increases (5% to 7.5% for K1 and 5% to 16% for K2 per weight percent of added sugar), and acetaldehyde had the smallest increases (up to 2.1% for K1 and 3.5% for K2). The data suggests that different stalk position of burley tobacco leaf may generate different smoke yields.

The limitations of the study included the analytical methods information, and the data collection of single measurements or the averages of multiple measurements, which the authors did not disclose.

**Study 3**

In the BAT study [29] from the table below, three series of experimental cigarettes (nonventilated filtered) containing various sugar levels were produced in 2003 (series D), 2004 (series E) and 2005 (series F) with identical design features. The authors stated that the tobacco blend used in all cigarettes was a typical American blend; however, the exact blend composition was not described. Thirteen individual ingredients were dissolved in water and added to the blend, resulting in cigarettes containing 2.5–10.5% of the sugar ingredients or 0.8-2.4% of cellulose. The aldehydes in mainstream smoke (under the ISO or more intense conditions) were analyzed in three replicates by an HPLC-UV method after derivatization with 2,4-dinitrophenylhydrazine (DNPH). The coefficient of variations (CV) for both formaldehyde and acrolein was 11%.

The main observations are as follows:

- All sugars, sugar-containing ingredients (honey, molasses, corn syrup, maple syrup), and cellulose, at all inclusion levels examined, increased the yield of formaldehyde in mainstream smoke under the ISO smoking regimen (see Table 3).
- Up to 60% increases in formaldehyde yield were observed at different sugar inclusion levels. Moreover, a combination of white sugar and 0.9% acetic acid caused even larger increases (up to 90%) than white sugar alone.
- Different types of syrup ingredients caused different magnitudes of the increases, probably due to various levels of sugars present in the syrups, the presence of amino compounds (which inhibit the pyrolytic formation of aldehydes) in some of the ingredients (e.g., honey), and the general variability of the analytical methodology.
- Compared to the ISO smoking regimen, the Canadian intense smoking regimen resulted in similar magnitudes of increases in formaldehyde for invert sugar, but less increases for brown sugar.
- The effects on other aldehydes (e.g., acrolein) were varied or generally smaller (less than 16% increases).
- The presence of the saccharides generally had either no statistically significant effect, or produced small decreases in the mainstream smoke yields of TPM and TNCO.

**Table 3.** Formaldehyde yield percent increases (ISO smoking regimen) relative to saccharides added to three series of experimental cigarettes (R.R. Baker, 2006)

| Ingredient (maximum cigarette level, %)* | Series D (2003) | | Series E (2004) | | Series F (2005) | |
|---|---|---|---|---|---|---|
| | Ingredient level (%) | Formaldehyde (%) change | Ingredient level (%) | Formaldehyde (%) change | Ingredient level (%) | Formaldehyde (%) change |
| D-Fructose (0.37) | | | 6.2 | 32 | 7.0 | 34 |
| Glucose (0.15) | | | 6.2 | 34 | 7.0 | 22 |
| Fructose + glucose | | | 4.1 + 4.1 | 61 | | |
| Invert sugar (7.0) | 7.0 | 63 | 8.2 | 56 | 7.0 | 20 |
| White sugar (5.0) | 2.5 | 20 | | | 7.0 | 29 |
| | 5.0 | 30 | | | | |
| | 7.5 | 47 | | | | |
| | 10.5 | 40 | | | | |
| White sugar + 0.9% acetic acid | 5.0 | 37 | | | | |
| | 10.5 | 90 | | | | |
| Brown sugar (5.7) | 6.2 | 53 | 2.1 | 7.3 | 7.0 | 17 |
| | | | 4.2 | 17 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | 6.2 | 27 | | |
| | | | 8.2 | 37 | | |
| Corn syrup (1.8) | | | 6.2 | 41 | 7.0 | 17 |
| Molasses (5.35) | 5.3 | 27 | 2.0 | 4.9 | 7.0 | 19 |
| Sugar cane syrup (1.5) | | | 2.5 | 17 | 7.0 | 24 |
| Maple syrup (6.5) | | | 7.0 | 24 | 7.0 | 8.0 |
| Honey (4.1) | | | 3.1 | 2.4 | 7.0 | 19 |
| Cellulose (2.2) | 0.8 | 20 | | | | |
| | 1.6 | 30 | | | | |
| | 2.4 | 27 | | | | |

* Typical maximum level used on British American Tobacco cigarettes.
** Blank cell means no data.

**Study 4**
This RJR study [33] compared a "reference cigarette" (RC) containing 3% high fructose corn syrup (HFCS) to 2 test cigarettes (TC) containing 4% (TC1) and 5% (TC2) of HFCS, respectively. All cigarettes contained a "standard commercial blend" and HFCS was added in the burley casing. As the added HFCS increased from 3% to 5%, the only statistically significant change in smoke yield (under the FTC smoking regimen) observed was catechol (less than 8%) among the 22 constituents tested (including TNCO, formaldehyde, acetaldehyde, acrolein, B[a]P, and TSNAs). Formaldehyde increased by 21%, from 13.2 to16.0 μg/cig. However, the author stated that such increase was not statistically significant considering the method variability.

Another part of this study was to compare the effects of corn syrup/invert sugar (Control Cigarette 1, RC1) to HFCS at the same application levels of 3%. Two test cigarettes containing the same amount of HFCS were investigated: TC1 processed under the "standard drying condition" of 115.5$^{o}$C and TC2 under a higher temperature at 160 $^{o}$C. Formaldehyde significantly increased by 17%, from 19.5 μg/cig to 22.9 μg/cig in TC1 and by 27% in TC2 (24.8 μg/cig) compared to the control. NNK significantly decreased by 24% in TC2 compared to the control. The result indicated that switching from corn syrup/invert sugar to HFCS and high drying temperature of tobacco blend could increase formaldehyde yields.

A limitation of this publication is the lack of sufficient information (e.g., the method variability and standard deviations of the experimental cigarettes) to allow verification of the statistical comparisons.

**Study 5**
In this German government sponsored study [31], an additive-free commercial tobacco blend consisting of 50% Virginia tobacco, 20% burley tobacco, 20% tobacco stems and 10% Oriental tobacco was used for the experimental cigarettes. Sucrose was added to the tobacco blend at 0% (control), 1.5%, 2.1% and 4.8%.[5] The study involved two kinds of King size, filter-ventilated cigarettes with mainstream smoke "condensate levels" (tar) and filter ventilation levels of 6 mg with 47% and 10 mg with 27%, under the ISO smoking regimen. Smoke analyses were conducted using the Health Canada standard methods. However, no method performance

[5] This study also investigated the effects of glycerol and cocoa in addition to sucrose.

information was provided. Furthermore, the results were presented only as bar graphs with no indication of statistical significance.

Compared to the corresponding control cigarettes, it appears that there were no substantial changes in the yields of TNCO, B[a]P, and acetaldehyde in test cigarettes containing sucrose. The TSNAs were generally reduced. However, the yields of formaldehyde, 1,3-butadiene, and isoprene appeared to increase substantially. It is difficult to determine the magnitude of these increases since the numerical data were not reported.

**Study 6**

Although this was a Philip Morris International (PMI) study [32], all the test cigarettes containing three levels of sucrose (1.6%, 2.1%, and 4.8%) and the control cigarettes were identical to those reported in Study 5 above [31]. Machine smoking was carried out under both the ISO and the Health Canada Intense (HCI) smoking regimens. Analytical methodologies were also the same as those in Study 5. Smoke yields were reported as mean values and standard errors (SE). The yields and percent changes of the HPHCs most relevant to SE review are included in Appendix 1A-1D.

The most consistent changes were an increase in formaldehyde and a decrease in TSNAs. The addition of 4.8% sucrose consistently led to increases of up to 40% in formaldehyde yield (under both the ISO and CI regimens) in both types of test cigarettes. NNN and NNK yields typically decreased up to 30% when sucrose was added in the tobacco.

**Study 7**

This Philip Morris USA study [30] investigated King size experimental filtered cigarettes with 30% ventilation. The tobacco blend, provided in a separate publication [35], contained bright (35%), burley (23%), Oriental (15%), and reconstituted tobacco sheet (27%). Eleven saccharides at different levels were tested, including the commonly used invert sugar, sucrose, honey, molasses, and high fructose corn syrup (HFCS). Analytical methods for smoke constituents were briefly described in the Gaworski et al. paper [35] but not method performance information. The HPHC yields under the ISO smoking regimen were presented as percentage values relative to the control cigarettes. The results for tar and the HPHCs listed on the FDA's abbreviated HPHC list are included in Appendix 2.

Statistically significant increases up to 40% in formaldehyde quantities were observed when cleargum, HFCS, honey, invert sugar, maltodextrin, and sucrose were added. These increases appeared to be somewhat associated with the amount of ingredients added. For example, when sucrose was added at 33 mg (4.7%), 72 mg (10.3%), and 100 mg (14.3%) per cigarette, formaldehyde yields were 106%, 114%, and 140%, respectively, relative to the control cigarette. We noted that compared to several other studies discussed previously, the amount of sugars is much higher when a 40% increase in formaldehyde yield is observed. This is probably because the tobacco blend in this study contained reconstituted tobacco (27%), which could contain DAP [36] that inhibits formaldehyde formation [21]. For acrolein, there were significant increases of up to 23% when sorbitol, HFCS, invert sugar and sucrose were used. For acetaldehyde, only invert sugar at all three inclusion levels of 3.6%, 7.1%, and 14.3%, caused moderate increases of 10-12%. Sucrose at the low inclusion level and D-sorbitol at the high inclusion level caused significant decreases in acetaldehyde. The yields of 4-aminobipheyl, NNN and NNK (especially

NNN) typically decreased compared to the controls, although not all decreases were statistically significant. For other HPHCs (including TNCO), no significant changes were observed for most of the carbohydrate ingredients tested.

**Study 8**

In this PMI study [2], Roemer et al. pooled data from the abovementioned Studies 4, 6, and 7 [21, 30, 32] and conducted a statistical analysis. The authors found significant correlations between the mainstream yields and the sugar inclusion levels for 10 HPHCs. Roemer et al. reported that at the sugar inclusion level of 5%, there was a 25% increase in formaldehyde yield over the control with no added sugar. But only a quarter of the observed variation in formaldehyde yield could be attributed to the sugar addition. Furthermore, six other constituents (acrolein, 2-butanone, isoprene, benzene, toluene, benzo[k]fluoranthene) increased significantly by 7-12%, and three constituents (4-aminobiphenyl, NNN, and N-nitrosodimethylamine) decreased significantly by 12-21% at a sugar inclusion level of 5%.

There are two potential limitations to this data analysis. First, the authors stated that data from three separate studies could be pooled together because of similarities in cigarette construction, smoking condition, and analytical method. However, the authors did not take into consideration tobacco blend differences. For example, the Coggins et al. study (Study 7) used reconstituted tobacco in the test cigarettes, whereas the Roemer et al. (Study 6) study did not. As discussed earlier, reconstituted tobacco could inhibit the formaldehyde formation. Second, the cigarettes tested in three different studies were from three different manufacturers during different time periods. These factors along with differences in cigarette design features and analytical variability due to different labs can also contribute to the variations in this analysis.

### 3.3.4 Studies of experimental cigarettes containing sugar-casing mixtures

In this type of study published by both BAT and PMUSA, sugars were contained in casing mixtures. BAT published three papers on the effects of sugar-containing casing mixtures on smoke chemistry [37-39]. These studies reported that formaldehyde yields significantly increased by up to 73% for casing mixtures (containing over 1% sugars) relative to controls (no casing mixtures). PMUSA has published a similar study that showed a 60-65% increase in formaldehyde yield following the addition of a “group” of ingredients containing 4.2-6.3% corn syrup [40, 41]. However the casing mixtures not only included sugar or sugar-containing ingredients, but also a wide variety of other ingredients (e.g., gums, cellulose, acetic acid, humectants and flavors). It is difficult to attribute the effects to any specific individual ingredient.

### 3.3.5 Market survey studies

Three market survey studies [27, 42, 43] examined the relationships between acetaldehyde yield in smoke and total sugar content in tobacco in various commercial cigarette brands. The Seeman et al. study [42] analyzed hundreds of commercial cigarettes manufactured by PMUSA smoked under the FTC smoking regimen. Despite a large number of brands, no statistically significant correlation between the total reducing sugar content and acetaldehyde or acetaldehyde/tar ratio was observed. The authors concluded that acetaldehyde yield was affected more by cigarette design characteristics (filter ventilation, filtration, and paper porosity) than by reducing sugars. In another study, Cahours et al. [27] examined the European commercial cigarettes ($N = 97$) and found no correlation between total sugar content (fructose + glucose + sucrose) and acetaldehyde yields under the ISO smoking regimen.

In a 1975 market survey study conducted by Imperial Tobacco, Phillpotts et al. analyzed sugar content and the total aldehyde yield in cigarettes from 10 European countries [43]. The study found that for the 40 UK commercial cigarettes, sugar content was unrelated to the total aldehyde yield, although acetaldehyde was related to TPM yield. Seeman et al. [44] reviewed the literature (including this Phillpotts study) and concluded that sugars do not increase the mainstream yield of acetaldehyde than tobacco on a weight-by-weight basis. Structural materials such as cellulosic materials are the main source of acetaldehyde in the mainstream cigarette smoke [44]. However, the data from the Phillpotts study was later re-analyzed by two other groups and different conclusions were reached. A 2008 re-analysis by O'Connor and Hurley showed that sugar content significantly accounted for 23% variability in aldehyde yields, if analysis was limited to filtered cigarettes only [45]. O'Connor and Hurley further pointed out that tobacco industry studies often normalized acetaldehyde yield to tar or TPM, which may obscure a sugar-aldehyde association. However, in 2012, Cahours et al. also re-analyzed the same dataset from the Phillpotts et al. study and concluded that the country and tar level, not the sugar content or a design feature (with or without filter), were significant factors influencing the total volatile aldehyde yields in smoke [27].

A major limitation of these market survey studies is that the effects of a particular ingredient on the HPHC levels are confounded by different product composition and design characteristics. Therefore, results from such studies should be interpreted with caution.

### 3.4 Effect on chemosensory properties

Tallhout et al. [1] reported that the added sugars and other sweeteners give tobacco smoke a "sweet" taste that is attractive to adolescent smokers. However, industry researchers [2, 9] argued that a very small amount of unchanged sugars (about 0.5%) transferred into the mainstream smoke [23] are unlikely to render a sweet sensation, due to the relatively high taste thresholds for sucrose, fructose, and glucose.

Literature seems to suggest that sugars in cigarettes have at least two major effects on the sensory perception. First, acid forming carbohydrates and basic constituents (e.g., ammonia and nicotine) can affect smoke pH, playing an important role on sensory impression [5]. Air-cured burley tobacco, which contains very low sugar content and higher nitrogen, generates smoke that is considerably more alkaline than flue-cured or Oriental tobacco [46]. Higher smoke pH causes the sensory perception of increased "nicotine strength", harshness, and impact.[6] Conversely, many American blend cigarette smokers find the acidic smoke of Virginia blend cigarettes to have "unbalanced" taste. Acids from sugar pyrolysis can neutralize the harsh taste and throat impact of tobacco smoke. Sugars, primarily used as casing ingredients for burley tobacco, are known to "balance" the sensory impact of nicotine [5, 47].

[6] According to Richard R. Baker (Chapter 12. Smoke Chemistry. In Tobacco: Production, Chemistry and Technology, 1999), "impact" is the localized sensation felt momentarily at the back of throat and is highly specific to nicotine; "irritation" is a lingering, harsh sensory property of smoke.

A 1992 RJR study [7] is a good example to illustrate this effect. The study demonstrated that although glucose alone, gave a "chemical offtaste" above 4.0% level, it was the amount of sugar, not the type, that significantly affected smoke pH and nicotine, which decreased with increasing sugar level. For example, when the amount of glucose added to low-mid stalk burley tobacco increased from 0 to 16%, the smoke pH decreased from 7.2 to 6.6. Taste evaluation indicated that throat impact and harshness decreased as the sugar level increased, until a plateau value of ~ 10%. The study concluded that the optimum sugar to nicotine ratio for smoothness of cased burley tobacco was 3.3 to 1.

Second, the combustion/pyrolysis of sugars renders a more agreeable smell of caramel (burnt sugar) flavor that are appealing. Sugars are known to react with natural tobacco nitrogenous compounds via Maillard browning reactions to form a wide variety of flavor compounds (e.g., pyrazines) [47, 48]. Table 4 shows some of the browning reaction products in tobacco and/or smoke and their flavors (such as sweet, nutty, buttery) as reported by Leffingwell [47]. However, quantitative relationships on the sugar content and flavor compounds in smoke, in relation to sensory perception (chemo-sensory study) are not available.

**Table 4**. Types of browning reaction products of sugars and amino acids present in tobacco and/or smoke

| Types of compounds (number of compounds identified) | Smoke Flavor |
|---|---|
| Acids (4) | Pungent, buttery, sweet, Turkish |
| Aldehydes (15) | Pungent, harsh, sweet, nutty, spicy, fruity |
| Ketones (12) | Sweet, fruity, smoothing |
| Furans (11) | Sweet, herbaceous, roasted, oily |
| Pyrans (2) | Sweet, flue-cured like |
| Pyrazines (14) | Buttery, nutty, earthy, burley, dull |
| Pyrroles (7) | Sweet, cheery, hot, peppery |

## 4 Conclusions

The reviewed publications indicate that cigarettes contain both natural and added saccharides. The added saccharides are typically simple sugars (sucrose, fructose, and glucose) or sugar-containing ingredients (e.g., honey, corn syrup, molasses, fruit juices or extracts) used as casing on air-cured tobacco. The effects of added sugars or sugar-containing ingredients on smoke chemistry can be summarized as follows:

- Pyrolysis studies of individual saccharides indicated that numerous volatile and non-volatile compounds including carbonyls (e.g., formaldehyde, acrolein, and acetaldehyde), furans (e.g., furfural), and aromatic hydrocarbons (e.g., benzene, toluene, and B[a]P) could be formed under various conditions.
- Studies of cigarettes containing radio-labelled sugars showed that less than 0.5% of sugars were transferred into mainstream smoke unchanged, and acetaldehyde (0.05-0.06% radioactivity) and benzene (<0.01% radioactivity) were among the pyrolytic products in mainstream smoke.

- Added sugars can cause increases in the mainstream smoke yields of aldehydes (especially formaldehyde), as well as decreases in the yields of NNN, NNK, and 4-ABP. When sugars were the only additives, and added at the typical level of 5% or more in American blended cigarettes, the formaldehyde yield in mainstream smoke could increase by up to 40%, along with increased yields in other HPHCs such as acrolein and benzene.
- Sugars can improve the sensory perception of cigarette smoke by lowering the smoke pH, which in turn, neutralizes the harsh taste and throat impact, and by generating a pleasant smell of caramel.

There has been no detailed information on how sugars influence the smoke chemistry of the newly deemed tobacco products, such as cigar, pipe, and hookah tobacco.

## 5 Recommendations for Chemistry SE Review

In SE Review, a new product is compared to a specific predicate product in terms of product characteristics. Based on the above discussion, it is clear that increased sugar levels can cause higher smoke yields in formaldehyde (and possibly in acrolein and benzene), and decreased sugar levels can cause higher smoke yields in NNN, NNK and 4-ABP. New products often differ from the corresponding predicate product in more than one product characteristics, which can further complicate the smoke chemistry. It is the applicant's responsibility to provide evidence and scientific rationale as to why difference in sugar levels between the new and predicate products do not raise different questions of public health. In general, reviewers should follow the existing policies outlined in the Chemistry Reviewer's Guide regarding the issues related to sugars. Additional recommendations regarding several specific scenarios related to cigarette products include:

- If the sugar level is the only difference between the new and predicate product, and the difference is less than 1% relative to the tobacco filler weight (although this can mean more than 5% between the new and predicate products on a relative basis), it is unlikely that any significant change in HPHC yields will be observed given analytical variability. Therefore, HPHC testing may not be needed.
- If the difference in sugar level exceeds 5% relative to the tobacco filler weight, require mainstream smoke HPHC data as follows;
    - For formaldehyde, acrolein, and benzene, if the new product has higher sugar levels.
    - For NNN, NNK, and 4-ABP, if the new product has lower sugar levels.
- If the difference in sugar level between the new and predicate product is greater than 1% but less than 5% relative to the tobacco filler weight or there is a change in sugar type, smoke data for the above HPHCs may be required in consideration of changes in other product characteristics, such as tobacco blend and design characteristics.

In addition, it is also recommended that Office of Science (OS) conduct research to quantitatively assess the effect of sugar levels in tobacco products on flavor compounds in smoke relative to sensory perception and user behavior. OS should also consider developing appropriate product standards on added sugars in future.

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**Appendix 1A**. HPHC yields in mainstream smoke of the 6 mg cigarettes under the ISO smoking regimen (data from the Roemer et al. 2010 study)

| HPHC | Unit | Control | | Sucrose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1.60% Inclusion | | | 2.10% Inclusion | | | 4.80% Inclusion | | |
| | | Mean | SE | Mean | SE | % Change | M | SE | % Change | Mean | SE | % Change |
| CO | (mg/cig) | 6.45 | 0.11 | 5.5 | 0.17 | -14.7 | 6.24 | 0.13 | -3.3 | 6.39 | 0.03 | -0.9 |
| Nicotine | (mg/cig) | 0.539 | 0.011 | 0.465 | 0.009 | -13.7 | 0.568 | 0.017 | 5.4 | 0.511 | 0.006 | -5.2 |
| 'Tar' | (mg/cig) | 6.48 | 0.09 | 5.68 | 0.14 | -12.3 | 6.63 | 0.18 | 2.3 | 6.48 | 0.17 | 0.0 |
| Formaldehyde | (ug/cig) | 15.5 | 0.4 | 16.3 | 0.3 | 5.2 | 14.3 | 1 | -7.7 | 18.5 | 0.7 | 19.4 |
| Acetaldehyde | (ug/cig) | 315 | 9 | 309 | 15 | -1.9 | 314 | 12 | -0.3 | 318 | 9 | 1.0 |
| Acrolein | (ug/cig) | 30.6 | 1.4 | 31.1 | 2.5 | 1.6 | 29.2 | 1.2 | -4.6 | 30.9 | 1.4 | 1.0 |
| B[a]P | (ng/cig) | 6.16 | 0.14 | 5.94 | 0.05 | -3.6 | 5.65 | 0.18 | -8.3 | 6.57 | 0.14 | 6.7 |
| 1,3-Butadiene | (ug/cig) | 24.8 | 0.5 | 25 | 1.8 | 0.8 | 25.2 | 1.2 | 1.6 | 25.2 | 0.4 | 1.6 |
| Isoprene | (ug/cig) | 194 | 4 | 204 | 12 | 5.2 | 213 | 10 | 9.8 | 202 | 2 | 4.1 |
| Acrylonitrile | (ug/cig) | 5.11 | 0.37 | 5.77 | 0.01 | 12.9 | 5.41 | 0.35 | 5.9 | 5.77 | 0.06 | 12.9 |
| Benzene | (ug/cig) | 26.9 | 0.7 | 27.1 | 0.7 | 0.7 | 26.1 | 0.6 | -3.0 | 27.2 | 0.2 | 1.1 |
| Toluene | (ug/cig) | 42.6 | 1.7 | 43.1 | 0.9 | 1.2 | 41.7 | 1.3 | -2.1 | 43.5 | 0.3 | 2.1 |
| NNN | (ng/cig) | 61.1 | 3.3 | 46.8 | 1.7 | -23.4 | 56.3 | 2.8 | -7.9 | 51.4 | 0.6 | -15.9 |
| NNK | (ng/cig) | 21.1 | 0.8 | 14.7 | 0.6 | -30.3 | 21.5 | 0.5 | 1.9 | 17 | 0.4 | -19.4 |

* Shaded data are statistically significantly different relative to the control

Appendix 1B. HPHC yields in mainstream smoke of the 10 mg cigarettes under the ISO smoking regimen (data from the Roemer et al. 2010 study)

| HPHC | Unit | Control | | Sucrose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1.60% Inclusion | | | 2.10% Inclusion | | | 4.80% Inclusion | | |
| | | Mean | SE | Mean | SE | % Change | Mean | SE | % Change | Mean | SE | % Change |
| CO | (mg/cig) | 9.75 | 0.11 | 8.99 | 0.26 | -7.8 | 9.93 | 0.02 | 1.8 | 10.13 | 0.02 | 3.9 |
| Nicotine | (mg/cig) | 0.873 | 0.02 | 0.811 | 0.02 | -7.1 | 0.899 | 0.013 | 3.0 | 0.836 | 0.011 | -4.2 |
| 'Tar' | (mg/cig) | 11.1 | 0.3 | 10.5 | 0.2 | -5.4 | 11.5 | 0.2 | 3.6 | 11.4 | 0.1 | 2.7 |
| Formaldehyde | (ug/cig) | 24.7 | 1 | 28.7 | 1.1 | 16.2 | 28.1 | 1.2 | 13.8 | 34.6 | 1.5 | 40.1 |
| Acetaldehyde | (ug/cig) | 457 | 8 | 460 | 7 | 0.7 | 501 | 3 | 9.6 | 510 | 7 | 11.6 |
| Acrolein | (ug/cig) | 46.1 | 0.3 | 47.4 | 1.6 | 2.8 | 50.4 | 0.8 | 9.3 | 53.6 | 0.1 | 16.3 |
| B[a]P | (ng/cig) | 9.86 | 0.35 | 9.4 | 0.16 | -4.7 | 9.58 | 0.12 | -2.8 | 11.51 | 0.55 | 16.7 |
| 1,3-Butadiene | (ug/cig) | 34.2 | 1.2 | 33.5 | 0.4 | -2.0 | 37.3 | 0.7 | 9.1 | 38.6 | 1.7 | 12.9 |
| Isoprene | (ug/cig) | 281 | 8 | 271 | 5 | -3.6 | 309 | 5 | 10.0 | 314 | 15 | 11.7 |
| Acrylonitrile | (ug/cig) | 8 | 0.33 | 7.62 | 0.51 | -4.8 | 10.59 | 0.34 | 32.4 | 8.57 | 0.56 | 7.1 |
| Benzene | (ug/cig) | 36.2 | 1.2 | 33.9 | 0.9 | -6.4 | 38.8 | 1 | 7.2 | 38.9 | 2.4 | 7.5 |
| Toluene | (ug/cig) | 57.7 | 2.9 | 55 | 1.1 | -4.7 | 63.9 | 1.7 | 10.7 | 62.9 | 3.1 | 9.0 |
| NNN | (ng/cig) | 87 | 4.9 | 70 | 2.2 | -19.5 | 84.5 | 4 | -2.9 | 63.7 | 2.6 | -26.8 |
| NNK | (ng/cig) | 28.1 | 1.5 | 24.6 | 0.4 | -12.5 | 29.9 | 0.7 | 6.4 | 33.3 | 0 | 18.5 |

* Shaded data are statistically significantly different relative to the control

**Appendix 1C**. HPHC yields in mainstream smoke of the 6 mg cigarettes under the HCI smoking regimen (data from the Roemer et al. 2010 study)

| HPHC | Unit | Control | | Sucrose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1.60% Inclusion | | | 2.10% Inclusion | | | 4.80% Inclusion | | |
| | | Mean | SE | Mean | SE | % Change | Mean | SE | % Change | Mean | SE | % Change |
| CO | (mg/cig) | 26.5 | 1.1 | 23.6 | 0.5 | -10.9 | 22.7 | 1 | -14.3 | 23.1 | 0.2 | -12.8 |
| Nicotine | (mg/cig) | 1.63 | 0.05 | 1.5 | 0.04 | -8.0 | 1.57 | 0.04 | -3.7 | 1.53 | 0.04 | -6.1 |
| 'Tar' | (mg/cig) | 28.7 | 0.9 | 25.8 | 1.6 | -10.1 | 24.4 | 0.8 | -15.0 | 24.3 | 0.4 | -15.3 |
| Formaldehyde | (ug/cig) | 73.2 | 8 | 82.1 | 1.3 | 12.2 | 77 | 3 | 5.2 | 97.8 | 3.3 | 33.6 |
| Acetaldehyde | (ug/cig) | 1131 | 29 | 1011 | 40 | -10.6 | 1057 | 16 | -6.5 | 1064 | 49 | -5.9 |
| Acrolein | (ug/cig) | 119 | 1 | 112 | 3 | -5.9 | 120 | 0 | 0.8 | 124 | 5 | 4.2 |
| B[a]P | (ng/cig) | 19.2 | 0.3 | 15.8 | 0.3 | -17.7 | 17.3 | 0.9 | -9.9 | 19.4 | 0.4 | 1.0 |
| 1,3-Butadiene | (ug/cig) | 83.7 | 3.4 | 77.2 | 2.7 | -7.8 | 83.6 | 1.6 | -0.1 | 76.9 | 3.7 | -8.1 |
| Isoprene | (ug/cig) | 631 | 2 | 581 | 20 | -7.9 | 711 | 39 | 12.7 | 590 | 28 | -6.5 |
| Acrylonitrile | (ug/cig) | 23 | 0.4 | 21.2 | 1.2 | -7.8 | 23.6 | 0.8 | 2.6 | 23.1 | 1.9 | 0.4 |
| Benzene | (ug/cig) | 83.3 | 2.2 | 68.5 | 4.9 | -17.8 | 84.4 | 4.8 | 1.3 | 76.5 | 5.3 | -8.2 |
| Toluene | (ug/cig) | 147 | 4 | 122 | 9 | -17.0 | 159 | 7 | 8.2 | 137 | 8 | -6.8 |

* Shaded data are statistically significantly different relative to the control

**Appendix 1D**. HPHC yields in mainstream smoke of the 10 mg cigarettes under the HCI smoking regimen (data from the Roemer et al. 2010 study)

| HPHC | Unit | Control | | Sucrose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1.60% Inclusion | | | 2.10% Inclusion | | | 4.80% Inclusion | | |
| | | Mean | SE | Mean | SE | % Change | Mean | SE | % Change | Mean | SE | % Change |
| CO | (mg/cig) | 26.4 | 1.8 | 27.6 | 0.5 | 4.5 | 27 | 0.5 | 2.3 | 26.4 | 0.7 | 0.0 |
| Nicotine | (mg/cig) | 1.96 | 0.03 | 1.94 | 0.09 | -1.0 | 1.93 | 0.06 | -1.5 | 1.85 | 0.07 | -5.6 |
| 'Tar' | (mg/cig) | 32.6 | 1 | 33.3 | 2.2 | 2.1 | 32 | 1.3 | -1.8 | 30.8 | 0.3 | -5.5 |
| Formaldehyde | (ug/cig) | 86.9 | 4.3 | 84.8 | 3.2 | -2.4 | 93.3 | 1.7 | 7.4 | 107.9 | 4.6 | 24.2 |
| Acetaldehyde | (ug/cig) | 1169 | 31 | 1167 | 33 | -0.2 | 1246 | 49 | 6.6 | 1075 | 22 | -8.0 |
| Acrolein | (ug/cig) | 130 | 1 | 131 | 4 | 0.8 | 135 | 2 | 3.8 | 123 | 5 | -5.4 |
| B[a]P | (ng/cig) | 22.5 | 0.7 | 19.3 | 0.6 | -14.2 | 20.9 | 1.1 | -7.1 | 21 | 1 | -6.7 |
| 1,3-Butadiene | (ug/cig) | 88.8 | 2.3 | 88.7 | 0.9 | -0.1 | 92.2 | 2.2 | 3.8 | 90.5 | 3 | 1.9 |
| Isoprene | (ug/cig) | 688 | 22 | 670 | 15 | -2.6 | 772 | 7 | 12.2 | 701 | 13 | 1.9 |
| Acrylonitrile | (ug/cig) | 26.3 | 1.6 | 22.9 | 1.4 | -12.9 | 27.5 | 1.4 | 4.6 | 25.3 | 0.8 | -3.8 |
| Benzene | (ug/cig) | 87.8 | 4.2 | 82.8 | 3.6 | -5.7 | 90 | 3.9 | 2.5 | 91.5 | 2.2 | 4.2 |
| Toluene | (ug/cig) | 156 | 6 | 152 | 6 | -2.6 | 162 | 7 | 3.8 | 168 | 7 | 7.7 |
| NNN | (ng/cig) | 181 | 2 | 148 | 8 | -18.2 | 173 | 3 | -4.4 | 140 | 5 | -22.7 |
| NNK | (ng/cig) | 61 | 1.8 | 50.8 | 1.8 | -16.7 | 68.1 | 1.8 | 11.6 | 58.2 | 1.3 | -4.6 |

* Shaded data are statistically significantly different relative to the control

**Appendix 2**. Relative HPHC yields (relative to controls) in cigarettes containing different carbohydrate ingredients (data from the Coggins et al., 2011 study)

| Ingredient name & level (mg/g) | Smoke constituent (% of control cigarette) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tar | Nicotine | CO | 1,3-BD | Isoprene | Formal-dehyde | Acetal-dehyde | Acrolein | o-Toluidine | 4-Amino-biphenyl | Benzene | Toluene | NNN | NNK | B[a]P | Acrylo-nitrile |
| **13-Cyclodextrin** | | | | | | | | | | | | | | | | |
| 25 | 98.7 | 104 | 107 | 100 | 100 | 110 | 100 | 101 | 105 | 97.7 | 91.1 | 90.0 | 91.0 | 85.5 | 100 | 93.8 |
| 50 | 98.5 | 105 | 100 | 96.4 | 92.9 | 115 | 95.3 | 101 | 99.0 | 85.0 | 90.2 | 92.0 | 81.9 | 72.6 | 98.3 | 93.1 |
| **Cleargum** | | | | | | | | | | | | | | | | |
| 23.5 | 100 | 93.5 | 104 | 102 | 94.7 | 126 | 98.4 | 104 | 94.9 | 92.7 | 89.5 | 84.3 | 93.8 | 100 | 104 | 84.2 |
| 47 | 101 | 94.0 | 105 | 89.4 | 89.4 | 138 | 94 | 101 | 96.0 | 92.1 | 88.8 | 90.4 | 90.0 | 97.3 | 103 | 85.6 |
| **D-Sorbitol** | | | | | | | | | | | | | | | | |
| 15 | 100 | 95.1 | 98.5 | 101 | 91.3 | 102 | 94.0 | 97.9 | 96.2 | 94.9 | 89.8 | 87.7 | 88.3 | 87.5 | 96.3 | 95.8 |
| 45 | 98.8 | 93.1 | 97.0 | 121 | 95.6 | 102 | 100 | 115 | 90.8 | 82.6 | 90.5 | 88.6 | 77.2 | 83.8 | 90.9 | 94.1 |
| 100 | 97.7 | 91.5 | 88.0 | 110 | 92.3 | 102 | 91.0 | 123 | 86.8 | 76.8 | 83.8 | 83.6 | 75.2 | 83.9 | 82.9 | 82.0 |
| **High fructose corn syrup (HFCS)** | | | | | | | | | | | | | | | | |
| 33 | 100 | 99.2 | 100 | 89.6 | 95.1 | 103 | 99.6 | 99.8 | 99.0 | 96.5 | 99.2 | 102 | 86.2 | 94.8 | 102 | 97.5 |
| 66 | 100 | 99.6 | 101 | 107 | 104 | 129 | 102 | 113 | 104 | 99.1 | 107 | 111 | 84.2 | 97.4 | 107 | 103 |
| 100 | 100 | 96.6 | 100 | 107 | 102 | 120 | 99.4 | 114 | 102 | 96.5 | 110 | 114 | 75.7 | 97.4 | 112 | 103 |
| **Honey** | | | | | | | | | | | | | | | | |
| 33 | 99.3 | 90.3 | 108 | 98.0 | 98.1 | 116 | 96.8 | 104 | 103 | 102 | 99.5 | 97.9 | 78.2 | 100 | 104 | 93.6 |
| 48 | 99.4 | 92.1 | 115 | 108 | 104 | 109 | 101 | 104 | 100 | 103 | 103 | 102 | 82.1 | 101 | 103 | 109 |
| 66 | 99.9 | 89.8 | 111 | 101 | 96.5 | 133 | 100 | 109 | 109 | 98.7 | 103 | 102 | 73.7 | 97.1 | 106 | 95.8 |
| **Invert Sugar** | | | | | | | | | | | | | | | | |
| 25 | 102 | 102 | 101 | 98.4 | 98.6 | 118 | 110 | 114 | 92.1 | 91.7 | 105 | 108 | 79.6 | 99.3 | 115 | 134 |
| 50 | 102 | 98.4 | 98.1 | 104 | 104 | 122 | 108 | 111 | 87.9 | 68.3 | 106 | 104 | 79.6 | 106 | 106 | 116 |
| 100 | 99.5 | 97.6 | 106 | 82.0 | 88.1 | 133 | 112 | 120 | 76.4 | 72.8 | 110 | 114 | 70.1 | 104 | 110 | 110 |
| **Maltodextrin** | | | | | | | | | | | | | | | | |
| 20.3 | 100 | 94.1 | 110 | 93.3 | 93.3 | 128 | 100 | 102 | 97.0 | 94.5 | 96.7 | 96.7 | 89.2 | 101 | 103 | 91.3 |
| 41 | 100 | 94.0 | 107 | 89.9 | 89.9 | 132 | 97.6 | 104 | 94.3 | 89.7 | 93.0 | 94.2 | 91.5 | 111 | 110 | 90.4 |
| **Molasses** | | | | | | | | | | | | | | | | |
| 4 | 100 | 96.9 | 93.4 | 110 | 100 | 109 | 96.6 | 103 | 98.1 | 96.3 | 94.1 | 90.9 | 91.8 | 87.7 | 98.9 | 86.4 |
| 40 | 100 | 99.1 | 93.0 | 113 | 101 | 112 | 94.5 | 96.6 | 103 | 106 | 94.4 | 92.6 | 88.0 | 87.0 | 99.8 | 92.9 |
| 80 | 100 | 98.1 | 95.1 | 125 | 104 | 119 | 99.6 | 102 | 102 | 95.7 | 101 | 99.8 | 80.6 | 87.0 | 105 | 93.0 |
| **Plum juice concentrate (PJC)** | | | | | | | | | | | | | | | | |
| 0.1 | 100 | 102 | 102 | 111 | 107 | 94.0 | 101 | 96.0 | 105 | 102 | 106 | 107 | 105 | 108 | 104 | 105 |
| 1 | 102 | 103 | 103 | 105 | 104 | 95.0 | 103 | 103 | 106 | 105 | 103 | 104 | 107 | 106 | 100 | 105 |
| 10 | 101 | 100 | 100 | 106 | 104 | 93.0 | 102 | 101 | 103 | 98.0 | 104 | 105 | 97 | 101 | 100 | 104 |
| **Raisin juice concentrate (RJC)** | | | | | | | | | | | | | | | | |
| 20 | 100 | 99.1 | 99.2 | 100 | 98.6 | 107 | 102 | 100 | 100 | 117 | 98 | 93.4 | 74.7 | 71.8 | 107 | 95.5 |
| 50 | 100 | 95.5 | 103 | 97.6 | 99.3 | 117 | 107 | 105 | 105 | 105 | 105 | 103 | 73.0 | 76.1 | 110 | 102 |
| 100 | 100 | 93.4 | 104 | 90.1 | 97.1 | 135 | 104 | 107 | 100 | 105 | 100 | 101 | 68.5 | 76.7 | 108 | 94.7 |
| **Sucrose** | | | | | | | | | | | | | | | | |
| 33 | 100 | 99.4 | 89.2 | 82.6 | 87.3 | 106 | 89.7 | 96.5 | 79.1 | 74.1 | 99.2 | 100 | 74.9 | 100 | 97.3 | 103 |
| 72 | 100 | 98.0 | 104 | 85.9 | 98.3 | 114 | 100 | 107 | 70.0 | 66.3 | 112 | 108 | 71.9 | 104 | 93.1 | 124 |
| 100 | 100 | 97.6 | 106 | 93.0 | 101 | 140 | 105 | 116 | 64.5 | 60.6 | 111 | 110 | 66.5 | 88.9 | 93.7 | 125 |

* Grayed areas indicate that the changes are statically significant different.