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LIST OF ABBREVIATIONS

Abbreviation	Definition
4NQO	4-nitroquinoline-1-oxide
ADI	acceptable daily intake
AUC	area under the curve
B(a)P	benzo(a)pyrene
C_{max}	maximum concentration
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CRO	Contract Research Organization
CRP2.1	CORESTA Smokeless Tobacco Reference Product 2.1
DMBA	7,12-dimethylbenz(a)anthracene
(b) (4)	[redacted]
DRF	Dose Range Finder
EFSA	European Food Safety Authority
ENDS	Electronic Nicotine Delivery Systems
EPA	Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association
FPG	Finished Powder Granulate
GLP	Good Laboratory Practice
GRAS	Generally Regarded as Safe
HPHC	harmful and potentially harmful constituent
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
ivMN	In vitro micronucleus
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOQ	limit of quantification
MetSal	methyl salicylate
miRNA	microribonucleic acid
mRNA	messenger ribonucleic acid
MN	Micronucleus
MRTPA	Modified Risk Tobacco Product Application
NDMA	N-nitrosodimethylamine

Abbreviation	Definition
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	nicotine-derived nitrosamine ketone or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NRT	nicotine replacement therapy
NRU	neutral red uptake
OECD	Organisation for Economic Co-operation and Development
PK	pharmacokinetic(s)
PMTA	Premarket Tobacco Product Application
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QRA	quantitative health risk assessment
RQ	risk quotient
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks
SCF	European Union's Scientific Committee on Food
SD	Standard Deviation
SENCAR	sensitive to carcinogens
SKU	stock keeping unit
SNFA	Swedish National Food Agency
ST	smokeless tobacco
TDI	tolerable daily intake
TPM	total particulate matter
TSNA	tobacco-specific nitrosamine
US	United States
USDHHS	US Department of Health and Human Services
USP	United States Pharmacopeia
WHO	World Health Organization

1 INTRODUCTION

Swedish Match USA, Inc. (hereafter referred to as Swedish Match) is submitting this Premarket Tobacco Product Application (PMTA) for ZYN®, in accordance with the requirements under Section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). ZYN is currently marketed in the United States (US), Sweden, Denmark, and selected locations in Europe. Although ZYN has been marketed in the US since 2014 (ie, prior to 08 August 2016), the product is a "new tobacco product" under Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the US as of 15 February 2007.

This summary presents scientific evidence demonstrating that the ZYN products are "appropriate for the protection of the public health" (Section 910[c](2)[A] of the FD&C Act) regarding the risks and benefits to the population as a whole, including users and non-users of ZYN as part of this PMTA.

1.1 Product and Relevant Comparators

ZYN is a non-heated, tobacco-free, smoke-free, and spit-free nicotine pouch for oral use and with an appearance similar to Swedish snus products. The product is intended for adult tobacco and nicotine consumers. Use of ZYN does not involve any inhalation of smoke or vapor. ZYN comes in 10 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) and two nicotine strengths (3 and 6 mg per pouch). ZYN is intended to be used under the upper lip for up to 60 minutes and is then discarded. Therefore, exposure to harmful and potentially harmful constituents (HPHCs) only involves those that are taken up through the oral, mucous membranes, or extracted to the saliva that is subsequently swallowed.

In the absence of other relevant Food and Drug Administration (FDA) guidance documents, the *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS)* Guidance for Industry (June 2019) (FDA PMTA ENDS Guidance 2019) is relied on for this PMTA because the guidance can be applied to a smokeless nicotine product, such as ZYN. In addition, this application is also reflective of the proposed rule for PMTAs (FDA Proposed Rule 2019).

In the PMTA Electronic Nicotine Delivery Systems (ENDS) Guidance, the FDA recommends that the new product be compared to existing products within the same category and to products in different categories.

In terms of health effects, a reasonable comparator to ZYN is cigarettes as cigarette smoking accounts for the vast majority of tobacco-related morbidity and pre-term mortality in the US and by far represent the most commonly used tobacco product on the US market.

Consumer data from the Study (b) (4) shows that moist snuff was the most commonly used tobacco product the weeks before starting to use ZYN. Therefore, in this PMTA, ZYN is compared with one moist snuff reference product, CRP2.1 (Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) Smokeless Tobacco Reference Product 2.).

Bridging to Swedish snus products is relevant since the products are similar in terms of use topography. In this PMTA, ZYN is also compared with the existing smokeless tobacco (ST) product General Snus.

1.1.1 General Snus

In this PMTA, ZYN is bridged to Swedish snus products including General Snus, which received PMTA marketing authorizations (PM0000010 - PM000017) on 10 November 2015 and modified risk orders (MR0000020 – MR0000022, MR0000024 – MR0000025, and MR0000027 – MR0000029) on 22 October 2019. Both the ZYN and General Snus products can be categorized as smokeless pouch products, are used in the same way (between the gum and the upper lip), and are similar in shape and size (although ZYN is slightly smaller). Both products are manufactured by the same company. The General Snus products to which the ZYN products are compared are produced under Swedish Match proprietary quality standard GOTHIATEK®. The ZYN products are produced under a quality management system ensuring that almost none of the HPHCs, which are governed by the GOTHIATEK standard, are present in quantities quantifiable using present analytical techniques.

As noted in the (FDA PMTA TPL Review 2015), Section V. Conclusions and Recommendations, the topline reasons for granting PMTA marketing authorization of General Snus included the following:

- The manufacturing under the GOTHIATEK quality system as described above.
- The General Snus products have significantly lower levels of what are likely the most carcinogenic constituents in tobacco products (N-nitrosonornicotine [NNN] and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) compared to >97% in the ST products currently on US market.
- The levels of other HPHCs in General Snus are similar to or lower than the levels in other ST products.
- When used exclusively instead of other US market ST products or cigarettes, General Snus offers potential for reductions in oral cancer.
- When used exclusively instead of cigarettes, General Snus offers lower risk of developing respiratory diseases (ie, chronic obstructive pulmonary disease [COPD], emphysema, and chronic bronchitis) and certain cancers (such as oral, esophageal, and lung).
- It is anticipated that there is a low likelihood of non-user uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

As noted in the FDA MRTPA TPL Review 2019 for General Snus,

- “The applicant has demonstrated that, as actually used by consumers, the eight General Snus products sold or distributed with the proposed modified risk information will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. The claim ‘Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis’ is scientifically accurate.”
- “In sum, FDA’s assessment of the scientific evidence supports the conclusion that exclusive users of snus have lower risk relative to cigarette smokers for each of these

health outcomes: mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. This assessment supports the revised modified risk claim as scientifically accurate. Overall, the available scientific evidence demonstrates that the products that are the subject of these applications, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users."

- "Subsequent to the completion of FDA's review, Rostron and colleagues (2018) conducted a systematic review and meta-analysis of studies pertaining to smokeless tobacco use and circulatory disease risk, providing a more comprehensive examination of this relationship, including more recent data (eg, Timberlake et al., 2017). Based on this review, risk of ischemic heart disease was not increased in Swedish studies of current smokeless tobacco users who were never smokers (versus non-users) (relative risk [RR]=1.04, 0.93-1.16, n=3), but was significantly increased in US studies of smokeless tobacco users who were never smokers (RR=1.17, 95% 1.08-1.27, n=3). By comparison…cigarette smoking has been found to increase risk of cardiovascular disease by a factor of about 1.5- to 3-fold. This most recent review provides clear evidence that the heart disease risks due to Swedish snus use are lower than the risks from cigarette smoking."

This PMTA presents a full assessment of ZYN, demonstrating that it compares even favorably to General Snus and is appropriate for the protection of the public health.

1.1.2 CRP2.1

ZYN was also compared to CRP2.1, which is an American style loose moist snuff ST product that was produced without added flavorings, except for those required to produce a product that is characteristic of the style. It is manufactured for use in scientific studies as a reference standard product and is packaged in plastic cans that contain 34 g of the product (CORESTA 2019).

1.2 HPHCs and Quantitative Health Risk Assessments

Full details of the HPHCs present in ZYN compared to General Snus and CRP2.1 is set forth in this document (Section 3).

In its evaluation of HPHCs in the General Snus PMTAs (FDA PMTA TPL Review 2015), FDA focused mainly on NNN and NNK and noted that the "products contain significantly lower levels of NNN and NNK compared to over 97% in the ST products currently on US market. Because NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers using ST products. Assuming persons who would have used other US ST products use these product instead, an individual using these products with reduced NNN levels could decrease the excess cancer risk by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of US-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor." No threshold level has been set for NNN and NNK in relation to the risk of cancer from a toxicological standpoint. However, the levels

of carcinogenic substances such as tobacco-specific nitrosamines (TSNAs) (eg, NNN and NNK) and benzo(a)pyrene (B[a]P) are not quantifiable in ZYN (Section 3), whereas General Snus contains low levels of TSNAs and B(a)P.

In the FDA PMTA ENDS Guidance 2019, FDA recommends testing for HPHCs, and ZYN contains no nitrosamines or polycyclic hydrocarbons. Out of the 93 HPHCs identified in cigarette smoke only 20 are present in General Snus. Swedish Match analyzed 45 HPHCs and 13 product-specific analytes for ZYN, and 37 of the HPHCs were below the limit of quantification (LOQ). The levels of the seven measurable constituents in ZYN, omitting nicotine, were lower than or generally similar to those in General Snus or CRP2.1. Notably, ZYN does not contain measurable quantities of TSNAs, such as NNN, or B(a)P (Section 3). By comparing the actual consumer exposure against valid threshold limit values set by recognized authorities in quantitative health risk assessments (QRAs), where possible, the levels of the constituents found in ZYN (formaldehyde, acetaldehyde, coumarin, naphthalene, (b) (4), and (b) (4), were below the established health-based threshold limit values. Under reasonably foreseeable conditions of use of ZYN, hence the levels do not raise concern from a public health perspective and supports that ZYN is appropriate for the protection of the public health. Thus, the toxicological safety profile of ZYN represents a significant improvement over snus.

The nicotine content of ZYN is lower compared to the General Snus products, which received PMTA marketing authorizations (PM0000010 PM0000017) on 10 November 2015 and modified risk orders (MR0000020 – MR0000022, MR0000024 – MR0000025, and MR0000027 – MR0000029) on 22 October 2019. As noted in the FDA PMTA TPL Review 2015, “these nicotine values are within the reported ranges from other marketed US moist snuff.” Nicotine pharmacokinetic (PK) studies on ZYN are provided as part of this application (Section G.6 Human Health Impact Evaluation Summary, Section 5).

1.3 Information Included in This Document to Support the PMTA

This document summarizes the research findings of chemistry studies conducted with ZYN, including the levels of HPHCs in ZYN. The HPHCs in ZYN were compared to those in General Snus and CRP2.1, as discussed. QRAs were performed for measurable HPHCs and (b) (4) (b) (4). This document also summarizes the mutagenic and genotoxic potential of ZYN, and CRP2.1, as determined by *in vitro* toxicity testing, which is supplemented by *in vitro* and *in vivo* data on snus and other ST products from the published literature. Key questions from the FDA PMTA ENDS Guidance 2019 addressed in this summary and the corresponding location in the document are provided in Table 1.

Table 1 Key Questions From the PMTA ENDS Guidance and Location in This Document

Key Question	Location
Summary of nonclinical studies relevant to the PMTA.	Section 2 (overall) Section 3 (HPHCs) Section 5 (toxicology)
What are the HPHCs in ZYN and at what levels are HPHCs present?	Section 3
Does the available toxicological data indicate a relative benefit compared to use of other tobacco products?	Section 3 Section 4 Section 5
What is the carcinogenicity potential?	Section 5 Section 6
What are the potential biological effects after *in vitro* and *in vivo* testing?	Section 5 Section 6

ENDS=Electronic Nicotine Delivery Systems; HPHC=harmful and potentially harmful constituents; PMTA=Premarket Tobacco Product Application.

2 OVERVIEW OF NONCLINICAL STUDIES

The nonclinical development program was designed to be consistent with the FDA guidance for industry entitled *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* dated June 2019 (FDA PMTA ENDS Guidance 2019).

As the FDA considers the chemical composition of a product as a major indicator of risk to consumer's health, Swedish Match conducted extensive product testing including chemical analyses of ZYN, and the characterization of HPHCs are listed in Table 2. The levels of HPHCs in all strengths and flavors of the finished product of ZYN and the analysis of those in ZYN, relative to comparators General Snus and CRP2.1, are discussed in Section 3. This is part of the broad characterization of ZYN, and the product stability and the remainder of the characterization of ZYN is described in Section G.3 Product Manufacturing and Controls Summary. Risk assessments are discussed in Section 4.

In vitro toxicology studies have been conducted with all flavors of ZYN 6 mg to determine its genotoxic potential. A listing of the toxicology studies conducted in support of the PMTA for ZYN is in Table 3. The nonclinical toxicology studies conducted with ZYN are summarized in Section 5. As nicotine, the active ingredient in ZYN, has been studied extensively and is well characterized, *in vivo* nonclinical studies have not been conducted with ZYN. There is published literature on the toxicology of Swedish snus and, although ZYN does not contain tobacco, Swedish snus complements and serves as a surrogate for ZYN due to the following similarities:

- Both ZYN and General Snus are smokeless, pouched products that are used in the same manner (ie, between the gum and the upper lip) and are similar in shape and size, although ZYN is slightly smaller.
- Both products are manufactured by the same company with similar quality control systems but in separate production lines, and the process is overseen by the same staff of scientists and technicians.
- As demonstrated across clinical studies with ZYN (Study (b) (4) and Study (b) (4)), the PK profiles (area under the curve [AUC] and maximum concentration [C_{max}]) demonstrate that ZYN 3 and 6 mg deliver nicotine in the range of already established smokeless products on the market (Section G.6 Human Health Impact Evaluation Summary, Section 4.1).
- Both products have low levels of HPHCs; the majority of the HPHCs were below quantifiable levels in ZYN, and those HPHCs that could be quantified in ZYN were generally at lower levels than those in snus.

The literature describing *in vitro* toxicology studies and *in vivo* research studies with Swedish snus and with other ST products is described in Section 6.

Table 2 Listing of Chemistry Studies Conducted in Support of ZYN

Test Product	Purpose	Location in PMTA
ZYN Chill 3 mg ZYN Chill 6 mg ZYN Cinnamon 3 mg ZYN Cinnamon 6 mg ZYN Citrus 3 mg ZYN Citrus 6 mg ZYN Coffee 3 mg ZYN Coffee 6 mg ZYN Cool Mint 3 mg ZYN Cool Mint 6 mg ZYN Fresh 3 mg ZYN Fresh 6 mg ZYN Peppermint 3 mg ZYN Peppermint 6 mg ZYN Smooth 3 mg ZYN Smooth 6 mg ZYN Spearmint 3 mg ZYN Spearmint 6 mg ZYN Wintergreen 3 mg ZYN Wintergreen 6 mg	Quantify HPHCs and product-specific analytes	Section H.1.2.3.4.1 Chill (8136) Characterization Results Section H.1.2.3.4.2 Chill (8137) Characterization Results Section H.1.2.3.4.1 Cinnamon (8128) Characterization Results Section H.1.2.3.4.2 Cinnamon (8129) Characterization Results Section H.1.2.3.4.1 Citrus (8122) Characterization Results Section H.1.2.3.4.2 Citrus (8123) Characterization Results Section H.1.2.3.4.1 Coffee (8124) Characterization Results Section H.1.2.3.4.2 Coffee (8125) Characterization Results Section H.1.2.3.4.1 Cool Mint (8105) Characterization Results Section H.1.2.3.4.2 Cool Mint (8106) Characterization Results Section H.1.2.3.4.1 Fresh (8140) Characterization Results Section H.1.2.3.4.2 Fresh (8141) Characterization Results Section H.1.2.3.4.1 Peppermint (8107) Characterization Results Section H.1.2.3.4.2 Peppermint (8108) Characterization Results Section H.1.2.3.4.1 Smooth (8134) Characterization Results Section H.1.2.3.4.2 Smooth (8135) Characterization Results Section H.1.2.3.4.1 Spearmint (8109) Characterization Results Section H.1.2.3.4.2 Spearmint (8110) Characterization Results Section H.1.2.3.4.1 Wintergreen (8111) Characterization Results Section H.1.2.3.4.2 Wintergreen (8112) Characterization Results
General Dry Mint Portion Original Mini General Portion Original Large General Mint Portion White Large General Portion White Large General Wintergreen Portion White Large CRP2.1	Quantify HPHCs and product-specific analytes	Section H.1.2.3.6 Coresta Moist Snuff Batch Analysis Section H.1.2.3.6 General Snus Batch Analysis

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; PMTA=Premarket Tobacco Product Application.

Table 3 Listing of Toxicology Studies Conducted in Support of ZYN

Type of Study/ Study Number	Species and Strain	Method of Administration	Test Product(s)	Duration of Dosing/ Doses	GLP Compliance	Testing Facility	Location in PMTA
Mutagenicity							
Bacterial reverse mutation assay (Ames test)(b) (4)	(b) (4)	*In vitro*	ZYN Chill 6 mg ZYN Cinnamon 6 mg ZYN Citrus 6 mg ZYN Coffee 6 mg ZYN Cool Mint 6 mg ZYN Fresh 6 mg ZYN Peppermint 6 mg ZYN Smooth 6 mg ZYN Spearmint 6 mg ZYN Wintergreen 6 mg CRP2.1	(b) (4)			Section H.2.3 Study (b) (4) Report
Genotoxicity							
In vitro micronucleus assay(b) (4)	(b) (4)	*In vitro*	ZYN Chill 6 mg ZYN Cinnamon 6 mg ZYN Citrus 6 mg ZYN Coffee 6 mg ZYN Cool Mint 6 mg ZYN Fresh 6 mg ZYN Peppermint 6 mg ZYN Smooth 6 mg ZYN Spearmint 6 mg ZYN Wintergreen 6 mg CRP2.1	(b) (4)			Section H.2.3 Study (b) (4) Report

(b) (4) CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; GLP=Good Laboratory Practice; PMTA=Premarket Tobacco Product Application.

3 ANALYSIS OF HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN ZYN

As the chemical composition of the product is a major indicator of risk to consumers, Swedish Match commissioned broad product characterization analyses, which included chemical testing of product-specific analytes and HPHCs. In addition to describing Swedish Match's Chemical Quality Control Program and the background explaining how analytes were selected, this section describes the quantities of HPHCs in ZYN. Comparisons are made between the HPHCs in ZYN and those found in the ST product General Snus, which is also the bridging product for ZYN (Section 1.1.1). Comparisons are also made between the HPHCs in ZYN and those in the moist snuff reference product, CRP2.1 (Section 1.1.2).

Unlike combustible tobacco products (such as cigarettes, cigars, or heated tobacco products) that expose non-users to the HPHCs contained in the side-stream smoke, non-user exposure is of no relevance to ZYN, nor other products in the ST category. Similarly, ZYN users are not exposed to many of the HPHCs found in ENDS.

3.1 Introduction to the Analysis of HPHCs, Product-Specific Analytes, and Nicotine-Related Compounds in ZYN and the Comparators

ZYN is produced using high-purity nicotine bitartrate dihydrate (nicotine salt), complying with the purity criteria of the United States Pharmacopeia (USP). (b) (4) [redacted] The ingredients are approved for food. The nicotine salt and ingredients are simply blended together (b) (4) [redacted] in the manufacturing process of ZYN.

Various priority lists of toxicants have been proposed for the evaluation of tobacco products, and the lists are mainly based on risk assessments. The FDA established a list of 93 HPHCs in tobacco products and tobacco smoke (FDA Established List of HPHCs 2012) and issued draft guidance on the reporting of an abbreviated list of 18 HPHCs in mainstream cigarette smoke and nine HPHCs in ST products (FDA Reporting HPHCs Draft Guidance 2012). The PMTA ENDS Guidance (FDA PMTA ENDS Guidance 2019) also lists HPHCs. Swedish Match adheres to these guidance documents and other historical documents, such as the 2010 FDA draft list that defines HPHCs for tobacco smoke or ST products (Section H.2.2 Historical List of HPHCs - xlsx).

The Swedish Match list of analytes contains 45 HPHCs listed by FDA, which Swedish Match considers relevant to test in smokeless products. These HPHCs belong to different chemical classes, such as volatile organic compounds, polycyclic aromatic hydrocarbons, nitrosamines, metals, radionuclides, alkaloids, and mycotoxins. The Swedish Match list of analytes also contains 13 compounds that are product-specific and/or required by external authorities or by the internal quality standard on snus products (GOTHIATEK®). All the results from this testing can be found in the references found in Table 2. The reasons for inclusion and Chemical Abstracts Service registry numbers of each analyte in the battery of testing are shown in Table 4.

The chemical constituents of all ZYN products produced by Swedish Match have been thoroughly investigated at least three to four times on a yearly basis. The contents of a great number of constituents are determined both at production and at best before date, and both

internal and external limits have been set. These limits are designed using optimal production techniques and available state of the art analytical methods.

ZYN products are typically analyzed for the same test battery of compounds, and the test battery has changed over time to ensure satisfaction of all internal requirements on product quality, as well as conformity with all external requirements for ST by relevant national authorities.

The HPHCs and product-specific analytes in ZYN (Chill, Cinnamon, Citrus, Coffee, Cool Mint, Fresh, Peppermint, Smooth, Spearmint, and Wintergreen flavors, all at 3 and 6 mg per pouch) were compared to those in the five varieties of pouched snus product of General Snus, which received PMTA marketing authorizations (PM0000011, PM0000012, PM0000014, PM0000016, and PM0000017) on 10 November 2015 and modified risk orders (MR0000021, MR0000022, MR0000025, MR0000028, and MR0000029) on 22 October 2019. The HPHCs in ZYN were also compared to those in CRP2.1, which is an American-style loose moist snuff.

Details about the comparators are as follows:

- PM0000011/MR0000021: General Dry Mint Portion Original Mini (6 g)
- PM0000012/MR0000022: General Portion Original Large (24 g)
- PM0000014/MR0000025: General Mint Portion White Large (24 g)
- PM0000016/MR0000028: General Portion White Large (24 g)
- PM0000017/MR0000029: General Wintergreen Portion White Large (24 g)
- CRP2.1 (1.2 oz/34 g)

Table 4 Reasons for Inclusion in the Analytical Battery of Testing

Analyte	CASRN	Reason for Inclusion		
		Health Risk (FDA/HPHCs)	Product-Specific	Requirements External/Internal
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	CA	-[a]	Limit on ST products (SNFA) (sum of NNK+NNN)
5-Methyl chrysene	3697-24-3	CA	-	-
Acetaldehyde	75-07-0	CA, RT, AD	-	GOTHIATEK
Acrolein	107-02-8	RT	-	-
Acrylamide	79-06-1	CA	-	-
Aflatoxins (sum of Aflatoxin B1, B2, G1, and G2)	NA	CA (Aflatoxin B1)	-	Limit on ST products (SNFA)
Ammonium ion	147-98-03-9	RT	-	-
Anabasine	494-52-0	AD	-	NAB precursor
Anatabine	571-49-7	-	-	NAT precursor
Arsenic	744-38-2	CA, CT, RDT	-	GOTHIATEK
Bacteria	NA	-	✓	GOTHIATEK

Analyte	CASRN	Reason for Inclusion		
		Health Risk (FDA/HPHCs)	Product-Specific	Requirements External/Internal
Benzo[a]anthracene	56-55-3	CA,CT	-	-
Benzo[a]pyrene	50-32-8	CA	-	Limit on ST products (SNFA); GOTHIATEK
Benzo[b]fluoroanthene	205-99-2	CA, CT	-	-
Benzo[c]phenanthrene	195-19-7	CA	-	-
Benzo[k]fluoroanthene	207-08-9	CA, CT	-	-
Benz[j]aceanthrylene	202-33-5	CA	-	-
Beryllium	7440-41-7	CA	-	-
Cadmium	744-43-9	CA, RT, RDT	-	GOTHIATEK
Chloride	16887-00-6	-	✓	Recommendation for daily intake (SNFA)
Chromium	7440-47-3	CA, RT, RDT	-	GOTHIATEK
Chrysene	218-01-9	CA, CT	-	-
Coumarin	91-64-5	Banned in food	✓	Internal ingredient policy
Crotonaldehyde	4170-30-3	CA	-	GOTHIATEK
Cyclopenta[c,d]pyrene	27208-37-3	CA	-	-
Dibenzo[a,h]anthracene	53-70-3	CA	-	-
Dibenzo[a,e]pyrene	192-65-4	CA	-	-
Dibenzo[a,h]pyrene	189-64-0	CA	-	-
Dibenzo[a,i]pyrene	189-55-9	CA	-	-
Dibenzo[a,l]pyrene	191-30-0	CA	-	-
Ethanol	64-17-5	-	✓	-
Ethyl carbamate	51-79-6	CA, RDT	-	-
Formaldehyde	50-00-0	CA, RT	-	GOTHIATEK
Glycerol	56-81-5	-	✓	-
Indeno[1,2,3-cd]pyrene	193-39-5	CA	-	-
Lead	7439-92-1	CA, CT, RDT	-	Limit on ST products (SNFA); GOTHIATEK
Mercury	7439-97-6	CA, RDT	-	GOTHIATEK
Moisture	NA	-	✓	Requested by CDC/HHS[b]
Naphthalene	91-20-3	CA, RT	-	-
Nickel	7440-02-0	CA, RT	-	GOTHIATEK
Nicotine	54-11-5	AD, RDT	✓	Requested by CDC/HHS[b]
Nitrate ion	14797-55-8	-	-	Precursor to nitrite
Nitrite ion	14797-65-0	-	-	GOTHIATEK

Analyte	CASRN	Reason for Inclusion		
		Health Risk (FDA/HPHCs)	Product-Specific	Requirements External/Internal
N-Nitrosoanabasine (NAB)	1133-64-8	-	-	Included in multimethod TSNA
N-Nitrosoanatabine (NAT)	887407-16-1	-	-	Included in multimethod TSNA
N-Nitrosonornicotine (NNN)	16543-55-8	CA	-	Limit on ST products (SNFA) (sum of NNK+NNN)
N-Nitrosodimethylamine (NDMA)	62-75-9	CA	-	GOTHIATEK
Nornicotine	494-97-3	AD	✓	-
Ochratoxin	37203-43-3	-	-	GOTHIATEK
pH	NA	-	✓	Requested by CDC/HHS[b]
Polonium-210	NA	CA	-	-
Propylene glycol	57-55-6	-	✓	Limit on ST (SNFA)
Starch and sugars	NA	-	✓	-
Selenium	7782-49-2	RT	-	-
Uranium-235	NA	CA, RT	-	-
Uranium-238	NA	CA, RT	-	-
Water activity	NA	-	✓	-
Water content	NA	-	✓	-

AD=addictive; CA=carcinogen; CASRN=Chemical Abstracts Service Registry Number; CDC=US Centers for Disease Control and Prevention; CT=cardiovascular toxicant; FDA=Food and Drug Administration; HHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; RDT=reproductive or developmental toxicant; RT=respiratory toxicant; SNFA=Swedish National Food Agency; ST=smokeless tobacco; TSNA=tobacco-specific nitrosamine.

Note: Nicotine metabolites (cotinine and nicotine-N-oxide) and tobacco alkaloids (anabasine, anatabine, β-nicotyrine and myosmine) were also included in the battery of testing. Limits on ST are set forth by SNFA (LIVSFS 2012 and LIVSFS Amendment 2016).

[a] Not applicable

[b] Requested by CDC/HHS (USDHHS 2009)

3.2 Methods for the Analysis of HPHCs, Product-Specific Analytes, and Nicotine-Related Compounds in ZYN and the Comparators

As part of Swedish Match's Chemical Quality Control Program, the ZYN products were sampled from the production line and kept in room temperature or freezer according to CORESTA guidelines prior to analysis, see Guideline No. 11 - Technical Guideline for Sample Handling of Smokeless Tobacco and Smokeless Tobacco Products, July 2011 (Section H.1.2.3.2 CORESTA Guide No 11).

Samples were collected quarterly from fresh batches of ZYN and data presented in this application were tested in duplicate or in triplicate and generally testing occurred from 2016 to 2018. The extent of batch testing provides a robust representation of product variability of ZYN. The General Snus comparators were tested similarly, whereas 10 replicates of the ST comparator, CRP2.1, were tested. The sampling and analytical testing approach was appropriate for the comparison of ZYN with ST comparators, CRP2.1 and General Snus.

The majority of the HPHC testing was performed by (b) (4), whereas the testing of polonium was performed by (b) (4), both of which hold accreditation to the International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 17025. All testing is within the scope of the accreditation, unless otherwise noted. Testing of other analytes was performed at Swedish Match (b) (4) and (b) (4). A description of each method and the validation summary are included (Section H.1.2.3.2 Summary of Methods).

Each stock keeping unit (SKU) of ZYN was tested for HPHCs and product-specific analytes and reported on per-dry weight basis and per unit of use. In this section, only the results based on per unit of use is presented and discussed as this is considered to the most relevant basis for a comparison. Similarly, nicotine-related compounds (eg, tobacco alkaloid and nicotine metabolites) content were also analyzed. In calculations of unit of use of CRP2.1 the weight of 1.97 g have been used (Hatsukami et al 1988). In calculations of unit of use of General Snus, the weight of 1.0 g have been used or 0.3 g for PM0000011/MR0000021.

3.3 Results for the Analysis of HPHCs, Product-Specific Analytes, and Nicotine-Related Compounds in ZYN and the Comparators

There are 93 HPHCs identified in cigarette smoke (FDA Established List of HPHCs 2012), and only 20 of these HPHCs have been quantified in General Snus, which is a marketed product. Of the 45 HPHCs tested for ZYN, 37 were below the LOQ. Importantly, the levels of TSNAs (eg, NNN and NNK) and B(a)P in ZYN were below LOQ; whereas, General Snus contains low levels of TSNAs and occasionally also low levels of B(a)P (see Section H.1.2.3.6 General Snus Batch Analysis).

In short, the levels of the seven quantifiable HPHCs, omitting free nicotine, in ZYN were lower than those in General Snus for acetaldehyde, (b) (4), nornicotine, and (b) (4) or were almost always lower for naphthalene, which was higher in ZYN Citrus only. (b) (4) Only formaldehyde was increased in the ZYN products compared to General Snus. The levels of HPHCs in ZYN were always lower than those in the CRP2.1 reference product comparator based on per unit of use, and (b) (4)

The average HPHC levels combining all ZYN SKUs are shown in Table 5. This table also shows the range of percentage reduction of the HPHCs in ZYN relative to the average values found in CRP2.1 and General Snus. To calculate the range in percentage reduction, the minimum and maximum reported values of the replicates of all SKUs of ZYN combined were compared to the average value of CRP2.1 and General Snus, respectively. When the levels of analytes for both ZYN and a comparator were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by "NA". For incidences where the maximal individual replicate level for ZYN was below the LOQ, the values were set to the LOQ for the percent reduction calculations to provide the most conservative estimate.

Studying the percentage reduction values compared to General Snus in Table 5, it shows that many HPHCs are below LOQ for both ZYN and General Snus, and no reduction could be calculated as indicated by "NA". Where HPHC levels were found in General Snus, ZYN gives a significant reduction for the majority of those HPHCs.

As mentioned previously and as can be seen in Table 5, the levels of HPHCs in ZYN were always lower than those in the CRP2.1 reference product comparator based on per unit of use, and (b) (4)

To better illustrate the percentage reduction listed in Table 5, the same ranges in which HPHCs are reduced in ZYN compared to CRP2.1 are shown in Figure 1, whereas the corresponding ranges in change for ZYN compared to General Snus are shown in Figure 2.

Table 5 Overall Summary of HPHCs Measured in ZYN Compared to Those in CRP2.1 and General Snus

HPHC	Average HPHCs in all SKUs of ZYN (Per Unit of Use)	% Reduction Compared to CRP2.1	% Reduction Compared to General Snus
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/unit)	(b) (4)	>99.8	>92.2
5-Methylchrysene (ng/unit)		NA	NA
Acetaldehyde (µg/unit)		77.3-97.0	61.6-95.0
Acrolein (µg/unit) [a]		NA	NA
Acrylamide (ng/unit)		>92.5	>93.9
Aflatoxin B1 (ng/unit)		NA	NA
Ammonium ion (mg/unit)		99.4-99.6	67.3-78.2
Anabasine (µg/unit)		99.6-99.9	98.2-99.5
Arsenic (µg/unit)		>85.5	>82.6
Benz[j]aceanthrylene (ng/unit)		NA	NA
Benzo[a]anthracene (ng/unit)		>99.9	NA
Benzo[a]pyrene (ng/unit)		>99.9	NA
Benzo[c]phenanthrene (ng/unit)		>99.8	NA
Benzo[b]fluoroanthene (ng/unit)		>99.9	NA
Benzo[k]fluoroanthene (ng/unit)		>99.7	NA
Beryllium (µg/unit)		NA	NA
Cadmium (µg/unit)		>98.5	>90.9
Chromium (µg/unit)		60.2-92.6	81.3-(0.2) [b]
Chrysene (ng/unit)		>99.9	>82.0
Coumarin (µg/unit) [c]		>98.1 4.6 - (-182.1) [b,c]	NA (-1879) [b] - (-5751) [b,c]
Crotonaldehyde (µg/unit)		NA	NA
Cyclopenta[c,d]pyrene (ng/unit)		>97.6	NA

HPHC	Average HPHCs in all SKUs of ZYN (Per Unit of Use)	% Reduction Compared to CRP2.1	% Reduction Compared to General Snus
Dibenzo[a,h]anthracene (ng/unit)	(b) (4)	>98.9	NA
Dibenzo[a,e]pyrene (ng/unit)		NA	NA
Dibenzo[a,h]pyrene (ng/unit)		NA	NA
Dibenzo[a,i]pyrene (ng/unit)		NA	NA
Dibenzo[a,l]pyrene (ng/unit)		NA	NA
Ethyl carbamate (ng/unit)		NA	NA
Formaldehyde (µg/unit)		18.9-80.8	34.6-(176.5) [b]
Glycerol (mg/unit)		NA	NA
Indeno[1,2,3-cd]pyrene (ng/unit)		>99.5	NA
Lead (µg/unit)		>89.1	>66.1
Mercury (µg/unit)		NA	NA
Naphthalene (ng/unit)		85.2-98.1	61.7-(205) [b]
Nickel (µg/unit)		87.5-97.1	73.3-93.8
Nicotine, free nicotine (mg/unit)		18.4-81.3	75.7-(6.4) [b]
Nitrite ion (µg/unit)		93.0-97.3	10.9-65.7
N-Nitrosodimethylamine (NDMA) (ng/unit)		>98.7	NA
N-Nitrosonornicotine (NNN) (µg/unit)		>99.9	>97.5
Nornicotine (µg/unit)		98.0-99.7	96.1-99.5
Polonium-210 (radioisotope) (Bq/unit) [d]		NA	>36.0
Propylene glycol (mg/unit) [e]		NA	86.8-96.3
Selenium (µg/unit)		NA	NA

HPHC	Average HPHCs in all SKUs of ZYN (Per Unit of Use)	% Reduction Compared to CRP2.1	% Reduction Compared to General Snus
Uranium-235 (Bq/unit)	(b) (4)	NA	NA
Uranium-238 (Bq/unit)		NA	NA

Source: Section H.2.2 Assessment of HPHCs and Analytes, All Replicates

BLOQ=below the limit of quantification; CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; NA=not applicable; SKU=stock keeping unit.

Note: The average HPHC levels for all ZYN SKUs were calculated by averaging each SKU's found level and for instances where the individual SKU's average was below the LOQ, the value was set to the LOQ to provide the most conservative estimate. To calculate the percent reduction, the minimum and maximum reported values of the replicates of all SKUs of ZYN were compared to the average value of CRP2.1 and General Snus, respectively. When the levels of analytes for both ZYN and a comparator were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA. For incidences where the maximal individual replicate level for ZYN was below the LOQ, the values were set to the LOQ for the percent reduction calculations to provide the most conservative estimate. In addition to these HPHCs, an expanded list of analytes that includes nicotine metabolites and tobacco alkaloids in the individual flavors and nicotine strengths of ZYN compared to General Snus and CRP2.1 is tabulated in the Appendix (Section 9).

[a] Acrolein was not tested in the comparator CRP2.1 and no comparison could be made.

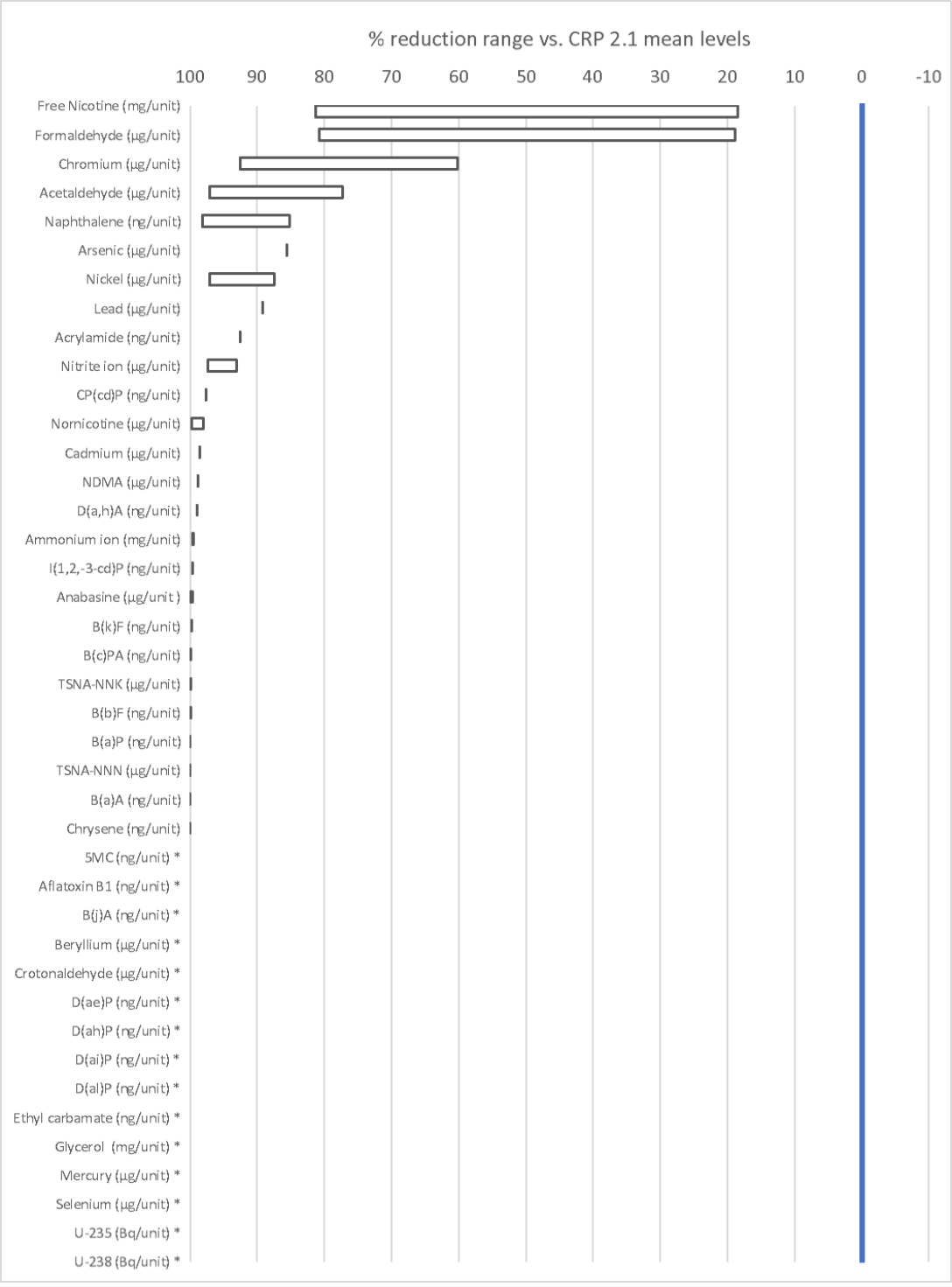
[b] Increases are noted in parentheses.

[c] (b) (4) .

[d] (b) (4) Polonium-210 was not tested in the comparator CRP2.1 and no comparison could be made.

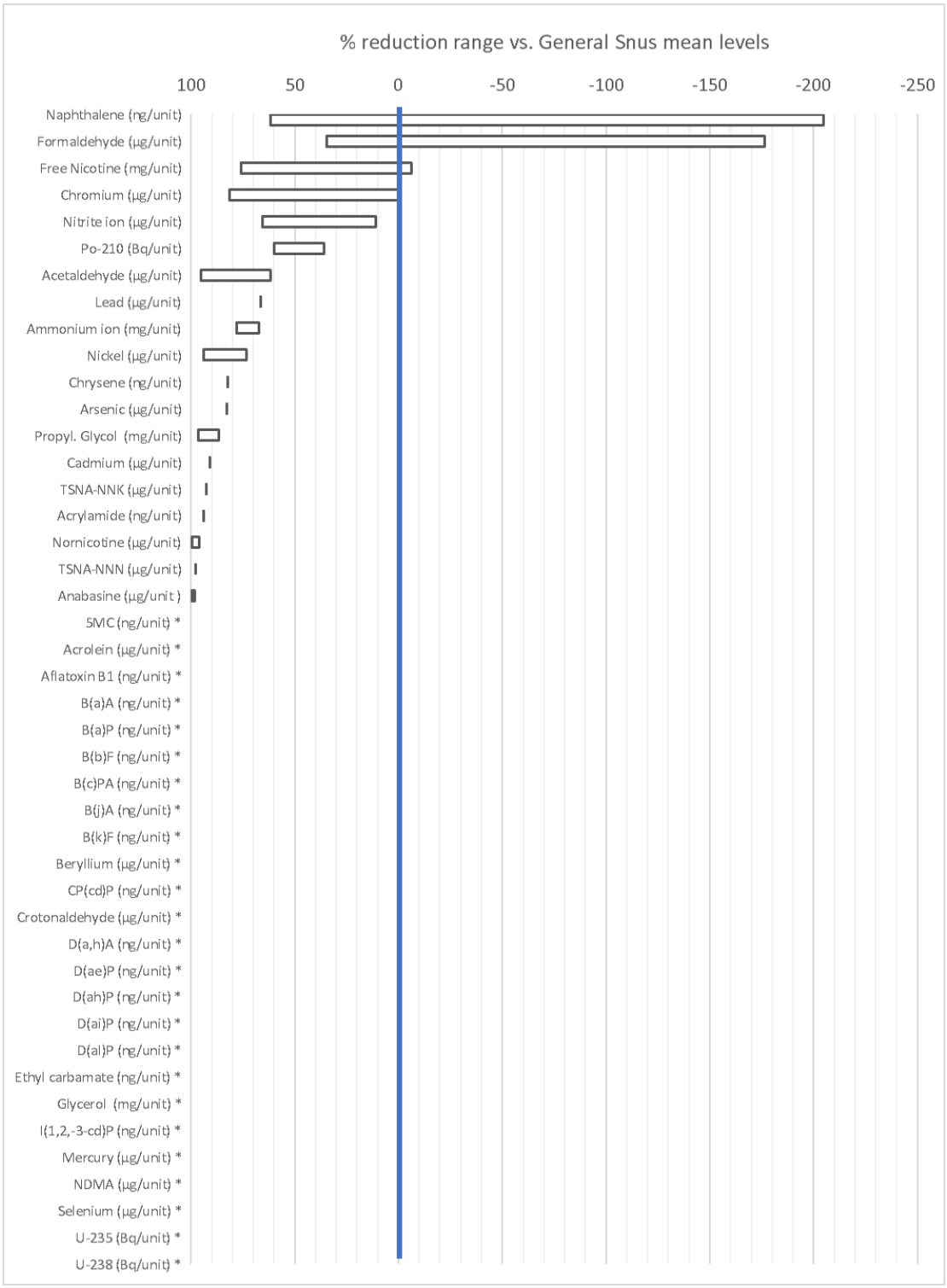
[e] Propylene glycol was not found at quantifiable levels in CRP2.1 and therefore no reduction could be calculated, and the comparison is only based on General Snus.

Figure 1 Comparison of the HPHCs in ZYN to Those in CRP2.1



Source: Section H.2.2 Assessment of HPHCs and Analytes, Averages
Note: To calculate the percent reduction, the minimum and maximum reported value of the replicates of all SKUs of ZYN were compared to the average value of CRP2.1. An "*" next to the analyte name indicates that the levels for both ZYN and the comparator were below the LOQ, and no reduction can be calculated. The blue line marks the threshold of "no change", ie, if the levels found for ZYN and the comparator would be equal.

Figure 2 Comparison of the HPHCs in ZYN to Those in General Snus



Source: Section H.2.2 Assessment of HPHCs and Analytes, Averages
Note: To calculate the percent reduction, the minimum and maximum reported value of the replicates of all SKUs of ZYN were compared to the average value of General Snus. An "*" next to the analyte name indicates that the levels for both ZYN and the comparator were below the LOQ, and no reduction can be calculated. The blue line marks the threshold of "no change", ie, if the levels found for ZYN and the comparator would be equal.

(b) (4) With this exception it can clearly be seen in Figure 1 that the maximum HPHC level found in all individually tested ZYN products always falls below the level found in CRP2.1. Thus, over the extended period of time testing the ZYN products, it has been shown that the HPHC levels are consistently and significantly lower than the levels found in the moist snuff comparator product CRP2.1.

As previously mentioned, Figure 2 illustrates the range in percentage change of HPHC levels in ZYN compared to General Snus, using the minimum and maximum HPHC level found of all tested ZYN samples. Naphthalene levels have a higher upper range in ZYN compared to General Snus and this is solely due to the levels found in ZYN Citrus. Formaldehyde is the only compound where a general increase from the low levels found in General Snus can be observed. The free nicotine upper level and chromium upper level are reaching up to the levels found in General Snus but an absolute majority of the tested ZYN falls below the levels found in General Snus. To further sum up the findings, for 25 of the HPHCs, the levels were below LOQ in both General Snus and in ZYN, and for 15 of the HPHCs, a consistent and significant reduction in levels could be observed for ZYN.

A collective summary and location of the tables that compare the HPHCs, nicotine-related compounds in the individual flavors and nicotine strengths of ZYN to General Snus and CRP2.1 on a per-dry weight basis and per unit of use is shown in Table 6, and the individual SKU data and comparisons of each SKU to General Snus and CRP2.1 are presented in the Appendix (Section 9). The tables show the average levels of each analyte in ZYN, the corresponding levels in the comparators, and the percent change that was observed relative to ZYN. As can be seen from these tables, out of the HPHCs that were detected in ZYN, acetaldehyde and formaldehyde were reported with a quantifiable mean value in all SKUs.

- Acetaldehyde
  - Compared to General Snus, the amount of acetaldehyde in ZYN ranged from (b) (4) (b) (4) based on per unit of use.
  - Compared to CRP2.1, the amount of acetaldehyde in ZYN ranged from (b) (4) based on per unit of use.
- Formaldehyde
  - Compared to General Snus, the amount of formaldehyde in ZYN ranged from (b) (4) (b) (4) based on per unit of use.
  - Compared to CRP2.1, the amount of formaldehyde in ZYN ranged from (b) (4) (b) (4) based on per unit of use.

Other analytes that were found at quantifiable levels in selected SKUs of ZYN and are summarized as follows:

- Coumarin (ZYN Cinnamon 3 and 6 mg), (b) (4)
- Naphthalene (found in ZYN Citrus 3 and 6 mg and ZYN Fresh 3 and 6 mg) (b) (4)

- Nitrite (ZYN Chill 6 mg, ZYN Citrus 6 mg, and ZYN Fresh 6 mg) (b) (4) [redacted]
- Nornicotine (ZYN Chill 3 mg, ZYN Cinnamon 3 and 6 mg, ZYN Coffee 3 and 6 mg, ZYN Cool Mint 6 mg, ZYN Peppermint 6 mg, ZYN Spearmint 6 mg, and ZYN Wintergreen 6 mg) (b) (4) [redacted].
- (b) (4) [redacted]

The ratios of tobacco alkaloids and nicotine metabolites to nicotine are compliant with the purity criteria in the USP monograph for nicotine (as shown in the Appendix, Table 13).

- Nicotine-N-oxide, a primary metabolite of nicotine, was detected in some ZYN products (ZYN Cinnamon 3 mg and 6 mg, ZYN Coffee 3 mg and 6 mg, and ZYN Spearmint 3 mg and 6 mg) and (b) (4) [redacted]

Of particular note, although the majority of HPHCs could not be quantified in ZYN, some might be present at unquantifiable trace levels. To account for potential trace values of HPHCs or other analytes in ZYN and to enable numerical comparisons to General Snus and CRP2.1, it was assumed that the LOQ were measured values in ZYN. Using this approach, the most conservative estimate of each potential trace value in ZYN was determined relative to the comparators. In the instances when the value for an analyte was below the LOQ in ZYN, the ratio was calculated using the LOQ value, and it was assumed that the amount of the HPHC in the comparator was 100% and that the difference was the percent reduction in ZYN. These values were labeled with a "greater than" symbol to denote that the calculated percent reduction represents the worst case scenario for ZYN. When values for an analyte were below the LOQ for both ZYN and the comparator, the ratio could not be calculated.

The vast majority of all HPHCs and product-specific analytes that were analyzed in ZYN were at levels below the LOQ for the appropriate method in question. The levels of the constituents acetaldehyde, (b) (4) nornicotine, and (b) (4) quantified in ZYN were lower or similar to those in General Snus with the exception of naphthalene and coumarin that were found at higher levels in two SKUs, respectively. Only one constituent, formaldehyde, was higher in all flavors of the ZYN product. The levels of HPHCs in ZYN were always lower than those in the CRP2.1 reference product comparator, and (b) (4) [redacted]. Notably, ZYN does not contain measurable quantities of TSNA (NNN and NNK) or B(a)P, which were present at low levels in General Snus. The broad chemical characterization of ZYN has shown that the product contains a very limited number of HPHCs, of which most were significantly reduced compared to the levels found in CRP2.1 and General Snus.

Table 6 Summary of Data Tables of HPHCs and Nicotine-Related Compounds for All Flavors and Nicotine Strengths of ZYN Compared to Those in General Snus or CRP2.1

ZYN Product	Unique ID	US Item Number	HPHC Content		Nicotine-Related Compounds	
			Dry Weight	Unit of Use	As Is	Unit of Use
Chill 3 mg	8136	920510	Table 14	Table 15	Table 16	Table 17
Chill 6 mg	8137	920520	Table 18	Table 19	Table 20	Table 21
Cinnamon 3 mg	8128	906510	Table 22	Table 23	Table 24	Table 25
Cinnamon 6 mg	8129	906520	Table 26	Table 27	Table 28	Table 29
Citrus 3 mg	8122	907510	Table 30	Table 31	Table 32	Table 33
Citrus 6 mg	8123	907520	Table 34	Table 35	Table 36	Table 37
Coffee 3 mg	8124	904510	Table 38	Table 39	Table 40	Table 41
Coffee 6 mg	8125	904520	Table 42	Table 43	Table 44	Table 45
Cool Mint 3 mg	8105	900510	Table 46	Table 47	Table 48	Table 49
Cool Mint 6 mg	8106	900520	Table 50	Table 51	Table 52	Table 53
Fresh 3 mg	8140	921510	Table 54	Table 55	Table 56	Table 57
Fresh 6 mg	8141	921520	Table 58	Table 59	Table 60	Table 61
Peppermint 3 mg	8107	901510	Table 62	Table 63	Table 64	Table 65
Peppermint 6 mg	8108	901520	Table 66	Table 67	Table 68	Table 69
Smooth 3 mg	8134	914510	Table 70	Table 71	Table 72	Table 73
Smooth 6 mg	8135	914520	Table 74	Table 75	Table 76	Table 77
Spearmint 3 mg	8109	902510	Table 78	Table 79	Table 80	Table 81
Spearmint 6 mg	8110	902520	Table 82	Table 83	Table 84	Table 85
Wintergreen 3 mg	8111	903510	Table 86	Table 87	Table 88	Table 89
Wintergreen 6 mg	8112	903520	Table 90	Table 91	Table 92	Table 93

HPHC=harmful and potentially harmful constituent; ID=identification; US=United States.

3.4 Summary and Conclusions of HPHCs in ZYN

As the chemical composition of the product is a major indicator of risk to consumers, Swedish Match commissioned broad product characterization analyses of ZYN. The levels of constituents in ZYN were compared with those in the ST product General Snus, which is also the bridging product, and also compared with an American loose moist snuff reference product CRP2.1.

Two of the topline reasons for granting PMTA marketing authorization (FDA PMTA TPL Review 2015, Section V. Conclusions and Recommendations) of General Snus were:

- "The General Snus products have significantly lower levels of what are likely the most carcinogenic constituents in tobacco products (N-nitrosonornicotine [NNN] and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) compared to >97% in the ST products currently on US market.
- The levels of other HPHCs in General Snus are similar to or lower than the levels in other ST products."

FDA has established a list of 93 HPHCs in tobacco products and tobacco smoke (FDA Established List of HPHCs 2012). The Swedish Match list of analytes for characterization comprises 45 HPHCs and 13 product-specific analytes, altogether 58 compounds, which Swedish Match considers relevant to test in smokeless products. Of the 45 HPHCs tested for ZYN, 37 were below the LOQ. Notably, ZYN does not contain measurable quantities of the carcinogenic TSNAs, including NNN and NNK, or the carcinogenic polycyclic aromatic hydrocarbon B(a)P. The HPHCs acetaldehyde, (b) (4), and (b) (4) (b) (4) were found at quantifiable levels in ZYN, but the levels were lower in average compared to the levels found in General Snus. Only formaldehyde was increased on an average level in the ZYN products compared to General Snus, which contain low levels of formaldehyde. Naphthalene was generally lower in ZYN compared to General Snus, with the exception of (b) (4) (b) (4), and (b) (4) was detected only in (b) (4) at an increased level compared to General Snus. The levels of HPHCs found in ZYN were always lower than those in the CRP2.1 reference product comparator based on per unit of use, and the only exception was the flavoring substance (b) (4).

These results suggest that an individual using the smokeless product ZYN would be exposed to lower levels of HPHCs than those using a marketed smokeless product such as General Snus or moist snuff products. The exposure to HPHCs would be much lower than those from smoking combustible cigarettes (USDHHS 2010, Jaccard et al 2017).

4 RISK ASSESSMENTS FOR ZYN

To support evaluation of potential health risks with ingredients in ZYN, two approaches have been used, Quantitative health risk assessments (QRA) and Safety Assessment (SA). QRA was used for HPHCs and was based on the actual levels measured in ZYN together with the calculated consumer exposure compared to toxicological threshold limit values. For the SA of added ingredients (listed in Table 8), flavors and pouch material literature review were performed and were based on product recipes.

In addition, SA of all ingredients, flavors, and pouch material were undertaken prior inclusion in the products. All ingredients used in ZYN and flavor components are approved for food.

4.1 Quantitative Health Risk Assessments of HPHC in ZYN

In general, QRA is a three-step process that includes hazard identification, exposure assessment, and risk characterization. Swedish Match has used QRA to assess if potential risks from constituents in ZYN are acceptable from a public health perspective. Where possible, QRAs were performed for the HPHCs that were measurable in ZYN, and a QRA was also conducted for the flavor compound (b) (4).

The characterization data of HPHCs in ZYN (the source files are in Section H.1.2.3.4 Batch Analysis) were used for calculations in the QRAs. As ZYN is an oral smokeless product, heat-degraded byproducts should not be formed. The detected HPHC above LOQ in ZYN pouches were used to calculate the estimated daily consumer exposure. In the absence of extraction and uptake studies, a conservative assumption was applied and the extraction and uptake (bioavailability) was set to 100% in the calculations.

The QRAs were based on a daily usage of eight ZYN pouches/day (eight pouches of 0.4 g each), which corresponds to 3.2 g/day based on data from the consumer research Patterns of Use Study (b) (4) (Section H.3.1.1.1 Report Body, Table 12). Body weight was set to 60 kg (used to calculate daily intake in µg/kg body weight per day).

Hazard assessments were based on published toxicological data, health-based threshold limit values and scientific opinions from creditable sources such as European Commission Exclusive Scientific Committees, European Food Safety Authority (EFSA), World Health Organization (WHO), Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA), and US Environmental Protection Agency (EPA). Although acceptable daily intake (ADI)/tolerable daily intake (TDI) values have not been adopted by FDA for use in ST products, though the toxicological data underlying ADI/TDI is thoroughly evaluated.

Assessments for ZYN were based on oral toxicology studies, which is the most appropriate route of exposure to how ZYN is used, and health-based threshold limit values (ADI/TDI). Risk quotient (RQ) was calculated for each HPHC above LOQ where possible. RQs are important concepts in risk assessment and are used by regulatory authorities such as EPA to describe the risk posed by a chemical under a realistic exposure scenario for how that chemical is used. An RQ less than or equal to one indicates that adverse effects are not likely to occur and is generally considered indicative of acceptable risk. Although an RQ greater than one is generally considered indicative of unacceptable risk, it is not a statistical probability that harm will occur.

RQ can also be used as a tool to assess how much an exposure concentration exceeds the threshold limit value.

Table 7 provides a summary of the QRAs for measurable constituent that were assessed for ZYN. Further details of the risk characterizations and calculations are found in in the sources noted in the table.

Table 7 Summary of Quantitative Health Risk Assessments for HPHCs in ZYN

HPHC	Detected Level in ZYN (µg/g)	Daily Intake[a] (µg/kg bw)	ADI/TDI (µg/kg bw/day)	Source ADI/TDI	RQ	RQ <1, Acceptable Risk
Acetaldehyde[b]	(b) (4)					
Coumarin[c]						
Formaldehyde[d]						
Naphthalene[e]						
Nicotine-N-oxide[f]						
(b) (4)						
Nornicotine[h]						
(b) (4)						

Source: Section H.2.1 Quantitative Risk Assessment Acetaldehyde; Section H.2.1 Quantitative Risk Assessment Coumarin; Section H.2.1 Quantitative Risk Assessment Formaldehyde; Section H.2.1 Quantitative Risk Assessment Naphthalene; Section H.2.1 Quantitative Risk Assessment Nitrite; Section H.2.1 Quantitative Risk Assessment Propylene Glycol.

ADI=acceptable daily intake; bw=body weight; EFSA=European Food Safety Authority; EPA= Environmental Protection Agency; JECFA=Joint FAO/WHO Expert Committee on Food Additives; NA=not applicable; RQ=risk quotient; TDI=tolerable daily intake.

[a] Assumptions: Daily use of ZYN 3.2 g (eight pouches/day) and 60 kg human; no data available for oral ADI/TDI.
[b] The highest mean value in ZYN Wintergreen 3 mg. (b) (4) .
[c] The highest mean value in ZYN Cinnamon 6 mg. (b) (4) .
[d] The highest mean value in ZYN Wintergreen 3 mg. (b) (4) .
[e] The highest mean value in ZYN Citrus 6 mg. (b) (4) .
[f] The highest mean value in ZYN Spearmint 6 mg. (b) (4) .
[g] The highest mean value in ZYN Fresh 6 mg. (b) (4)
[h] The highest mean value in ZYN Coffee 6 mg. (b) (4)
[i] The highest mean value in ZYN Coffee 3 mg. (b) (4)
[j] Oral reference dose (not ADI/TDI).

The RQs of all of the HPHCs at the highest measurable levels indicate that adverse effects are not likely to occur as RQ <1 (ranging from (b) (4) of the respective TDI/ADI).

This assessment included formaldehyde, which was the only HPHC increased in all ZYN products compared to General Snus. The total exposure to formaldehyde from using ZYN is less than (b) (4) of the TDI of (b) (4) µg/kg/body weight per day. To address the daily potential exposure of formaldehyde from General Snus and CPR2.1 compared to ZYN, the daily use needs to be taken into consideration and not only the amount per unit. The estimated daily consumption of pouched and loose snus are 12 g and 29 g respectively (Digard et al 2009), and the average pinch size among ST users is 1.97g (Hatsukami et al 1988). Based on chemical control analyses (Section H.1.2.3.6 Coresta Moist Snuff Batch Analysis, Section H.1.2.3.6 General Snus Batch Analysis), (b) (4) Hence, the daily exposure to

formaldehyde is similar for ZYN and General Snus, whilst the formaldehyde exposure from CRP2.1 is more than three-fold higher but still below the ADI-level set by WHO.

For nornicotine and nicotine-N-oxide, no established ADI/TDI values were available, and no QRAs were performed. However, the worst-case daily intakes were calculated (b) (4) and (b) (4) µg/kg body weight per day, respectively), based on 100% uptake and eight pouches/day. This is much lower compared to the levels in the comparator products, General Snus and CRP2.1.

Based on these QRAs, Swedish Match concludes that the levels of formaldehyde, acetaldehyde, coumarin, naphthalene, nitrite, and propylene glycol in ZYN were below current health-based threshold values. Under reasonably foreseeable conditions of use of ZYN, the levels do not raise concern from a public health perspective and support that ZYN is appropriate for the protection of the public health.

4.2 Safety Assessment of Ingredients

In addition to nicotine bitartrate dihydrate, the ZYN products consist of sweetener, stabilizer, fillers, pH-adjusters, ie, ingredients and flavors which constitute the product together with the pouch material that encloses the pouch. All ingredients have been assigned either a Flavor and Extract Manufacturers Association (FEMA) number or a regulation number in Title 21 of the Code of Federal Regulations (CFR). The ingredients have been used safely in a wide array of consumer products including food, drugs, and over-the-counter health and cosmetic products. Table 8 shows the ingredients in ZYN products. See source documents for ZYN products' target quantities in mg per pouch (Section H.1.1.1.1 Chill (8136), Section H.1.1.1.1 Cinnamon (8128), Section H.1.1.1.1 Citrus (8122), Section H.1.1.1.1 Coffee (8124), Section H.1.1.1.1 Cool Mint (8105), H.1.1.1.1 Fresh (8140), Section H.1.1.1.1 Peppermint (8107), Section H.1.1.1.1 Smooth (8134), Section H.1.1.1.1 Spearmint (8109), H.1.1.1.1 Wintergreen (8111), Section H.1.1.1.2 Chill (8137), Section H.1.1.1.2 Cinnamon (8129), Section H.1.1.1.2 Citrus (8123), Section H.1.1.1.2 Coffee (8125), Section H.1.1.1.2 Cool Mint (8106), Section H.1.1.1.2 Fresh (8141), Section H.1.1.1.2 Peppermint (8108), Section H.1.1.1.2 Smooth (8135), Section H.1.1.1.2 Spearmint (8110), Section H.1.1.1.2 Wintergreen (8112)).

Table 8 Summary of ZYN Ingredients

Ingredient	Grade	Unique ID	CASRN	Function
Acesulfame K	Food grade	(b) (4)	[redacted]	Sweetener
Hydroxypropyl cellulose	USP	(b) (4)	[redacted]	Stabilizer
Maltitol	Food grade	(b) (4)	[redacted]	Filler
Microcrystalline cellulose	(b) (4)	(b) (4)	[redacted]	Filler
Sodium bicarbonate	Food grade	(b) (4)	[redacted]	pH adjuster
Sodium carbonate	Food grade	(b) (4)	[redacted]	pH adjuster

CASRN=Chemical Abstracts Service Registry Number; EP=European Pharmacopeia; ID= ID=identification; JP=Japanese Pharmacopoeia; NF=National Formulary; USP=United States Pharmacopeia.

4.2.1 Acesulfame K

Acesulfame potassium is approved for use in food as a non-nutritive sweetener. It is included in the ingredient list on the food label as acesulfame K, acesulfame potassium, or Ace-K. It is about 200 times sweeter than sugar and is often combined with other sweeteners.

FDA approved acesulfame potassium (US FDA 21 CFR 172 800) for use in specific food and beverage categories in 1988, and in 2003 it was approved as a general-purpose sweetener and flavor enhancer in food, except in meat and poultry, under certain conditions of use. It is heat stable, meaning that it stays sweet even when used at high temperatures during baking, making it suitable as a sugar substitute in baked goods.

Acesulfame potassium is typically used in frozen desserts, candies, beverages, and baked goods. More than 90 studies support its safety.

4.2.2 Hydroxypropyl Cellulose and Microcrystalline Cellulose

Hydroxypropyl cellulose is included in US FDA 21 CFR 172 870. EFSA has recently re-evaluated hydroxypropyl cellulose and microcrystalline cellulose in its Opinion "Re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as food additives" (EFSA 2018). They concluded that no adverse effects were reported after repeated doses up to 35 g per person of microcrystalline cellulose or powdered cellulose. In addition, oral ingestion of some modified celluloses up to (b) (4) mg per person per day for eight months in patients suffering from diarrhea or constipation was well tolerated.

4.2.3 Maltitol

Maltitol is included in US FDA 21 CFR 101 80. Maltitol, a disaccharide sugar alcohol, is composed of glucose and sorbitol. Maltitol and maltitol syrups are self-affirmed generally regarded as safe (GRAS) based on petition to the FDA. The European Union's Scientific Committee on Food (SCF) and JECFA concluded that maltitol is safe and assigned the safest category of an ADI for maltitol of "not specified." (b) (4) is composed of 50% to 55% maltitol and up to 50% (b) (4) (WHO 1993).

A sub-chronic toxicity study for 13 weeks was conducted on (b) (4) (b) (4) fed to rats at 0, 1.25, 2.5, or 5% in the diet. There was reported to be no treatment related effects at the end of the 13-week period (SCF 1999).

4.2.4 Sodium Bicarbonate & Sodium Carbonate

Sodium bicarbonate and sodium carbonate are both included in US FDA 21 CFR 184 1 and are GRAS approved. They are common pH adjusters in food, and bicarbonates also serves a crucial biochemical role in the physiological pH buffering system in humans. Sodium bicarbonate and sodium carbonate are also common ingredients in antacid formulas in substantially higher concentrations than are found in ZYN (Hamm et al 2015).

4.2.5 Safety Assessment Ingredients Conclusion

Swedish Match finds these ingredients to present a low level of concern, if any, due to their regulatory status, widespread use and the low levels found in ZYN compared to other consumer products.

4.3 Safety Assessment of Flavors

All the flavor component in ZYN are meticulously scrutinized by Swedish Match. All flavor components are approved by the EU Regulation to be used in food (Regulation EC No 1334 2008). They are also all food grade compliant and whenever possible GRAS approved flavors are used. All of Swedish Match flavor components used in ZYN except the aromatic oils (like spearmint oil etc.) have FLAVIS Number (FL No). EFSA do not allocate FL No to aromatic oils, which are mixtures by themselves. This number means that the specific flavor component has been evaluated by EFSA (or previously JECFA).

As described below, EFSA's evaluation of flavor components are extensive including taking into consideration the actual exposure for consumers in their risk assessments (EFSA 2010). Swedish Match carefully follows and adapts to any re-evaluation from EFSA or any amendment of the Annex I of Regulation 1334/2008, which can include flavor bans, restriction or maximum usage levels in different product categories (Regulation EC No 1334 2008 Annex I 2012). Swedish Match carefully monitors and adapts the flavor content and concentration in ZYN products in order to not exceed the levels a consumer might ingest on a daily basis according to EFSA. Whenever an ADI/TDI or any other point of departure is available Swedish Match conducts QRAs to secure that threshold limit values will not be exceeded during normal reasonably foreseeable use of ZYN.

4.3.1 European Food Safety Authority Flavoring Group Evaluations

Swedish Match relies on the credibility of EFSAs risk assessment regime. EFSA regularly adopts opinions on each chemical group, known as flavoring group evaluations. To assess safety, intake levels, absorption, metabolism, and toxicity of individual substances are evaluated. Where EFSA identifies data gaps – for instance on toxicity or exposure – it notifies the need for further data to the applicant and to the European Commission. In the course of its work EFSA has asked manufacturers to provide further data on around 400 substances. EFSA re-assesses those substances once the required data are received. A complete evaluation is needed for the substances to be included on the EU list (Regulation EC No 1334 2008). The European Commission maintains a register of flavorings notified by Member States as present on the EU market. It may remove substances during the evaluation program, particularly when EFSA identifies safety concerns.

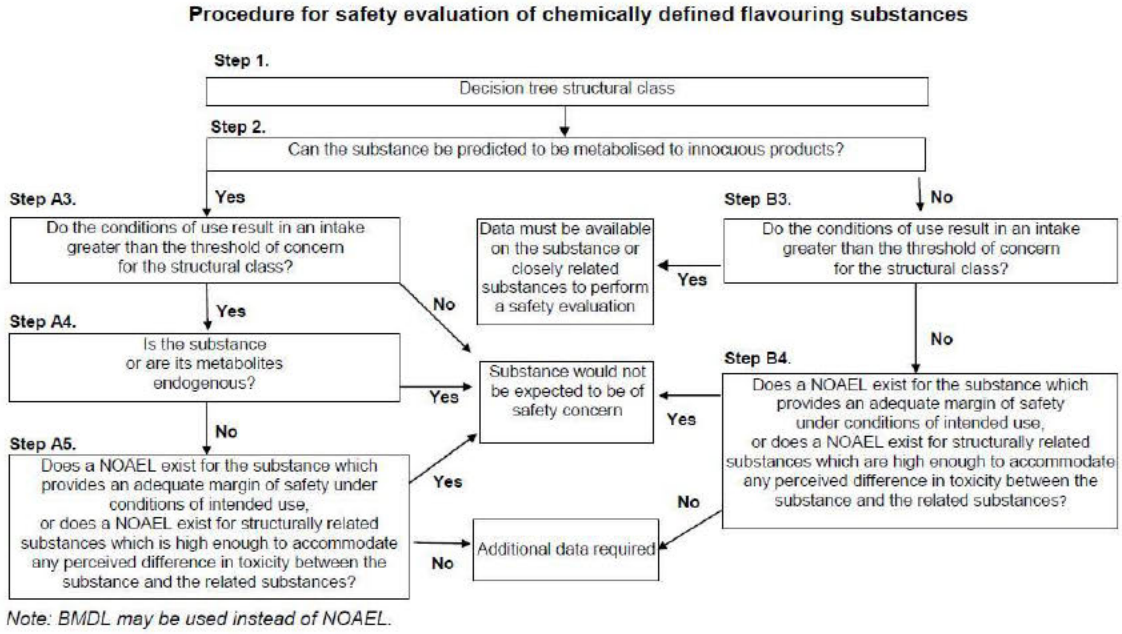
Some flavoring substances evaluated by EFSA have already been assessed by other risk assessment bodies such as JECFA. EFSA always takes account of any relevant conclusions available when it assesses flavoring substances. EFSA's assessments put more emphasis on the potential genotoxicity of flavoring substances, which is not prioritized to the same degree in the evaluations carried out by other risk assessment bodies such as JECFA. In addition to the flavoring group evaluation program, EFSA assesses the safety of individual flavoring substances in response to requests from the European Commission and other risk managers. It has issued opinions for instance on camphor and coumarin.

In this evaluation, EFSA asks the industry for all available toxicological data both in open literature as well as the industry's own confidential data. This data can include, but is not limited to, 90-day sub chronic studies, one to two years chronic studies, reprotoxicity/developmental studies. To the very minimum the genotoxic potential of flavoring substances is assessed by

EFSA prior to any further evaluation. And the companies must also perform a dietary exposure estimate and a quantitative risk assessment whenever possible.

When a flavor component is evaluated by EFSA or JECFA, the review includes both hazard identification (toxicological studies) and risk assessment (exposure assessment), and subsequently risk characterization for the amount found in food at the EU level. After this procedure the flavor is allocated a FL No and included in the union list of flavorings (Regulation EC No 1334 2008 Annex I 2012) in 2012 with Regulation EU 872/2012. A schematic picture of the procedure how EFSA evaluates flavors is shown in Figure 3.

Figure 3 Procedure for EFSAs Safety Evaluation of Chemically Defined Flavoring Substances



Source: EFSA 2010.
BMDL=benchmark dose level; NOAEL=no-observed-adverse-effect-level.

Since 2003, the EFSA has played an important part in preparing this list by evaluating the safety of thousands of flavoring substances, publishing 170 scientific opinions to date. Currently, over 2,500 flavoring substances have been deemed fit for inclusion in the EU list which entered into force on 22 October 2012. This significant program of scientific work, which is still ongoing, has played and continues to play a critical role in ensuring that flavoring substances used in foods are of no safety concern for consumers.

4.3.2 Quantitative Health Risk Assessment for (b) (4)

Swedish Match performed a QRA to assess if potential risks from the flavor component (b) (4), also known as (b) (4) which is an ingredient in ZYN Wintergreen 3 and 6 mg (Section H.2.1 Quantitative Risk Assessment (b) (4)). The FDA has previously raised concerns about not exceeding ADI threshold limit value of (b) (4) mg/kg/day for (b) (4) (WHO 2019), and this QRA was undertaken to verify that the ADI is not exceeded during reasonably foreseeable use by a consumer using ZYN Wintergreen.

The QRA was based on a daily usage of eight ZYN pouches/day (eight pouches of 0.4 g each), which corresponds to 3.2 g/day, based on data from the consumer research Patterns of Use Study (b) (4) (Section H.3.1.1.1 Report Body, Table 12), and body weight was set to 60 kg (used to calculate daily intake in µg/kg body weight and day). The end-product's content of MetSal in ZYN Wintergreen is 3.02% (weight by weight) based on the recipe.

Swedish Match conducted a clinical study (b) (4) on the extraction of (b) (4) during use (Section H.3.1.2.1 Report Body). The extracted amount of (b) (4) was calculated by using the average reference concentration of (b) (4) by weight (in mg/g in 10 unused pouches) and multiplying this value with the individual measured weight of each pouch used in the study. From this value, the remaining used pouch (b) (4) content is subtracted to get a value for the extracted amount of (b) (4). The average extraction was (b) (4)

Table 9 provides a summary of the QRA for (b) (4) in ZYN Wintergreen. Further details of the risk characterization and calculations are found in Section H.2.1 Quantitative Risk Assessment Methyl Salicylate.

Table 9 Summary of Quantitative Health Risk Assessment for Methyl Salicylate (ZYN Wintergreen)

Flavor component	Quantity in ZYN (%)[a]	Extraction (%)[b]	Daily intake[c] (µg/kg bw day)	ADI (µg/kg bw day)	Source ADI	RQ	RQ <1, Acceptable risk
(b) (4)							

Source: Section H.2.1 Quantitative Risk Assessment (b) (4)
ADI=acceptable daily intake; bw=body weight; (b) (4); (b) (4) RQ=risk quotient.
Note: Daily usage of eight pouches/day corresponds to 3.2g ZYN. Human body weight was set to 60kg.
[a] Based on the recipe.
[b] Based on the clinical data in Study (b) (4) Section H.3.1.2.1 Report Body).
[c] Assumptions: daily use of ZYN 3.2 g (eight pouches/day) and 60 kg human.

Based on our assessment, the total daily exposure from (b) (4) using ZYN Wintergreen reaches (b) (4) of the established a health-based reference value of 0.5 mg/kg/day. The JECFA ADI for (b) (4) (WHO 2019) will not be exceeded during reasonably foreseeable use of ZYN Wintergreen.

When considering potential penetration enhancing effects of (b) (4) and the apprehension about greater uptake of other HPHCs, (b) (4) did not impact AUC or C_{max} for nicotine in clinical studies (b) (4)) (Section H.3.1.2.4 Report). This suggests no penetration enhancing effects from (b) (4) on nicotine uptake.

There is no clinical data showing whether a penetration enhancing effect can occur for other HPHCs. However, QRAs were performed for the few HPHC found in ZYN. The QRA were performed assuming "worst case" scenarios (assuming 100% extraction and uptake) and the RQs were far below one (Table 7). Considering the HPHC levels found in ZYN, the potential for (b) (4) penetration enhancing effects may be of less relevance.

Swedish Match concludes that the level of (b) (4) in ZYN Wintergreen is not likely to have any adverse effect on public health.

4.4 Safety Assessment of Pouch Material

The pouch paper consists of (b) (4) and (b) (4) The exact composition of the pouch paper is a trade secret of the vendor. All the material in the portion pouch fabric are in compliance with the following FDA regulations for indirect food additives: paper and paperboard components (US FDA 21 CFR 176 170) and adhesive (US FDA 21 CFR 175 105).

Swedish Match concludes that the ingredients of the pouch material are not likely to have any adverse effect on public health.

4.5 Summary and Conclusions of Risk Assessments for ZYN

By comparing the actual consumer exposure of HPHCs and ingredients against valid threshold limit values set by recognized authorities in our QRAs, the levels of formaldehyde, acetaldehyde, coumarin, naphthalene, (b) (4) and (b) (4) in ZYN were below current health-based threshold values. Under reasonably foreseeable conditions of use of ZYN, the low levels of HPHCs present do not raise concern from a public health perspective and support that ZYN is appropriate for the protection of the public health.

Based on QRA, Swedish Match concludes that the low level of (b) (4) is not likely to have adverse effect on public health.

Swedish Match concludes that the ingredients, flavors, and pouch material are not likely to have any adverse effect on public health under reasonable and foreseeable use.

5 NONCLINICAL SAFETY OF ZYN

The mutagenic and genotoxic potential of each flavor of ZYN (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) 6 mg was assessed *in vitro* using the Ames assay and the micronucleus (ivMN) assay (Section H.2.3 Study (b) (4) Report). These assays, when performed in combination, have been shown to provide a high degree of sensitivity with predicting genotoxic rodent carcinogens. For each of the mutagenicity and genotoxicity assays on ZYN, testing was also conducted on an ST comparator, CRP2.1. Collectively, these assays provide an appropriate assessment of the potential of ZYN to result in mutagenicity and/or genotoxicity *in vitro*. The study was conducted on ZYN (b) (4)

This study was conducted in compliance with the applicable requirements of the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) using validated methods.

5.1 In Vitro Genotoxicity Study to Assess Potential Mutagenic and/or Genotoxic Response Associated with ZYN and CRP2.1

5.1.1 Test Items, Sample Generation, and Extraction

5.1.1.1 Test Items for Mutagenicity and Genotoxicity Testing

The study was conducted using extracts of ZYN and CRP2.1 (referred to as test items). The test items used in the study are described in Table 10; for further details on batches used, see Section H.2.3 Study (b) (4) Report.

Table 10 Test Items and Identification in Support of Mutagenicity and Genotoxicity Testing

Test Item/Unique ID	Description	Date of Manufacture
CRP2.1	Comparator Product: CORESTA Reference Product	April 2016
8106	ZYN Cool Mint 6 mg	10 June 2019
8108	ZYN Peppermint 6 mg	5 June 2019
8110	ZYN Spearmint 6 mg	11 June 2019
8112	ZYN Wintergreen 6 mg	23 May 2019
8123	ZYN Citrus 6 mg	11 June 2019
8125	ZYN Coffee 6 mg	18 June 2019
8129	ZYN Cinnamon 6 mg	7 June 2019
8135	ZYN Smooth 6 mg (unflavored)	12 June 2019
8137	ZYN Chill 6 mg	13 June 2019
8141	ZYN Fresh 6 mg	14 June 2019

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; ID=identification.

5.1.1.2 Sample Generation and Extraction

The test items were dissolved in two steps, due to the dry product powder matrix, to facilitate an almost complete dissolution and maximum flavor release into the test solvent. In the first step, a small amount of deionized water was added to the product powder for the dissolution of the flavor carrier material and thus assist in the release of flavor. Absence of this initial water treatment could have resulted in an incomplete flavor extraction. The presence of water could also increase the solubility of inorganic salts. (b) (4)

The concentration in the stock extracts were (b) (4)

CRP2.1 extract was made using the same methodology for the dose finding part of the study. Due to microbial contamination found in the CRP2.1 test item for replicates two and three, the study plan was amended with a filtration step of the extracts to remove the microbial contamination.

For the Ames and ivMN tests, the match solvent control used in the assays consisted of (b) (4) For preparation of reference items and control substances, see Section H.2.3 (b) (4) Report.

5.1.1.3 Characterization of Test Items

For each test item subjected to the Ames or ivMN assay, nicotine content from ZYN (b) (4), as well as for the extracts, were determined by gas chromatography using a split mode of injection with a flame ionization detector. Average nicotine contents in ZYN extracts were (b) (4) mg/mL (mean ± SD, based on three extractions and all products) and (b) (4) mg/mL (mean ± SD, n=3) in CRP2.1extracts, respectively. Full method description and data are in Section H.2.3 Study (b) (4) Report.

For ivMN, pH, and osmolarity of tissue culture media with test item extracts were assessed (for details see study report).

5.1.1.4 Cigarette Reference Item for Mutagenicity and Genotoxicity Testing

For the Ames mutagenicity and ivMN genotoxicity assays, (b) (4) used a previously prepared, pooled sample of total particulate matter (TPM) extracts in (b) (4) from the Kentucky Reference 1R6F cigarette reference item smoked under Health Canada Intense conditions. Concentrations used in the study correspond to 0, 25, 50, 75, 100, 125, 250, and 500 µg TPM/plate in the Ames assay and 0, 75, 100, 150, and 200 µg TPM/plate in the ivMN assay. The reference item TPM extracts were stored in a cryofreezer (-70°C or below). TPM extracts were included as an internal tobacco product reference for the analytical part of the study and was hence not included in statistical and overall evaluation of the study. Mutagenicity and genotoxicity outcome presented below were only based on the criteria for an at least two-fold increase of the number of revertant colonies compared to the corresponding solvent controls in the Ames assay, and that the mean frequency of micronuclei at any dose exceeding the historical (b) (4) control for the ivMN assay.

5.1.1.5 Negative and Positive Controls

Negative controls in Ames assay were untreated cells, and solvent controls ± S9 (b) (4) Positive controls were strain specific controls based on the OECD guideline with the addition of B(a)P for strain TA98 + S9. It is required that the mean positive control value exhibited at least a three-fold increase over the respective mean negative control value for each tester strain to be accepted.

Negative controls in ivMN assay were solvent controls (b) (4)). Positive controls were assay specific controls based on OECD guideline.

5.1.2 Study Design and Methods: Assessment of Mutagenic Response Using the Ames Assay

The bacterial reverse mutation test, commonly called Ames test, uses *Salmonella typhimurium* strains that are deficient in deoxyribonucleic acid repair and unable to synthesize histidine. In the presence of a mutagenic compound, the defective histidine gene can be mutated back to the functional state, thereby restoring bacterial growth in a medium that lacks histidine. The mutant colonies are referred to as “revertants” and are counted and used for detecting mutagenic responses. Multiple strains are used, based on their ability for detecting specific mutational events. For example, TA100 and TA1535 are able to detect base-pair substitutions, TA102 is able to detect transition/transversion mutations, whereas TA98 and TA1537 are able to detect frameshift mutations. These assays are routinely performed with and without a metabolic activation system, which is prepared from the postmitochondrial fraction of the 9,000×g supernatant (S9) obtained from the liver homogenate of enzyme-induced rats. The presence or absence of the S9 metabolic activation system allows for the potential to detect indirect-acting or direct-acting genotoxic compounds, respectively.

The selection of the Ames mutagenicity assay as a test system was based on the requirements of the OECD Guideline Number 471 (hereinafter the “OECD TG 471”) (Organisation for Economic Co-operation and Development 1997) and those of the Health Canada official test method T-501, Second Edition, *Bacterial Reverse Mutation Assay for Mainstream Tobacco Smoke* (Health Canada 2004a).

In this study, the test items were assayed using these five different strains of *S. typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) both in the presence and absence of S9 that was obtained from Aroclor 1254-induced rat liver. The dose ranges were selected as per the recommendation of the OECD TG 471 and based on mg test item per mL solvent used for extraction. Concentrations of ZYN assumed that extraction was complete.

First, a dose range finder (DRF) was run with 10 concentrations of the test items (triplicate plate per test item and concentration) to identify the seven concentrations which were used for replicates two and three. All three repeats were used to assess revertant colony counts, toxicity and test item precipitation.

Cigarette reference item TPM smoke extract was applied to the Ames assay test system using the dosing in units of µg TPM/plate. ST test item extract was applied to Ames assay test system using units of mg product/plate for extract in (b) (4) .

5.1.2.1 Statistical Analysis and Acceptance of Analytical Results

Data were evaluated in two stages. In the first stage, the results from reference items and positive controls were compared to the CRO's historical in-house database, and for this study all data was acceptable. This was followed by analysis of the negative controls and solvents controls and test items. In the next stage the statistical analysis of the data was applied. In short, calculations of slopes followed by linear regression chi-square likelihood test and Dunnett's test were applied over the dose range to determine if at least one non-zero concentration exhibited a statistically significant increase in revertant counts compared to the solvent control (zero) concentration (for further details see study report).

5.1.2.2 Criteria for Determining a Positive Mutagenic Response of a Test Item in a Replicate Assay and Determination of the Overall Mutagenic Response

A response was considered biologically relevant when the number of revertant colonies per plate exceeded the corresponding number of solvent control revertant colonies per plate by at least two fold.

1. Among biologically relevant responses, a test item was considered mutagenic when:
    a. There was a concentration-related increase in revertant colonies observed over the range tested. In other words, if the slope of the line fit to the linear part of the concentration response curve, was positive and significantly different from zero (0).
    b. A statistically significant increase ($\alpha = 0.01$) in mean revertant colonies/plate was observed for at least one concentration compared to the solvent control using the Dunnett's test.
2. A test item was considered non-mutagenic when the number of revertant colonies per plate did not exceed the corresponding number of solvent control revertant colonies per plate by more than two fold.

A test item was regarded as non-mutagenic in the replicate assay if (2) is met or if neither (1a) nor (1b) was met.

A test item was regarded as mutagenic in the replicate assay if at least one of (1a) or (1b) is met.

A test item which gave a reproducible mutagenic response across all three replicate assays for a particular tester strain and metabolic activation was judged overall as mutagenic for that particular tester strain and metabolic activation.

A test item which gave a reproducible non-mutagenic response across all three replicate assays for a particular tester strain and metabolic activation was judged overall as non-mutagenic for that particular tester strain and metabolic activation.

For any test item in which the response was not reproducible across all three replicate assays for a particular tester strain and metabolic activation, to assist in establishing biological relevance of a result, the data was evaluated based on the following (expert judgement):

- The number of replicate assays that give a mutagenic response
- Comparison of the range of revertant counts observed across all test item doses versus the solvent controls (b) (4)) from this study and CRO's historical database

For all the test items, controls and reference item, the mean number of revertants per plate and the standard deviation for each dose level for each Ames mutagenicity assay were calculated and reported.

Statistical analysis was performed for all test items and solvent control as defined in study plan. Briefly, Ames mutagenicity slopes were determined for each test item replicate assay using a Poisson regression model predicting the number of revertants/plate from the test item sample dose (mg ZYN or CRP2.1 per plate). Once the model was fit, such that the maximum dose was retained, a Poisson straight line regression model was fit to the retained doses to determine the slope of a line fit to the linear portion of the curve. If fewer than three non-solvent control dose levels remained, no slope value was reported. The resulting slope statistic has the unit revertant colonies (or "revertants") per mg ZYN or CRP2.1. Ames slopes were also determined in units of revertants per mg nicotine using the nicotine content of the product powder extract on an "as is" basis in mg per mL.

5.1.3 Results: Ames Assay

All positive and negative control assay results and all solvent control assay results included in this study were found to be acceptable in regard to the assay requirements defined in the study plan. The test item solvent control (b) (4)) data were in line with the (b) (4) - control used in study and (b) (4) historical control data from the laboratory for all tested strains ± S9.

Although there were no statistical assessments made for the TPM reference item, it was considered to be mutagenic since it had a clear response (strains TA98 + S9 and TA1537 + S9) based on a more than two-fold increase in revertant colonies compared to its (b) (4) control, as well as clear dose response (see Table 11, which is relevant to all strains, and Figure 4 and Figure 9, which are relevant to TA98 and TA1537, respectively). Without metabolic activation (-S9), the same strains were mutagenic at the top dose tested (0.5 mg TPM/plate). The 10 graphs represented in the figures show the mean data from a repressive replicate (No 2) of the test item, with all concentrations tested included (Figure 4 is relevant to TA98 and is shown here as an example, whereas Figure 6, Figure 7, Figure 8, and Figure 9 are relevant to TA100, TA102, TA1535, TA1537, respectively, and are shown in the Appendix, Section 9.1.22). In these figures and in addition to the test items, the TPM reference data is included together with a line representing a two-fold change from its (b) (4) control used for making the mutagenicity call in Table 11. For the test item's mutagenic evaluation, their own solvent controls ((b) (4) were used, but their corresponding lines are not included in figures.

(b) (4)

Precipitation was not evident within the culture media used for this study or on any assay plate reported for this study. For the test items included in this study, evidence of toxicity varied with both test item replicate and strain. The number of toxic doses were at most six for replicate one and four for replicates two and three. The number of non-toxic doses was sufficient for the analysis.

High level summary data for the overall mutagenic response is presented in Table 11.

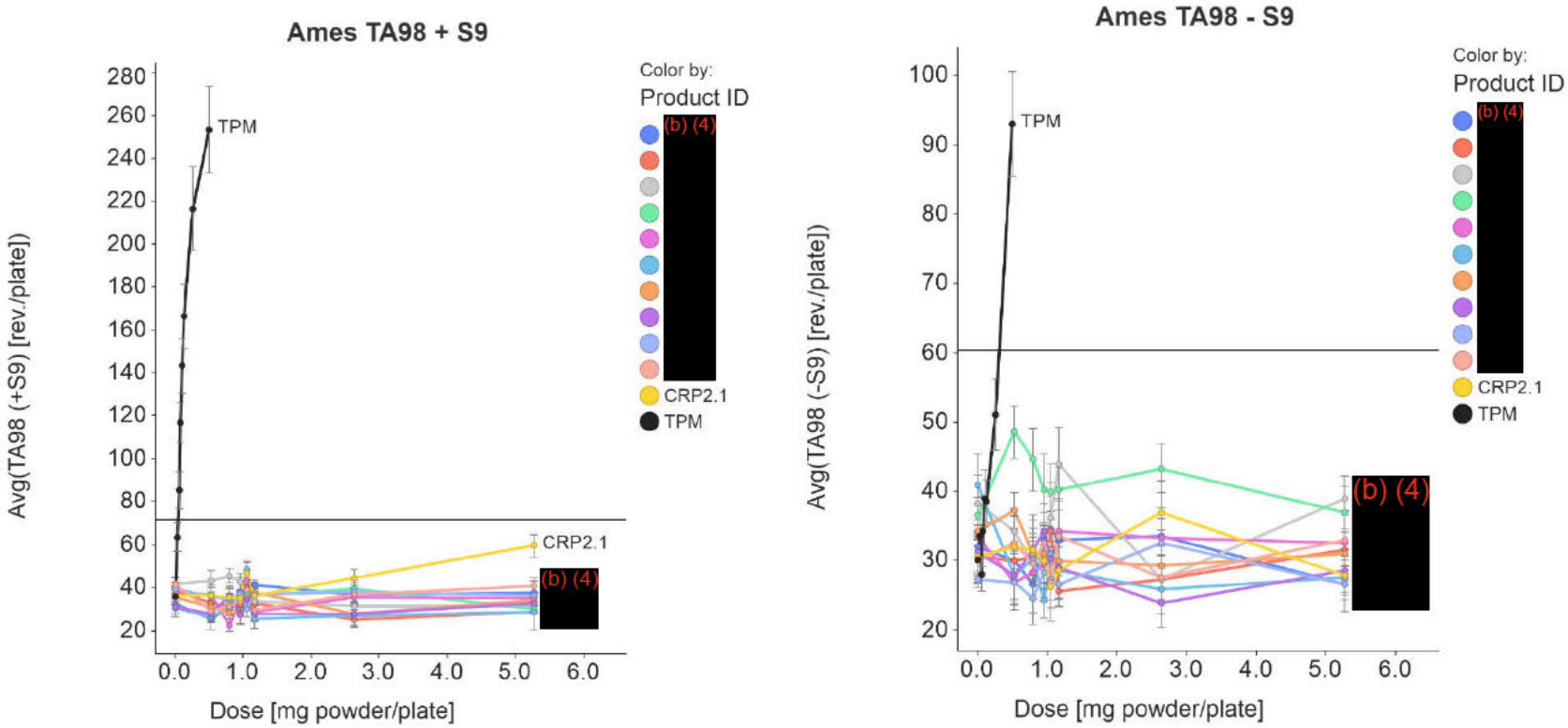
Table 11 Summary of the Overall Evaluation Mutagenic Response in the Different Strains in the Ames Assay

Product/ Unique ID	Ames Strain and Metabolic Activation (± S9)									
	TA98 (+S9)	TA100 (+S9)	TA102(+S9)	TA1535 (+S9)	TA1537 (+S9)	TA98 (-S9)	TA100 (-S9)	TA102 (-S9)	TA1535 (-S9)	TA1537 (-S9)
CRP2.1	-	-	-	-	-	-	-	-	-	-
8106	-	-	-	-	-	-	-	-	-	-
8108	-	-	-	-	-	-	-	-	-	-
8110	-	-	-	-	-	-	-	-	-	-
8112	-	-	-	-	-	-	-	-	-	-
8123	-	-	-	-	-	-	-	-	-	-
8125	-	-	-	-	-	-	-	-	-	-
8129	-	-	-	-	-	-	-	-	-	-
8135	-	-	-	-	-	-	-	-	-	-
8137	-	-	-	-	-	-	-	-	-	-
8141	-	-	-	-	-	-	-	-	-	-
TPM*	+	-	-	-	+	+	-	-	-	+

Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; ID=identification; TPM=total particulate matter.
Note: If the mutagenic response for a test item was reproducible across all replicate assays, the overall response is considered "mutagenic" (+). If the non-mutagenic response for a test item was reproducible across all replicate assays, the overall response is considered 'non-mutagenic' (-). If a mutagenic or non-mutagenic response for a test item is not reproducible across the replicate assays, the overall response is evaluated based on (1) the number of replicate assays which give a mutagenic response, (2) comparison of the range of revertant counts observed across all test item doses versus the solvent controls ((b) (4)) from this study and CRO's historical database.
For test items, only concentrations without limiting toxicity included in overall evaluation.
* Mutagenesis outcome for mean TPM only based on >2-fold change from mean solvent control (b) (4) n=8. No data on toxicity for TPM, hence top concentration included.

The mutagenic response of each test item extract in each replicate assay was evaluated in relation to their own solvent ((b) (4) control, followed by an overall assessment of the mutagenic response across all three replicate assays. For all strains TA98 (+S9 and -S9), TA100 (+S9 and -S9), TA102 (+S9 and -S9), TA1535 (+S9 and -S9) and TA1537 (+S9 and -S9), all test items had all three replicate assays deemed 'non-mutagenic' with one exception. Replicate two for ZYN Peppermint 6 mg in TA1535 (-S9) was deemed mutagenic based on the slope activity but replicates one and three were non-mutagenic. This is likely due to the lower solvent control colony counts, which led to the number of colonies on three plates slightly exceeding the number of solvent controls revertant colonies by two-fold. However, the overall assay response for the "ZYN Peppermint 6 mg" (test item 8108) test item was deemed non-mutagenic in strain TA1535 (-S9) based on the number of replicate assays that give a mutagenic response (one out of three). Hence, the overall assay response for each combination of test item (including the unflavored ZYN Smooth and the nine flavored ZYN along with the CRP2.1 reference tobacco product) and strain discussed above was also considered "non-mutagenic".

Figure 4 Ames Assay Data of Strain TA98 With and Without Metabolic Activation for ZYN, CRP2.1, and Cigarette TPM



Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Left panel: Mean ± SD of revertants in strain TA98 with metabolic activation (+S9).
Right panel: Mean ± SD of revertants in strain TA98 without metabolic activation (-S9).
Replicate 2 was selected as a representative replica for the test items. All tested concentrations included.
The horizontal line included for visualization represents 2-fold solvent control for TPM samples (b) (4) used for making mutagenicity call for reference TPM. For the overall mutagenic evaluation, the test items own solvent controls ((b) (4) were used.

In conclusion, the evaluation of the mutagenic response for all of the flavors of ZYN 6 mg in the Ames assay, all replicate extracts from each of the ZYN products were found to exhibit a non-mutagenic response in each of the five Ames assay strains in the presence or absence of S9 microsomal fraction (TA98±S9, TA100±S9, TA102±S9, TA1535±S9, and TA1537±S9) over the range of doses tested ([redacted]).

The results for ZYN are aligned with the outcome of testing CRP2.1 as all replicate extracts were found to exhibit a non-mutagenic response in each of the strains and in the presence or absence of S9 microsomal fraction over the range of doses tested [redacted]

5.1.4 Study Design and Methods: Assessment of Genotoxic Response Using the In Vitro Micronucleus Assay

The ivMN assay detects the presence of micronuclei in the cytoplasm of cells during interphase. Micronuclei may form from either chromosomal fragments or chromosomes that are unable to fully move during cellular division; thus, they are representative of damage that will be transmitted to daughter cells. Therefore, this assay can provide information for chemical compounds that may cause genetic damage via an aneugenic (cause an abnormal number of chromosomes) or clastogenic (causing breakages, leading to changes in sections of chromosomes) mode of action. Chinese hamster ovary (CHO-WBL) cells were used as the test system for the *in vitro* mammalian cell micronucleus genotoxicity assay during the study. Short-term treatment (3 hours ± 15 minutes) was conducted with the test articles in the absence (-S9, Schedule i) or presence of S9 metabolic activation system (+S9, Schedule ii), which was obtained from Aroclor 1254-induced rats, followed by recovery (27 ± 1 hour). Long-term continuous treatment (Schedule iii) of the cells was also performed (30 ± 1 hour) in the absence of S9 metabolic activation system (-S9).

The selection of the *in vitro* micronucleus assay as a test system is based on the requirements of the OECD Guideline for Testing of Chemicals Number 487, hereinafter referred to as "OECD TG 487" (Organisation for Economic Co-operation and Development 2016), and those of the Health Canada official test method T-503, Second Edition *In Vitro Micronucleus Assay for Mainstream Tobacco Smoke* (Health Canada 2004b). The dose ranges for ZYN and CRP2.1 were selected as per the recommendation in the OECD TG 487. Concentrations of ZYN assumed that extraction was complete.

In the DRF phase, the test items were assessed in eight non-zero doses plus the solvent control and positive control, for ivMN cytotoxicity (ie, cell proliferation only). Based on the results of the ivMN cytotoxicity response for the test items, the five non-zero dose levels for replicates two and three were selected. DRF was acceptable to use as replicate one, and slides were then prepared and scored for the five dose levels in parallel with replicates two and three.

Cells from each flask (two flasks per treatment and replica) were fixed with fixative (1:3 v/v glacial acetic acid:methanol) and slides were prepared using a cytospin centrifuge. Cells were then stained with Acridine Orange. Following slide preparation, 1,000 randomly selected cells were scored for the presence of micronuclei. Micronuclei not exceeding ⅓ of the main nucleus diameter, not overlapping with the main nucleus, and with distinct borders were included in the scoring.

Three replicates, each consisting of two flasks, were assayed for each dose level of each test item extract and for each solvent and positive control. A single flask was assayed for each reference item TPM extract in (b) (4) for further details see study report.

Cigarette reference item TPM extract was applied to the ivMN assay test system using dosing in units of µg TPM per mL. ST test item extract was applied to the ivMN assay test system using dosing in units of mg product per mL for test item extract in (b) (4) .

Acceptance criteria for the (b) (4) solvent control and positive controls were deemed acceptable if the average % MN across duplicate flasks were in keeping with the CRO's database of historical % MN results for the (b) (4) control under each treatment schedule or historical % MN results for each positive control substance and concentration. In addition, to assess whether the cells have multiplied adequately during the assay, there must be at least a 90 % increase in the number of viable cells at the time of harvest in the solvent control cultures.

5.1.4.1 Criteria for Determining a Positive Genotoxic Response

The criteria for determining a positive genotoxic response of a test item in a replicate assay was as follows:

1. A statistically significant increase ($\alpha = 0.01$) in mean frequency of micronuclei was observed for at least one concentration compared to the solvent control using Dunnett's test.
2. There was a concentration-related increase in the number of micronuclei per 1,000 scored cells over the range tested. In other words, if the slope of the line fit to the linear part of the concentration response curve, was positive and significantly different from zero (0) using the Chi-square likelihood-ratio test.
3. The mean frequency of micronuclei at any dose exceeded the historical (b) (4) control.

A test item was regarded as non-genotoxic in the replicate assay if any of (1), (2), and (3) is not met. Conversely, a test item was regarded as genotoxic in the replicate assay if each of (1), (2), and (3) is met.

When taking all three replicas (run as duplicate samples) into account an overall assessment of genotoxic response was made.

- A test item which gave a reproducible genotoxic response across all three replicate assays was considered overall as genotoxic.
- A test item which gave a reproducible non-genotoxic response across all three replicate assays was considered overall as non-genotoxic.
- A test item in which the genotoxic response was not reproducible across all replicate assays was deemed inconclusive/equivocal.

5.1.4.2 Statistical Analyses

Statistical analyses were performed for all test items and solvent control as defined in study plan. Briefly, statistical analysis of the genotoxicity slopes for the different test items in the ivMN assays were determined for each test item replicate assay using a Poisson regression model

predicting the number of micronuclei in 1,000 scored cells (MN) from the test item extract sample dose (mg ZYN or CRP2.1 per mL). Once the model was fit such that the maximum dose was retained, a Poisson straight line regression model was fit to the retained doses to determine the slope of a line fit to the linear portion of the curve. If fewer than three non-solvent control dose levels remained, no slope value was reported. The resulting slope statistic has the unit number of micronuclei (or "No. of MN") per (mg powder per mL) for test item extract. Micronucleus genotoxicity assay slopes were also determined on a basis of number of micronuclei in 1,000 scored cells per test sample "amount", with the "amount" of test sample expressed as "mg nicotine per mL", using the nicotine content of the product powder extract on an 'as is' basis in mg/mL.

In addition, an aliquot of each of the 10 ZYN and the CRP2.1 extracts in (b) (4) mixed with tissue culture media was also tested in single replicate for pH and osmolarity at all doses.

5.1.5 Results: In Vitro Micronucleus Assay

All (b) (4) solvent control assay results in regards to cell proliferation that were part of this study were found to be acceptable (>90% increase), and they were also deemed acceptable because the average % MN across duplicate flasks were in keeping the CRO's database of historical % MN results for the (b) (4) control under each treatment schedule. The (b) (4) control was also deemed acceptable.

All positive control assay results that were part of this study were found to be acceptable (based on historical control data). Based on the criteria for positive response, based on % micronuclei, the study revealed a dose response as well as an increase of %-micronuclei for the TPM extract, compared to historical (b) (4) controls in the different treatment schedules and in line with historical TPM data from the CRO reference cigarette Kentucky Reference 1R6F, and hence the TPM extract included in this study was classified as genotoxic in the assay (Table 12).

The test item doses for replicate 1 were (all three dosing schedules): (b) (4) (b) (4) mg product per mL) and for replicates two and three the following dose were used: (b) (4) mg product per mL). Cytotoxicity were seen for several different test items. However, the level of cytotoxicity was below 55% for all test items (see Figure 5, Figure 10, and Figure 11). Cytotoxicity is one factor used to identify the top dose in the ivMN assay, and higher concentrations were not tested because the highest dose was judged to be the maximally feasible dose under these conditions. As per OECD TG 487, generally, organic solvents (eg, (b) (4)) should not exceed 1% in treatment medium (v/v). Test items were extracted in water/DSMO (b) (4) corresponding to 94.74% (b) (4) in the extract (v/v). 100 µL of this (b) (4) extract was added to 9.9 mL of treatment medium to achieve a concentration of (b) (4) . The (b) (4) concentration of this mixture is 0.947 % (v/v), which is close to the 1% (v/v) (b) (4) limit in treatment medium. The genotoxic response of the ZYN and CRP2.1 extracts in (b) (4) in each replicate assay was evaluated, followed by an overall assessment of the genotoxic response across the two replicate assays. For all three treatment schedules, all of the test items had all three replicate assays deemed 'non-genotoxic' for the powder extract in (b) (4) .

Hence, the overall assay response for each combination of the test items and treatment schedule discussed above was also considered 'non-genotoxic'. The figures are representative examples from Schedule (i - iii) using replicate two for the 10 ZYN samples, as well as the CRP2.1 and

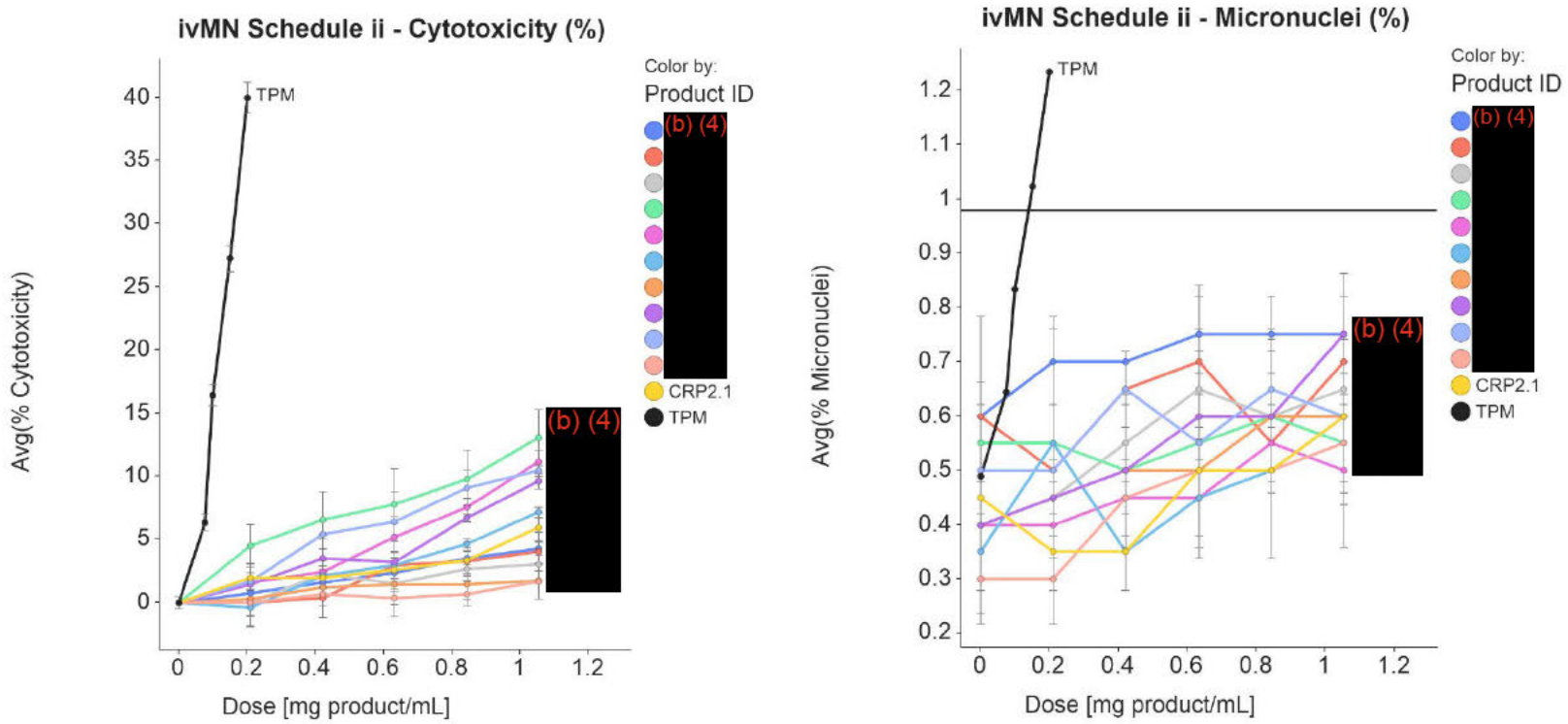
TPM samples and the left panels in the figures shows the cytotoxicity and the right panels the %-micronuclei (Figure 5 is relevant to schedule [ii] and is shown here as an example, whereas Figure 10 and Figure 11, which are relevant to schedule [i] and schedule [iii], respectively, are shown in the Appendix, Section 9.1.22). In addition to the test items, the TPM reference data is included together with a line representing a 2-fold change from its (b) (4) control used for making the genotoxicity call in Table 12.

Table 12 Summary of Evaluation of Overall Genotoxic Response in the In Vitro Micronucleus Assay

Product/Unique ID	Schedule (i)	Schedule (ii)	Schedule (iii)
CRP2.1	-	-	-
8106	-	-	-
8108	-	-	-
8110	-	-	-
8112	-	-	-
8123	-	-	-
8125	-	-	-
8129	-	-	-
8135	-	-	-
8137	-	-	-
8141	-	-	-
TPM*	+	+	+

Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; ID=identification; TPM=total particulate matter.
Note: Schedule (i) - short-term treatment (3 hours ± 15 minutes) in absence of metabolic activation (-S9) followed by recovery (27±1 hours).
Schedule (ii) - short-term treatment (3 hours ± 15 minutes) in presence of metabolic activation (+S9) followed by recovery (27±1 hours).
Schedule (iii) - long-term continuous treatment (30±1 hours) in absence of metabolic activation (-S9)
Genotoxic (+) and non-genotoxic (-).
Five non-zero concentrations were used for the test items in the range between (b) (4), except for TPM where 4 non-zero concentrations were used for short term treatment between 0-0.2 mg TPM per mL for long term treatment 0 -0.1mg TPM per mL.
* Genotoxicity response for mean TPM based only the frequency of micronuclei (%MN) observed over the dose range that exceeded that of the historical solvent control ((b) (4)). No statistical analysis was performed for TPM.

Figure 5 **In Vitro Micronucleus Assay Data for ZYN, CRP2.1 and Cigarette TPM, Short-term Treatment with Metabolic Activation (Schedule ii)**



Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter
Note: Results from *in vitro* micronucleus assays in CHO-WBL cells using short-term treatment with metabolic activation (+S9, Schedule ii). Replicate 2 was selected as a representative replicate for the test items. All tested concentrations are included. 1,000 cells were counted per slide.
Left panel: Mean ± SD for cytotoxicity.
Right panel: Mean ± SD for %-micronuclei.
The horizontal line included for visualization represents the 2-fold increase over solvent control for TPM samples (b) (4) used for making the genotoxicity call for the reference TPM. For the overall genotoxic evaluation, the test items' own solvent controls (b) (4) were used.

In conclusion, the evaluation of genotoxicity for all of the flavors of ZYN 6 mg in the *in vitro* micronucleus assay demonstrated that in all treatment schedules (short-term in the presence or absence of metabolic activation system, and long-term continuous treatment without metabolic activation), ZYN exhibited overall non-genotoxic responses over the range of doses tested (b) (4) [redacted]

The results for ZYN are aligned with the outcome of testing of CRP2.1, which exhibited a non-genotoxic response for all treatment schedules over the range of doses tested (b) (4) [redacted]

5.2 Conclusion: In Vitro Genotoxicity Studies Show No Mutagenic or Genotoxic Response with ZYN or CRP2.1

The *in vitro* toxicology studies conducted for each of the 10 flavors of ZYN 6 mg demonstrate that neither of the products are mutagenic or genotoxic under the study conditions employed. The lack of biological response associated with ZYN is aligned with the results of CRP2.1. The data from cigarette TPM, on the other hand, was positive in both assays, based on a more than two-fold increase of revertants in the Ames assay and more than two-fold increase of %-micronuclei in the ivMN assay compared to solvent control.

In a previous study, Swedish Match snus showed results in line with this data at similar concentrations in the Ames and ivMN assays (Coggins et al 2012).

The lack of genotoxic or mutagenic effects in *in vitro* studies indicates a low potential for carcinogenic effects of ZYN.

6 SYSTEMATIC LITERATURE REVIEW OF SNUS

Swedish Match began selling ZYN, a tobacco-free, smoke-free, and spit-free nicotine pouch, in 2014, and to date, there is no published literature on the use of ZYN. ZYN exposes the user to levels of nicotine that are similar to those found in snus, but as ZYN generally has reduced or no measurable levels of unwanted HPHCs, health effects of snus could be considered as a measure of maximum health risks. ZYN is closely related to Swedish snus (as described in Section 1), both in the context of product usage and production; therefore, a literature search was performed on Swedish snus as it is the most closely related product in the smokeless category.

The process surrounding the literature review is described in this section, and followed by selected literature that focuses on the toxicological assessment of Swedish snus.

A systematic literature review was commissioned by Swedish Match and was performed on Swedish snus as follows:

- Health effects of Swedish snus, both absolute and relative to combustible cigarette smoking, as well as *in vitro* and *in vivo* toxicology studies of Swedish snus
- Tobacco use behaviors and perceptions of risk pertaining to the use of Swedish snus

The systemic literature review was performed as part of an update to the 2013 ENVIRON Report (Section I.1 2013 Environ Report), which was previously conducted for the General Snus PMTA and Modified Risk Tobacco Product Application (MRTPA) and included a comprehensive review of the available literature on snus through December 2012 and also selected important new publications as available through April 2013.

6.1 Search Methods

Relevant literature included publications that have been published and/or made publicly available after 01 December 2012 (ie, the cut-off date for the MRTPA search) and were not included in the 2013 ENVIRON Report. Structured searches in PubMed/MedLine (http://www.pubmed.com), Scopus (http://www.scopus.com/), and ClinicalTrials.gov (http://clinicaltrials.gov/) were used to identify the relevant literature spanning across the disciplines and publication types of interest. Additionally, searches of selected, pre-determined government and nongovernment organization websites were also conducted to identify reports of primary data not traditionally captured in literature databases.

In addition, a retrospective literature search on the human health effects of Swedish snus was also conducted without a start date through 01 December 2012 because of a lack of a reproducible systematic approach regarding the literature search strategy described in the 2013 ENVIRON Report. Any potentially relevant studies identified through this search that were not included in the 2013 ENVIRON Report were evaluated and included in the update if deemed relevant.

All searches were completed on 28 July 2017.

6.2 Search Results

The objective of the update relating to the health effects for this PMTA was to identify and evaluate all original primary scientific studies published since 01 December 2012 through 28 July 2017, and not included in the previous review, and to comprehensively update previous conclusions contained within the following specific sub-sections of the 2013 ENVIRON Report:

- Section 4: Nonclinical toxicological studies with Snus
- Section 5: Human health effects of snus (including all previous and new endpoints)
- Appendix VI (to Section 5): Relative risks among snus users and smokers compared to non-tobacco users
- Appendix VII (to Section 5): Comparison of risks from dual use, switching, and quitting

The updated report (Section I.1 Health Effects and Meta-Analysis Update Report, Section 1) includes a summary of the conclusions from the 2013 ENVIRON Report listed above (which is comprehensive through December 2012), a presentation of new information (if available) for each endpoint, and an updated evaluation of the total available evidence and conclusion. Newly identified human health endpoints were presented with their own new summary, evaluation, and conclusion. This review and update of the 2013 ENVIRON Report (Section I.1 2013 Environ Report) was intended to be systematic, with the methods clearly and transparently presented so the literature searches and evaluations could be replicated. This systematic review was intended to comply with all relevant guidelines of the Preferred Reporting Items for systematic Reviews and Meta-Analyses (PRISMA) statement, a well-established and highly regarded standard for the reporting of systematic reviews and meta-analyses. The 27-item checklist of the protocol is provided in Section I.1 Health Effects and Meta-Analysis Update Report, Appendix A, with relevant page numbers cited for each item on the checklist.

Full details on search strategy and methods are provided in Section I.1 Health Effects and Meta-Analysis Update Report, Section 1. Methods and search results relevant to the nonclinical literature are detailed in Section I.1 Health Effects and Meta-Analysis Update Report, Section 1.2. Detailed screening results of the literature searches are provided in an adapted PRISMA inclusion/exclusion diagram in Section I.1 Health Effects and Meta-Analysis Update Report, Appendix C.

After detailed screening and review, nonclinical studies were identified and included in the qualitative syntheses, and these included five relevant primary studies on nonclinical toxicology and *in vitro* testing related to Swedish snus (Section I.1 Health Effects and Meta-Analysis Update Report, Section 5).

Although the documents listed above provide a full narrative of the Swedish snus literature, a selection of nonclinical literature is described in support of the ZYN PMTA. For example, as ZYN does not contain TSNAs, studies that are specific to TSNAs in snus are of no relevance to ZYN and are therefore not discussed.

6.3 Review of In Vitro and In Vivo Literature

There is no literature about the *in vitro* and *in vivo* toxicology of ZYN. ZYN contains nicotine, and nicotine is well characterized in the literature. ZYN exposes users to levels of nicotine that are similar to those in snus, but as ZYN generally has reduced or nonmeasurable levels of

unwanted HPHCs, health effects of snus could be considered as a measure of maximum health risk.

Therefore, a systematic review of the *in vitro* and *in vivo* studies of Swedish snus was performed. This section reviews the scientific literature describing those studies with Swedish snus (one example marketed in the US is General Snus) and with other ST products. The review is limited to work performed using the types of snus and moist snuff that are used in northern Europe and North America.

As noted in the FDA MRTPA TPL Review 2019 for General Snus, "In the scientific review of the original applications, epidemiological studies provided the strongest evidence for assessing the long-term health risk of Swedish snus use as compared to the risks from cigarette smoking. Although the epidemiological literature is not product-specific, the body of literature from Sweden and Norway is particularly relevant to the assessment of the long-term health risks of the General Snus products that are the subject of these MRTPAs, as noted in the 2016 TPL review (p.33):

> Many, if not all, of the studies included in the modified risk applications for the General Snus products did not include the specific products that are the subject of the applications. Rather, the studies included products that were available in Sweden and Norway. Swedish Match North America (SMNA) justifies the use of the studies by asserting that during the period of study, SMNA products dominated the Scandinavian snus market; that the SMNA products in those studies conformed to the GOTHIATEK® standard; and, any observed health effects are the result of use of products that meet the GOTHIATEK® standard.
>
> FDA's review of the eight General Snus products confirms that the eight General Snus products also conform to the GOTHIATEK® standard. It is reasonable to expect that General Snus products, when used in a manner similar to that observed in the submitted studies, would result in similar exposures and potential health effects as those reported in those studies."

The results are relevant to the toxicological evaluation of Swedish snus, which can be considered more hazardous than ZYN, and therefore, the literature surrounding Swedish snus and other ST products is a conservative surrogate for ZYN.

Toxicology data on Swedish snus are sparse, likely because the strength of the epidemiology data from Sweden obviates the need to obtain toxicology data retrospectively. Nevertheless, a review of the toxicology testing of ST products and oral cancer in laboratory animals has been published (Grasso and Mann 1998). Other reviews of various materials relating to ST products in general and oral cancer are also available (Eveson 1981, IARC 1985, Nilsson 1998, Shklar 1999) including that of the National Toxicology Program (NTP 2002). Much of the *in vivo* work focused on experimental animal models, not general toxicology studies, and also used a variety of ST products (eg, chewing tobacco and Asian tobacco) (IARC 2007). In reference to experimental *in vivo* studies, the 2008 Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) report stated the following:

"The majority of animal studies of snuff-associated carcinogenesis are old and the results are difficult to interpret. The experimental groups tended to be small and/or the animal models used were invasive, with tissue trauma possibly confounding the results. Most of the studies with

snuff have been negative or equivocal. Studies with snuff inserted into a surgically created canal of the lower lip of the rat do, however, indicate that snuff has a carcinogenic potential in this model" (SCENIHR 2008).

Notwithstanding this position, the SCENIHR report concluded, based on very few toxicology data points on ST products, that "these data coupled with evidence of genotoxic effects of extracts of moist snuff on various *in vitro* systems, and the presence of carcinogenic nitrosamines in the products, lead to the conclusion that moist snuff is carcinogenic in animals" (SCENIHR 2008). Since the SCENIHR report was published, a research paper of commercial Swedish snus products have clearly shown that these products have minimal (if any) activity in *in vitro* toxicology systems (Coggins et al 2012).

6.3.1 Literature Review of In Vitro Toxicology

6.3.1.1 Mutagenicity and Genotoxicity Literature

Extracts of Swedish snus and other ST products have been tested in a variety of *in vitro* toxicology assays, using tests designed to predict carcinogenicity in humans. The literature discussing mutagenicity and genotoxicity of ST products follows in this section.

The potential genotoxicity of aqueous and methylene chloride extracts of Swedish snus was reported by Jansson et al using test systems that included assays for the induction of mutation in four strains of *S. typhimurium*, sister chromatid exchanges in human lymphocytes, chromosome aberrations and gene mutations in CHO cells, and micronuclei in mouse bone marrow cells (Jansson et al 1991). Most of the results obtained for the aqueous extract were negative, with the exception of chromosome aberrations in the CHO cells, with and without metabolic activation. Results from the testing of the methylene chloride extract of Swedish snus were broadly negative (Jansson et al 1991). In contrast, cigarette smoke is markedly genotoxic using similar assay methods as those described above (DeMarini 2004).

An *in vitro* toxicological evaluation tested commercial and experimental Swedish Match snus extracts, along with a reference moist snuff (ie, Kentucky 2S3) (Coggins et al 2012). Aqueous extracts of the commercial Swedish snus (General Original Portion Large; Catch White Portion Large, Licorice; and Catch Dry White Portion Mini, Licorice) did not induce clear increases in mutation frequency in five strains of *S. typhimurium*, both in the presence and absence of metabolic activation (S9) in the Ames test at concentrations corresponding to 50 mg/plate (OECD TG 471 recommends a maximum test concentration for soluble noncytotoxic substances of 5 mg/plate [Organisation for Economic Co-operation and Development 1997]). Similarly, aqueous extracts did not induce clear increases in mutation frequency in L5178Y $tk^{+/-}$ cells, in neither the presence nor absence of metabolic activation (S9) in the mouse lymphoma assay. When aqueous extracts of the commercial Swedish snus were assessed in the micronucleus test, there were no increased numbers of micronucleated binucleate Chinese hamster fibroblast cells. A related *in vitro* test that is commonly used in combination with the above assays is the Neutral Red Uptake (NRU) assay, a test for cytotoxicity. Cytotoxicity is a major concern in genotoxicity assays (dead cells cannot mutate), and this factor has the potential to confound the interpretation of negative results. Aqueous extracts did not produce obvious differences between the cytotoxicity results obtained using Balb/c 3T3 cells. As discussed, the results of these assays were broadly negative for Swedish snus. In most cases, the results for the reference moist snuff were also negative, but there was one unequivocally positive response.

Mutagenicity of "four popular American moist snuff brands" was also studied using a *S. typhimurium* mutation assay (Shirname-More 1991a). Aqueous extracts of the four brands did not produce mutagenicity in either the presence or absence of metabolic activation (S9), and neither did dichloromethane and methanol extracts. Aqueous extracts of American moist snuff were also tested using human TK-6 and AHH-1 cells, and low levels of mutagenic activity was observed in both cell lines (Shirname-More 1991b). Taken together, American moist snuff showed some mutagenic activity.

Merne et al exposed cells to Ettan snus (Swedish Match) and US-type reference snuff extracts to investigate the potential genotoxic effects on the cells (human papillomaviruses [HPV])-positive and HPV-negative oral keratinocytes and oral HPV-negative fibroblasts), specifically, aneuploidy (abnormal number of chromosomes) (Merne et al 2014). The authors concluded that the effects varied by cell line but that they both increased the aneuploidy of HPV16 E6/E7-transformed oral epithelial cells. However, only US-type reference snuff extracts led to statistically significant increases in aneuploidy cells.

Song et al evaluated and compared the chemical composition and *in vitro* toxicity of seven conventional and 12 low-TSNA moist snuff products (including two Swedish Match products: Ettan Lossnus and General Mini Portion) in (b) (4) extracts (Song et al 2016). For the Swedish low-TSNA moist snuff products, a 22% increase in mutagenicity was observed at the highest extract concentration tested in the Ames assay. The micronucleus assay showed a statistically significant increase in the mean proportion of micronuclei with treatment of all products compared to controls, but there were no differences among the products. All ST products tested had minimal *in vitro* toxicity, and the observed different levels through increasing mutagenicity, less cell viability, and genetic damage across the moist snuff products were small.

Overall, studies with aqueous and (b) (4) extracts of Swedish snus did not show a mutagenic response in prokaryotic or eukaryotic systems, and although chromosome aberrations were observed in CHO cells in a historical study, most work indicates that Swedish snus does not exhibit a genotoxic response.

When a variety of ST products were tested *in vitro*, some cell lines showed increased aneuploidy, and some increases in mutagenic and genotoxic activity were observed. Increases in activity appeared to be similar among products tested and could be the result of product pooling.

Collectively, these data contrast with that reported for combustible cigarettes where positive responses have been routinely reported for mutagenicity, genotoxicity, and cytotoxicity (Roemer et al 2012, Jaccard et al 2019) and TSNAs have been shown to be mutagenic and genotoxic (IARC 2007).

6.3.2 Literature Review of Experimental In Vivo Studies

The long-term effects of ST products have been studied in the cheek pouch of Syrian golden hamsters (Section 6.3.2.1) and an artificial lip canal in rats (Section 6.3.2.2); the effects of oral swabbing of ST extracts (Section 6.3.2.3) and on the forestomach (Section 6.3.2.4) in rats provide context that is relevant to ZYN as the products are used in the same way.

The carcinogenicity of ST products was assessed in rodent feeding studies are discussed in Section 6.3.2.5. The developmental effects of nicotine are discussed in Section 6.3.2.6.

Other experimental work with ST products, such as those with tumor-promoting agents, are detailed in the systematic literature review reports (Section I.1 2013 Environ Report and Section I.1 Health Effects and Meta-Analysis Update Report, Section 1), and the topics not covered here were deemed out of scope for the discussion of snus in support of ZYN.

6.3.2.1 Cheek Pouch and Oral Mucosa Model in Hamsters

The cheek-pouch carcinogenesis model in Syrian golden hamsters is an animal system that is closely comparable with the development of pre-malignant and malignant lesions in human oral cancer, and it is one of the most well characterized animal system models for studying squamous cell carcinogenesis (Chen et al 2005, Schwartz et al 2000, Slaga and Gimenez-Conti 1992). The cellular and molecular changes that occur in the hamster cheek pouch carcinogenesis process have been compared to the mouse-skin system, in which a number of critical events have been well characterized (Slaga and Gimenez-Conti 1992). Numerous early studies with ST products and the hamster cheek pouch and oral mucosa have been reviewed by Grasso and Mann who concluded that ST products were not carcinogenic in this animal model (Grasso and Mann 1998). Subsequent studies are reviewed below.

When Ashrafi et al used conventional light microscopy and transmission- and scanning-electron microscopy to examine the hamster cheek pouch after 24 months of treatment with ST products, no tumors were seen. The long-term histological and electron-microscopic changes produced by ST product treatment were correlated with each other and were considered “similar to those reported in human leukoplakia without dyskeratosis” (Ashrafi et al 1992).

Summerlin et al used the hamster cheek pouch in a study designed to determine the histologic effects of combined exposures to a commercial ST product and ethyl alcohol. After 26 weeks, significant acanthosis of the pouch epithelium was noted in the ST product and ST product plus alcohol groups (Summerlin et al 1992). The authors suggested that the increased thickness of the epithelia of the pouch was similar to that noted in human ST product users, and “this study reaffirms the lack of carcinogenic potential of ST upon the hamster pouch mucosa and internal organs.”

6.3.2.2 Artificial Lip Canal Model in Rats

A surgical procedure to produce a “lip canal” in rats has been used to implant ST products (Hecht et al 1986, Hirsch et al 1986, Hirsch and Johansson 1983, Hirsch and Thilander 1981, Schwartz et al 2010) and other solid products. The procedure causes a substantial inflammatory response, and after healing, a mildly hyperplastic epithelium remains with formation of scar tissue for up to 13 months (Hirsch and Thilander 1981). It is difficult to meaningfully interpret findings in animals with such compromised tissues.

Nevertheless, Hirsch and Thilander injected ST product, twice daily for nine months into lip canals. After nine months, the epithelium of the canal was found to be mildly to moderately hyperplastic, and the adjacent connective tissue exhibited an inflammatory reaction that varied in degree from mild to severe (Hirsch and Thilander 1981).

Hirsch and Johansson subsequently used this model in a study of the long-term application of ST product, using twice-daily applications for up to 22 months. After nine to 12 months of treatment, the squamous epithelium of the canal exhibited mild to moderate hyperplasia, with mild to moderate inflammation in the underlying connective tissue. The lesions in the epithelium

and submucosa showed virtually no further changes (such as neoplasia) during the course of the study (Hirsch and Johansson 1983).

Hirsch also used this model with an ST product five days per week for 13 months, and groups of rats were euthanized one and four months after exposure had ceased. At the end of treatment, the oral mucosa of the rats exhibited hyperplastic, hyperorthokeratotic epithelium with focal mild atypia, focal ulcerations, and marked subepithelial fibrosis (Hirsch et al 1986). The incidence and/or severity of the changes decreased after the recovery phase.

Hecht et al also used the rat lip canal in a two-part experiment that examined the roles of moist snuff and TSNAs (Hecht et al 1986). A test canal was surgically created in the lower lip of groups of 21 to 32 F344 rats and either ST, a water-extract of ST, or ST enriched with water extract were inserted in the test canal five times weekly for 116 weeks. Among the 32 rats treated with ST, three had oral cavity tumors (one was a squamous cell carcinoma originating in the test canal and invading the gingiva, one was a papilloma of the test canal, and one was a papilloma of the hard palate). Oral cavity tumors were also observed in two of 21 rats treated with water-extracted ST and one of 32 rats treated with ST enriched with water extract. The difference in the incidence of tumors among the groups were not statistically significant. Based on these results, the authors concluded that “snuff can induce oral cavity tumors in F344 rats,” which they suggested “support the epidemiological observations which indicate that snuff dipping causes oral cancer in man.”

Schwartz et al conducted a study of four ST products, including the commercial Swedish snus Ettan using the rat lip canal model over a 12-month period (Schwartz et al 2010). The authors concluded that “while all [smokeless tobacco] products caused dysplasia, the products with lower levels of TSNA and unprotonated nicotine caused less, consistent with the model that tobacco with low levels of nitrosamines might potentially induce fewer carcinomas in human users.” Moreover, the Swedish snus produced much less pronounced changes in the oral mucosa of treated rats than the ST products with much higher TSNA values. Using a cell proliferation assay, Swedish snus did not show any differences from the control treatment.

6.3.2.3 Oral Swabbing Model in Rats

Topical applications have been used to investigate the effects of moist snuff extracts on oral carcinogenesis (Hecht et al 1986). The tumorigenic activities toward the oral cavity of moist snuff, its extracts, and the TSNAs NNN and NNK were evaluated in male F344 rats. No tumors were observed in rats treated with the moist snuff extract alone. Papillomas were observed in 3/30 rats treated with the moist snuff extract enriched with NNN and NNK, but these results were not statistically significant. Treatment with NNN and NNK led to an increased incidence of oral cavity papillomas (8/30 rats compared to 0/21 in controls). A total of four adenocarcinomas were noted in the lungs in the group treated orally with NNN/NNK (Hecht et al 1986). According to the authors, this confirmed that “NNK is a potent carcinogen in laboratory rodents that, independent of the route of administration, induces primarily lung adenocarcinomas” (Prokopczyk et al 2005).

6.3.2.4 Forestomach Model in Rats

Nilsson et al conducted an *in vivo* study in which Wistar rats consumed a tobacco slurry where 10 g of Ettan brand snus from Swedish Match was homogenized in 100 mL of water alone, as well as in conjunction with additives including blueberries and an extract from milk thistle that

might exert protective effects against soft tissue changes in the rat forestomach (Nilsson et al 2016). Following four weeks of oral treatment with snus slurry, observed effects included dilation of blood vessels in the submucosa and a thickening of the basal region of squamous epithelium forestomach due to a proliferation of cells in the basal layer, compared with controls. These results are consistent with snus's effects on the oral mucosa in humans and those reported in a study of snus placed in the rat lip canal (Schwartz et al 2010).

6.3.2.5 Smokeless Tobacco Product Feeding Studies in Rodents

Homburger et al conducted a two year chronic feeding study to investigate systemic carcinogenic effects of ST in inbred Syrian hamsters. The only effect of ST noted was a slower growth of the animals in one of the inbred lines but not in the other (Homburger et al 1976). The authors stated, "it is especially noteworthy that there were no tumors of the oral cavity, salivary glands, esophagus, nasopharynx, larynx, urinary bladder, gonads, or ear ducts in any of these animals." Heart rate, blood pressure (systolic and diastolic), electrocardiogram tracings, and packed cell volume were not affected by chronic feeding of ST at 20% inclusion in the diet.

More recently, Theophilus et al conducted a 90-day feeding study using snus-like products in rats and mice at nicotine doses of up to 120 mg/kg/day (Theophilus et al 2012). Key effects such as body weight reductions and organ weight changes occurred in rats and mice predominantly at the highest doses of test articles and positive control in the absence of treatment-related gross or histopathological changes. The doses evaluated spanned the no observable adverse effect level, the lowest observable adverse effect level, and the maximum tolerated dose.

6.3.2.6 Developmental Effects of Nicotine

Cigarette smoking, including nicotine exposure, during pregnancy is associated with a large number of adverse fetal, obstetrical, and developmental outcomes (Cnattingius 2004, Howe et al 2012, USDHHS 2010). Various components of cigarette smoke have been linked with different reproductive outcomes, including the suggestion that carbon monoxide in cigarette smoke is responsible for lower birth weights for infants born to mothers who smoked during pregnancy (Carmines and Rajendran 2008, USDHHS 2010). In addition, Baba et al have suggested that "antenatal exposure to nicotine is involved in the mechanisms by which tobacco use increases the risk of preterm birth" (Baba et al 2012).

Animal studies "suggest that nicotine alone may be a key chemical responsible for many of the long-term effects associated with maternal cigarette smoking" (Bruin et al 2010). Bruin et al reviewed the long-term effects of fetal and neonatal nicotine exposure on postnatal health. Based on this extensive review, largely based on animal studies, the authors concluded that "nicotine should no longer be considered the 'safe' component of cigarette smoke. In fact, many of the adverse postnatal health outcomes associated with maternal smoking during pregnancy may be attributable, at least in part, to nicotine alone."

As with all products containing nicotine, the use of ZYN is not advisable in women who are pregnant or who are lactating. Because Swedish snus, ZYN, and nicotine replacement therapy (NRT) deliver nicotine without the combustion products and risks associated with smoking, the cautions (or contraindications) for ZYN are expected to be the similar to those used for NRTs.

6.3.3 Key Literature Published After the Systematic Review

The biological effects elicited by the exposure to snus or cigarette smoke were assessed by a systems toxicology approach, which can provide mechanistic understanding of the processes underlying toxicity by complementing with computational analysis for an integrated assessment. The biological impact of repeated 72-hour exposure to extracts from both a commercial and a reference snus or TPM from cigarette smoke using human gingival epithelial organotypic cultures (Zanetti et al 2019). The extract concentrations were intended to mimic concentrations relevant for snus use in humans (based on mg nicotine per liter saliva in phosphate-buffered saline). Cell media with extracts were replaced every 24 hours, and samples were collected for inflammatory mediators, histology, and immunohistochemistry as well as for messenger ribonucleic acid (mRNA)/microribonucleic acid (miRNA) analysis. TPM induced marked morphological changes, independent on nicotine content, whereas snus extracts had minimal impact on cell morphology albeit higher nicotine content. Inflammatory mediators were assessed with transcriptomics (mRNA) as well as measuring secreted levels in the cell media using multiplex immune assays. To summarize, human gingival epithelial organotypic cultures treated with snus extracts induced mild, generally reversible biological changes, while TPM treatment induced substantial morphological and inflammatory alterations. Network enrichment analysis and integrative analysis of the global mRNA and miRNA expression profiles indicated a limited and mostly transient impact of the snus extracts, in particular on xenobiotic metabolism, while the effects of TPM were marked and sustained over time.

6.4 Conclusions Based on In Vitro and In Vivo Research Assessments in the Literature

Although ZYN is in a similar product category to snus, ZYN does not contain tobacco nor TSNAs, which are found in other ST products. *In vitro* toxicology testing of ZYN showed no mutagenic or genotoxic response (Section 5), and there is no literature about the *in vitro* and *in vivo* toxicology of ZYN. The toxicological profile of Swedish snus in the literature represents a conservative estimate for ZYN. Although epidemiologic evidence should weigh most heavily in the Center for Tobacco Products' assessment of ZYN, nonclinical studies can still play a role in justifying that Swedish snus and therefore ZYN is less harmful than combustible cigarettes.

In vitro studies with Swedish snus did not show a mutagenic response in prokaryotic or eukaryotic systems. Although chromosome aberrations were observed in CHO cells in a historical study, most work indicates that Swedish snus does not exhibit a genotoxic response.

When a variety of ST products were tested *in vitro*, some cell lines showed increased aneuploidy, and some increases in mutagenic and genotoxic activity were observed. As tobacco has demonstrated genotoxicity, the *in vitro* testing results are not unexpected. These data contrast with that reported for combustible cigarettes where positive responses have been routinely reported for mutagenicity, genotoxicity, and cytotoxicity.

In vitro testing with snus showed biological changes that were generally reversible, whereas morphological and inflammatory changes induced by TPM from cigarette smoke were marked and sustained over time.

In *in vivo* studies, test material was administered mixed in the diet, when ST was placed in hamster cheek pouches no carcinogenic potential was noted. When ST was inserted into surgical lip canals in rats the results varied: Hyperplasia and inflammation was reported in some instances without neoplasia, whereas dysplasia, oral cavity tumors, or promotion of carcinogenesis were

noted in other animal studies. Oral swabbing of ST extracts did not result in oral carcinogenesis, whereas ST extracts enriched with NNN and NNK did. In addition, no cancer or other systemic effects were observed in a lifetime feeding study in rats with ST.

There are clear limitations in the reported *in vivo* and *in vitro* studies of ST products and their components reviewed above, as the test material does not lend itself well to classical toxicological assays. Treatment-induced results can in many cases be due instead to the highly invasive nature of the treatment, leading to considerable difficulties in interpretation of reported findings.

Based on the literature, Swedish snus has minimal activity in state-of-the-art *in vitro* and *in vivo* toxicology assays, and this is aligned with the *in vitro* testing for ZYN, which showed no mutagenic or genotoxic response. This lends further support for the potential of the ZYN, which is in a similar product category to Swedish snus products and is the subject of this application, being less harmful than combustible cigarettes.

6.5 Biomarker Selection

In the FDA PMTA ENDS Guidance 2019, FDA recommends testing for HPHCs and biomarkers of harm/exposure (eg, cotinine, NNAL, and NNN). Of the 45 HPHCs tested for ZYN, 37 were below the LOQ. The levels of the seven measurable HPHCs, omitting free nicotine, in ZYN were lower or generally similar than those in General Snus or CRP2.1. Notably, ZYN does not contain measurable quantities of TSNAs, such as NNN, or B(a)P (Section 3). By comparing the actual exposure against valid threshold limit values set by recognized authorities in a QRA, the low levels of HPHCs that were detected in ZYN products are not likely to have adverse effect on public health as the exposure is well under current ADI and TDI levels. The toxicological safety profile of ZYN represents a significant improvement over snus, with the exception of the nicotine content, which is only marginally lower (3 or 6 mg for ZYN versus 8 to 12 mg for snus); therefore, Swedish Match did not measure biomarkers of harm/exposure in any of the clinical studies, as there are few measureable HPHCs.

Published studies are available that have investigated biomarkers of nicotine, TSNAs, cadmium, and selenium in regular users of traditional Swedish snus (Andersson et al 1994, Andersson et al 1995, Bolinder 1997,Bolinder et al 1997a, Bolinder et al 1997b, Bolinder and de Faire 1998, Eliasson et al 1995, Eliasson et al 1991, Ellingsen et al 2009, Heling et al 2008, Holm et al 1992, Richter et al. 2009b, as cited in Nilsson 2011, Österdahl and Slorach 1988, Post et al 2005, Wennberg et al 2006). Biomarkers of TSNAs are the main biomarkers measured and reported in the published literature; there is little information on biomarkers of other non-tobacco specific N-nitroso compounds for tobacco users. The flavor biomarker in ZYN Wintergreen, (b) (4) [redacted] and the QRA is described in Section 4.3.

7 SUMMARY AND CONCLUSIONS

Swedish Match investigated ZYN to determine whether the marketing of the product is appropriate for the protection of public health. ZYN currently comes in 10 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) and two nicotine strengths (3 mg and 6 mg per pouch).

As the chemical composition of the product is a major indicator of risk to consumers, Swedish Match commissioned broad product characterization analyses of ZYN. The levels of constituents in ZYN were compared with those in the ST product General Snus, which is also the bridging product, and with an American loose moist snuff reference product CRP2.1.

The vast majority of all constituents that were analyzed in ZYN were at levels below the limit of quantification. Notably, ZYN does not contain measurable quantities of TSNAs (NNN and NNK) or B(a)P, which were present at low levels in General Snus. The broad chemical characterization of ZYN has shown that the product contains a very limited number of harmful and potentially harmful constituents, of which most were significantly reduced compared to the levels found in General Snus. The levels of HPHCs found in ZYN were always lower than those in the CRP2.1 reference product comparator based on per unit of use, and the only exception was the flavoring substance coumarin that is specific to the ZYN Cinnamon product.

Based on the QRAs performed for measurable HPHCs in ZYN, the levels in ZYN were below health-based threshold limit values. Under reasonably foreseeable conditions of use of ZYN, the levels do not raise concern from a public health perspective and support that ZYN is appropriate for the protection of the public health.

Swedish Match finds other ingredients to present a low level of concern, if any, due to their regulatory status, widespread use and the low levels found in ZYN compared to other consumer products.

A QRA was also conducted for the flavor component, (b) (4) which is specific to ZYN Wintergreen. Based on the QRA, the low level is unlikely to have adverse effect on public health.

In vitro testing demonstrates the overall safety of all 10 flavors of ZYN as the studies described herein showed no mutagenic or genotoxic response. The lack of biological response associated with ZYN is aligned with the results of CRP2.1. The data from cigarette TPM on the other hand was positive in both assays, based on a more than two-fold increase of replicates in the Ames assay and more than two-fold increase of %-micronuclei in the ivMN assay compared to solvent control. In a previous study Swedish Match snus, showed results in line with this data in at similar concentrations in the Ames and ivMN assays. As there is no evidence from *in vitro* studies of genotoxic or mutagenic effects, this indicates a low potential for carcinogenic effects of ZYN.

The literature assessment of Swedish snus, which is in a similar product category to ZYN, showed minimal activity in toxicology assays. This lends further support for the potential of ZYN, being less harmful than combusted tobacco, most notably cigarettes.

Given the totality of evidence, Swedish Match believes that these nonclinical findings support that that authorization to market ZYN in the US would be appropriate for the protection of the public health.

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9 APPENDIX

9.1.1 Nicotine-Related Compounds Content to Nicotine Ratios in ZYN

Table 13 Nicotine-Related Compounds to Nicotine Ratios for ZYN Products

ZYN Product	n	Unique ID	Nicotine-Related Compounds/Nicotine Ratio (%)						
			Anabasine	Anatabine	Cotinine	Myosmine	Nicotine N-oxide	β-Nicotyrine	Nornicotine
Chill 3 mg	10	8136	(b) (4)						
Chill 6 mg	10	8137							
Cinnamon 3 mg	12	8128							
Cinnamon 6 mg	12	8129							
Citrus 3 mg	13	8122							
Citrus 6 mg	10	8123							
Coffee 3 mg	15	8124							
Coffee 6 mg	12	8125							
Cool Mint 3 mg	14	8105							
Cool Mint 6 mg	10	8106							
Fresh 3 mg	10	8140							
Fresh 6 mg	10	8141							
Peppermint 3 mg	18	8107							

ZYN Product	n	Unique ID	Nicotine-Related Compounds/Nicotine Ratio (%)						
			Anabasine	Anatabine	Cotinine	Myosmine	Nicotine N-oxide	β-Nicotyrine	Nornicotine
Peppermint 6 mg	12	[redacted]							
Smooth 3 mg	10								
Smooth 6 mg	10								
Spearmint 3 mg	10								
Spearmint 6 mg	12								
Wintergreen 3 mg	12								
Wintergreen 6 mg	12								

Source: (b) (4) [redacted]

Values are mean (SD).
ID=identification; SD=standard deviation.

9.1.2 Comparison of HPHCs in ZYN Chill 3 mg to Those in CRP2.1 and General Snus

Table 14 HPHC Content and Relevant Snus Components in ZYN Chill 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Chill 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/g)	(b) (4)	<0.015	(b) (4)						>99.6	(b) (4)			>90.8
5-Methyl chrysene (ng/g)		<5							NA				NA
Acetaldehyde (µg/g)	(b) (4)	<0.50							80.4				82.8
Acrolein (µg/g)	(b) (4)	<0.1							NA				NA
Acrylamide (ng/g)		<60							>82.1				>93.0
Aflatoxin B1 (ng/g)	(b) (4)	<0.1							NA				NA
Ammonium ion (mg/g)	(b) (4)	<0.5							>90.9				>73.9
Anabasine (µg/g as is)		<1.00							>97.8				>96.6
Arsenic (µg/g)	(b) (4)	<0.05							>65.5				>41.9
Benz[j]aceanthrylene (ng/g)		<0.6							NA				NA
Benzo[a]anthracene (ng/g)		<1							>99.9				>46.6
Benzo[a]pyrene (ng/g)		<0.6							NA				NA
Benzo[a]pyrene (ng/g)		<0.6							>99.8				NA
Benzo[b]fluoroanthene (ng/g)		<1							>99.7				>18.6
Benzo[c]phenanthrene (ng/g)		<1							>99.6				NA
Benzo[k]fluoroanthene (ng/g)		<1							>99.3				NA
Beryllium (µg/g)	(b) (4)	<0.05							NA				NA
Cadmium (µg/g)	(b) (4)	<0.05							>96.5				>89.4

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Chill 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chromium (µg/g)	(b) (4)	<0.15	(b) (4)						>82.3	(b) (4)			>78.9
Chrysene (ng/g)		<1							>99.9				>79.8
Coumarin (µg/g)		<0.09							>95.4				NA
Crotonaldehyde (µg/g)	(b) (4)	<0.1							NA				NA
Cyclopenta[c,d]pyrene (ng/g)		<1							>94.3				NA
Dibenzo[a,e]pyrene (ng/g)		<5							NA				NA
Dibenzo[a,h]anthracene (ng/g)		<0.6							>97.4				NA
Dibenzo[a,h]pyrene (ng/g)		<5							NA				NA
Dibenzo[a,i]pyrene (ng/g)		<5							NA				NA
Dibenzo[a,l]pyrene (ng/g)		<2							NA				NA
Ethyl carbamate (ng/g)		<30							NA				NA
Formaldehyde (µg/g)	(b) (4)	<0.25							7.8				(51.5)[b]
Glycerol (%)		<0.2							NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)		<1							>98.8				NA
Lead (µg/g)	(b) (4)	<0.10							>74.1				>61.2
Mercury (µg/g)	(b) (4)	<0.02							NA				NA
Naphthalene (ng/g)		<5							>95.6				>65.3
Nickel (µg/g)	(b) (4)	<0.10							>93.1				>92.9
Nicotine (mg/g)		<1.00							66.3				54.2
Nitrite (µg/g)		<1.0							>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Chill 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)	(b) (4)	<0.6	(b) (4)						>96.9	(b) (4)			NA
N-Nitrosonornicotine (µg/g) (NNN)	(b) (4)	<0.015							>99.8				>97.1
Nornicotine (µg/g as is)		<1.53							>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)[c]		NA							NA				NA
Propylene glycol (%)		<0.20							NA				>95.2
Selenium (µg/g)	(b) (4)	<0.05							>48.6				>49.7
Uranium-235 (Bq/kg)	(b) (4)	<0.02							NA				NA
Uranium-238 (Bq/kg)	(b) (4)	<0.25							NA				NA

Source (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested fo(b) (4) olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 15 HPHC Content and Relevant Snus Components in ZYN Chill 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Chill 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/unit)	(b) (4)	[redacted]								>99.8	[redacted]				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)	(b) (4)									91.9					86.3
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Chill 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoranthene (ng/unit)	(b) (4)	(b) (4)								>99.9	(b) (4)				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoranthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta-[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Chill 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Ethyl carbamate (ng/unit)	(b) (4)									NA					NA
Formaldehyde (µg/unit)										60.4					(35.0)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										>86.3					>60.9
Nicotine, batch average, free nicotine (mg/unit)										73.7					65.7
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethyl-amine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicot-ine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.9					99.7

Analyte/ HPHC	Analytical Procedure	ZYN Chill 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Polonium-210 (radioisotope) (Bq/unit)[d]	[redacted]									NA	[redacted]				NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested for [redacted]. Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 16 Nicotine-Related Compounds in ZYN Chill 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Chill 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>82.1
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 17 Nicotine-Related Compounds in ZYN Chill 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Chill 3 mg Per Unit			CRP2.1 Per-Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per-Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.3 Comparison of HPHCs in ZYN Chill 6 mg to Those in CRP2.1 and General Snus

Table 18 HPHC Content and Relevant Snus Components in ZYN Chill 6 mg Compared to CRP2.1 and General Snus on a Per-Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Chill 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/g)	(b) (4)								>99.6				>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)	(b) (4)								78.6				81.3
Acrolein (µg/g)	(b) (4)								NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)	(b) (4)								NA				NA
Ammonium ion (mg/g)	(b) (4)								>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)	(b) (4)								>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)	(b) (4)								NA				NA
Cadmium (µg/g)	(b) (4)								>96.5				>89.4

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Chill 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chromium (µg/g)	(b) (4)								>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)	(b) (4)								NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)	(b) (4)								10.9				(46.4)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)	(b) (4)								>74.1				>61.2
Mercury (µg/g)	(b) (4)								NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)	(b) (4)								>93.1				>92.9
Nicotine (mg/g)									32.2				8.0
Nitrite (µg/g)									93.3				56.9
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Chill 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosonornicotine (µg/g) (NNN)	(b) (4)								>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)	(b) (4)								>48.6				>49.7
Uranium-235 (Bq/kg)	(b) (4)								NA				NA
Uranium-238 (Bq/kg)	(b) (4)								NA				NA

(b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested for (b) (4) Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 19 HPHC Content and Relevant Snus Components in ZYN Chill 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Chill 6 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/unit)	(b) (4)	(b) (4)								>99.8	(b) (4)				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)	(b) (4)									92.4					87.2
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										99.6					98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Chill 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoroanthene (ng/unit)	[redacted]									>99.9	[redacted]				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>95.2					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										59.4					(38.6)[b]

Analyte/ HPHC	Analytical Procedure	ZYN Chill 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Glycerol (mg/unit)	(b) (4)									NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										69.9					14.4
Nicotine, batch average, free nicotine (mg/unit)										42.2					24.6
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.7					99.5
Polonium-210 (radioisotope) (Bq/unit)[d]										NA					NA
Propylene Glycol (mg/unit)										NA					96.3
Selenium (µg/unit)										>79.5					NA

(b) (4)

Analyte/ HPHC	Analytical Procedure	ZYN Chill 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	(b) (4)	(b) (4)								NA	(b) (4)				NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested for (b) (4) olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 20 Nicotine-Related Compounds in ZYN Chill 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Chill 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	[redacted]							>97.8				>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 21 Nicotine-Related Compounds in ZYN Chill 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Chill 6 mg Per Unit			CRP2.1 Per-Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.4 Comparison of HPHCs in ZYN Cinnamon 3 mg to Those in CRP2.1 and General Snus

Table 22 HPHC Content and Relevant Snus Components in ZYN Cinnamon 3 mg Compared to CRP2.1 and General Snus on a Per-Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cinnamon 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/g)	(b) (4)								>99.6				>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)	(b) (4)								>83.0				>85.1
Acrolein (µg/g)	(b) (4)								NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)	(b) (4)								NA				NA
Ammonium ion (mg/g)	(b) (4)								>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)	(b) (4)								>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)	(b) (4)								NA				NA
Cadmium (µg/g)	(b) (4)								>96.5				>89.4
Chromium (µg/g)	(b) (4)								>82.3				>78.9

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cinnamon 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chrysene (ng/g)	[redacted]								>99.9	[redacted]			>79.8
Coumarin (µg/g)									(255.8)[b]				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									8.4				(50.4)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									64.6				51.9
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									97.6				98.2

(b) (4)

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cinnamon 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Polonium-210 (radioisotope) (Bq/kg)	(b) (4)								NA	(b) (4)			NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

(b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 23 HPHC Content and Relevant Snus Components in ZYN Cinnamon 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone(NNK) (µg/unit)	(b) (4)	(b)	(4)			(b)	(4)			>99.8	(b)	(4)			>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)	(b) (4)									93.0					88.2
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										>100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoranthene (ng/unit)	[redacted]	[redacted]				[redacted]				>99.9	[redacted]				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoranthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)	(b) (4)									NA					NA
Cadmium (µg/unit)	(b) (4)									>98.5					>90.9
Chromium (µg/unit)	(b) (4)									>92.6					>81.3
Chrysene (ng/unit)										>100.0					>82.0
Coumarin (µg/unit)										(45.9)[b]					NA
Crotonaldehyde (µg/unit)	(b) (4)									NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Formaldehyde (µg/unit)	(b) (4)									62.4					(28.3)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)	(b) (4)									>89.1					>66.1
Mercury (µg/unit)	(b) (4)									NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)	(b) (4)									>97.1					>93.8
Nicotine (mg/unit)										85.5					58.7
Nicotine, batch average, free nicotine (mg/unit)										72.8					64.6
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)	(b) (4)									>99.9					>97.5
Nornicotine (µg/unit)										99.5					99.0
Polonium-210 (radioisotope) (Bq/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Propylene Glycol (mg/unit)	(b) (4)									NA					>96.3
Selenium (µg/unit)	(b) (4)									>79.5					NA
Uranium-235 (Bq/unit)	(b) (4)									NA					NA
Uranium-238 (Bq/unit)	(b) (4)									NA					NA

Source (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 24 Nicotine-Related Compounds in ZYN Cinnamon 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Cinnamon 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								99.3				97.6
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								97.6				98.2

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SD=standard deviation; SKU=stock keeping unit.

Table 25 Nicotine-Related Compounds in ZYN Cinnamon 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Cinnamon 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								99.9				98.5
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.5				99.0

Source (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SD=standard deviation; SKU=stock keeping unit.

9.1.5 Comparison of HPHCs in ZYN Cinnamon 6 mg to Those in CRP2.1 and General Snus

Table 26 HPHC Content and Relevant Snus Components in ZYN Cinnamon 6 mg Compared to CRP2.1 and General Snus on a Per-Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cinnamon 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/g)	(b) (4)								>99.6				>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)	(b) (4)								>83.5				>85.5
Acrolein (µg/g)	(b) (4)								NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)	(b) (4)								NA				NA
Ammonium ion (mg/g)	(b) (4)								>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)	(b) (4)								>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)	(b) (4)								NA				NA
Cadmium (µg/g)	(b) (4)								>96.5				>89.4

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cinnamon 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chromium (µg/g)	(b) (4)								>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									(285.6)[b]				NA
Crotonaldehyde (µg/g)	(b) (4)								NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)	(b) (4)								11.3				(45.8)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)	(b) (4)								>74.1				>61.2
Mercury (µg/g)	(b) (4)								NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)	(b) (4)								>93.1				>92.9
Nicotine (mg/g)									28.4				2.7
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cinnamon 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosonornicotine (µg/g) (NNN)	(b) (4)								>99.8				>97.1
Nornicotine (µg/g as is)									96.9				97.7
Polonium-210 (radioisotope) (Bq/kg as is)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)	(b) (4)								>48.6				>49.7
Uranium-235 (Bq/kg as is)	(b) (4)								NA				NA
Uranium-238 (Bq/kg as is)	(b) (4)								NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 27 HPHC Content and Relevant Snus Components in ZYN Cinnamon 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 6 mg Per-Unit				CRP2.1 Per-Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per-Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/unit)	(b) (4)	(b) (4)								>99.8	(b) (4)				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)	(b) (4)									93.2					88.5
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 6 mg Per-Unit				CRP2.1 Per-Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per-Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoroanthene (ng/unit)	[redacted]	[redacted]				[redacted]				>99.9	[redacted]				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)	(b) (4)									NA					NA
Cadmium (µg/unit)	(b) (4)									>98.5					>90.9
Chromium (µg/unit)	(b) (4)									>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										(57.7)[b]					NA
Crotonaldehyde (µg/unit)	(b) (4)									NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 6 mg Per-Unit				CRP2.1 Per-Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per-Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Formaldehyde (µg/unit)	(b) (4)	[redacted]								63.7	[redacted]				(23.6)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)	(b) (4)									>89.1					>66.1
Mercury (µg/unit)	(b) (4)									NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)	(b) (4)									>97.1					>93.8
Nicotine (mg/unit)										70.5					15.9
Nicotine, batch average, free nicotine (mg/unit)										40.7					22.7
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)	(b) (4)									>99.9					>97.5
Nornicotine (µg/unit)										99.4					98.7
Polonium-210 (radioisotope) (Bq/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cinnamon 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Propylene Glycol (mg/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				>96.3
Selenium (µg/unit)	[redacted]	[redacted]				[redacted]				>79.5	[redacted]				NA
Uranium-235 (Bq/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				NA
Uranium-238 (Bq/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 28 Nicotine-Related Compounds in ZYN Cinnamon 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Cinnamon 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								99.2				97.2
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								96.9				97.7

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 29 Nicotine-Related Compounds in ZYN Cinnamon 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Cinnamon 6 mg Per Unit			CRP2.1 Per-Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								99.8				98.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.4				98.7

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.6 Comparison of HPHCs in ZYN Citrus 3 mg to Those in CRP2.1 and General Snus

Table 30 HPHC Content and Relevant Snus Components in ZYN Citrus 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Citrus 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/g)	(b) (4)								>99.6				>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)	(b) (4)								85.9				87.5
Acrolein (µg/g)	(b) (4)								NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)	(b) (4)								NA				NA
Ammonium ion (mg/g)	(b) (4)								>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)	(b) (4)								>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)	(b) (4)								NA				NA
Cadmium (µg/g)	(b) (4)								>96.5				>89.4

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Citrus 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chromium (µg/g)	(b) (4)								>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)	(b) (4)								NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)	(b) (4)								4.3				(57.2)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)	(b) (4)								>74.1				>61.2
Mercury (µg/g)	(b) (4)								NA				NA
Naphthalene (ng/g)									81.8				(42.6)[b]
Nickel (µg/g)	(b) (4)								>93.1				>92.9
Nicotine (mg/g)									64.8				52.2
Nitrite (µg/g)									>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Citrus 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per-Dry Weight			Per-Dry Weight				Per-Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)	(b) (4)								>96.9	(b) (4)			NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested for (b) (4). Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 31 HPHC Content and Relevant Snus Components in ZYN Citrus 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/unit)	(b) (4)	(b) (4)								>99.8	(b) (4)				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)	(b) (4)									94.2					90.2
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[c]phenanthrene (ng/unit)	(b) (4)									>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										60.5					(34.5)[b]
Glycerol (mg/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Indeno[1,2,3-cd]pyrene (ng/unit)	(b) (4)									>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										92.5					(54.9)[b]
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										85.5					58.8
Nicotine, batch average, free nicotine (mg/unit)										73.0					64.7
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)[d]										NA					NA
Propylene Glycol (mg/unit)										80.0					96.3
Selenium (µg/unit)	(b) (4)									>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	(b) (4)	(b) (4)								NA	(b) (4)				NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested for (b) (4) s polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 32 Nicotine-Related Compounds in ZYN Citrus 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Citrus 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 33 Nicotine-Related Compounds in ZYN Citrus 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Citrus 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.7 Comparison of HPHCs in ZYN Citrus 6 mg to Those in CRP2.1 and General Snus

Table 34 HPHC Content and Relevant Snus Components in ZYN Citrus 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Citrus 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/g)	(b) (4)								>99.6				>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)	(b) (4)								86.2				87.8
Acrolein (µg/g)	(b) (4)								NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)	(b) (4)								NA				NA
Ammonium ion (mg/g)	(b) (4)								>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)	(b) (4)								>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)	(b) (4)								NA				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Citrus 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Cadmium (µg/g)	(b) (4)								>96.5				>89.4
Chromium (µg/g)	(b) (4)								>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)	(b) (4)								NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)	(b) (4)								11.6				(45.2)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)	(b) (4)								>74.1				>61.2
Mercury (µg/g)	(b) (4)								NA				NA
Naphthalene (ng/g)									77.3				(77.8)
Nickel (µg/g)	(b) (4)								>93.1				>92.9
Nicotine (mg/g)									28.4				2.7
Nitrite (µg/g)									92.9				53.9

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Citrus 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)	(b) (4)								>96.9	(b) (4)			NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg as is)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg as is)									NA				NA
Uranium-238 (Bq/kg as is)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested for (b) (4) olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 35 HPHC Content and Relevant Snus Components in ZYN Citrus 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 6 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (µg/unit)	(b) (4)									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)	(b) (4)									94.3					90.4
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[c]phenanthrene (ng/unit)	[redacted]									>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										63.7					(23.7)[b]
Glycerol (mg/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Indeno[1,2,3-cd]pyrene (ng/unit)	[redacted]									>99.5	[redacted]				NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										90.6					(92.6)[b]
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										70.9					17.1
Nicotine, batch average, free nicotine (mg/unit)										40.4					22.3
Nitrite (µg/unit)										97.1					62.3
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)[d]										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Citrus 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	(b) (4)									NA	(b) (4)				NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested (b) (4) Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 36 Nicotine-Related Compounds in ZYN Citrus 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Citrus 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 37 Nicotine-Related Compounds in ZYN Citrus 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Citrus 6 mg Per Unit			CRP2.1 Per-Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.8 Comparison of HPHCs in ZYN Coffee 3 mg to Those in CRP2.1 and General Snus

Table 38 HPHC Content and Relevant Snus Components in ZYN Coffee 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Coffee 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									79.1				81.7
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Coffee 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Crotonaldehyde (µg/g)	[redacted]								NA	[redacted]			NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									3.4				(58.7)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									63.9				51.0
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									98.5				98.9
Polonium-210 (radioisotope) (Bq/kg as is)									NA				NA
Propylene glycol (%)									NA				86.1
Selenium (µg/g)									>48.6				>49.7

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Coffee 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Uranium-235 (Bq/kg as is)	(b) (4)								NA	(b) (4)			NA
Uranium-238 (Bq/kg as is)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 39 HPHC Content and Relevant Snus Components in ZYN Coffee 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Coffee 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	(b) (4)									>99.8	(b) (4)				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										91.4					85.5
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Coffee 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoranthene (ng/unit)	(b) (4)									>99.9	(b) (4)				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoranthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Coffee 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Formaldehyde (µg/unit)	[redacted]									60.4					(-35.2)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										85.3					58.3
Nicotine, batch average, free nicotine (mg/unit)										72.1					63.6
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.7					99.4
Polonium-210 (radio isotope) (Bq/unit)										NA					NA
Propylene Glycol (mg/unit)										NA					89.5
Selenium (µg/unit)										>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Coffee 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	(b) (4)									NA	(b) (4)				NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 40 Nicotine-Related Compounds in ZYN Coffee 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Coffee 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								99.5				98.3
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								98.5				98.9

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 41 Nicotine-Related Compounds in ZYN Coffee 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Coffee 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.7				99.4

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.9 Comparison of HPHCs in ZYN Coffee 6 mg to Those in CRP2.1 and General Snus

Table 42 HPHC Content and Relevant Snus Components in ZYN Coffee 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Coffee 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]		[redacted]			[redacted]			>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									77.3				80.0
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Coffee 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Cadmium (µg/g)	[redacted]								>96.5	[redacted]			>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(3.7)[b]				(70.3)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									27.3				1.3
Nitrite (µg/g)									>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Coffee 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9	(b) (4)			NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>95.7				>96.9
Polonium-210 (radioisotope) (Bq/kg as is)									NA				NA
Propylene glycol (%)									NA				86.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg as is)									NA				NA
Uranium-238 (Bq/kg as is)									NA				NA

(b) (4)

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

Table 43 HPHC Content and Relevant Snus Components in ZYN Coffee 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytic-al Procedu-re	ZYN Coffee 6 mg				CRP2.1				% Reduct-ion Compar-ed to CRP2.1[a]	General Snus (5 SKUs)				% Reducti-on Compar-ed to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	(b) (4)									>99.8					>92.2
Acetaldehyde (µg/unit)	(b) (4)									90.7					84.3
Acrolein (µg/unit)	(b) (4)									NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)	(b) (4)									NA					NA
Ammonium ion (mg/unit)	(b) (4)									>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)	(b) (4)									>85.5					>82.6
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA
Benzo[b]fluoranthene (ng/unit)										>99.9					NA
Benzo[k]fluoranthene (ng/unit)										>99.7					NA

Analyte/ HPHC	Analytic-al Procedu-re	ZYN Coffee 6 mg				CRP2.1				% Reduct-ion Compar-ed to CRP2.1[a]	General Snus (5 SKUs)				% Reducti-on Compar-ed to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Beryllium (µg/unit)	[redacted]									NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Dibenzo[a,h]anth-racene (ng/unit)										>98.9					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										57.7					(44.3)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										70.6					16.3
Nicotine, batch average, free nicotine (mg/unit)										40.8					22.8
Nitrite (µg/unit)										>97.2					>64.4

Analyte/ HPHC	Analytic-al Procedu-re	ZYN Coffee 6 mg				CRP2.1				% Reduct-ion Compar-ed to CRP2.1[a]	General Snus (5 SKUs)				% Reducti-on Compar-ed to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
N-Nitrosodimethyla-mine (NDMA) (ng/unit)	[redacted]									>98.7	[redacted]				NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.1					98.3
Polonium-210 (radioisotope) (Bq/unit)										NA					NA
Propylene Glycol (mg/unit)										NA					89.5
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 44 Nicotine-Related Compounds in ZYN Coffee 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Coffee 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								98.7				95.6
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								95.7				96.9

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 45 Nicotine-Related Compounds in ZYN Coffee 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Coffee 6 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								99.7				97.4
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.1				98.3

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.10 Comparison of HPHCs in ZYN Cool Mint 3 mg to Those in CRP2.1 and General Snus

Table 46 HPHC Content and Relevant Snus Components in ZYN Cool Mint 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cool Mint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]		[redacted]			[redacted]			>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									77.6				80.3
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cool Mint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chromium (µg/g)	[redacted]								>82.3	[redacted]			>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(4.4)b				(71.5)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									63.7				50.7
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cool Mint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosonornicotine (µg/g) (NNN)	(b) (4)								>99.8	(b) (4)			>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg as is)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg as is)									NA				NA
Uranium-238 (Bq/kg as is)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 47 HPHC Content and Relevant Snus Components in ZYN Cool Mint 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										90.8					84.4
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										>99.9					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.8					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoroanthene (ng/unit)	[redacted]	[redacted]				[redacted]				>99.6	<1	[redacted]			NA
Benzo[c]phenanthrene (ng/unit)										>99.8	<1				NA
Benzo[k]fluoroanthene (ng/unit)										>99.3	<1				NA
Beryllium (µg/unit)										NA	<0.05				NA
Cadmium (µg/unit)										>98.5	0.219				>90.9
Chromium (µg/unit)										>92.6	0.320				>81.3
Chrysene (ng/unit)										>99.9	2.22				>54.9
Coumarin (µg/unit)										>98.1	<0.09				NA
Crotonaldehyde (µg/unit)										NA	<0.1				NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6	<1				NA
Dibenzo[a,e]pyrene (ng/unit)										NA	<5				NA
Dibenzo[a,h]anthracene (ng/unit)										>97.3	<0.6				NA
Dibenzo[a,h]pyrene (ng/unit)										NA	<5				NA
Dibenzo[a,i]pyrene (ng/unit)										NA	<5				NA
Dibenzo[a,l]pyrene (ng/unit)										NA	<2				NA
Ethyl carbamate (ng/unit)										NA	<30				NA
Formaldehyde (µg/unit)										57.2	2.12				(45.8)[b]

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Glycerol (mg/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>98.8					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>95.3					>4.2
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										>85.2					>57.8
Nicotine, batch average, free nicotine (mg/unit)										71.9					63.4
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	(b) (4)									NA	(b) (4)				NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 48 Nicotine-Related Compounds in ZYN Cool Mint 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Cool Mint 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8				>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 49 Nicotine-Related Compounds in ZYN Cool Mint 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Cool Mint 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		Per Unit			Per Unit				Per Unit			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6				>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.11 Comparison of HPHCs in ZYN Cool Mint 6 mg to Those in CRP2.1 and General Snus

Table 50 HPHC Content and Relevant Snus Components in ZYN Cool Mint 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cool Mint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									73.7				76.9
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cool Mint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Coumarin (µg/g)	[redacted]								>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(7.6)[b]				(76.8)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									26.7				0.4
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									98.2				98.7
Polonium-210 (radioisotope) (Bq/kg)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Cool Mint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Uranium-235 (Bq/kg)	(b) (4)								NA	(b) (4)			NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 51 HPHC Content and Relevant Snus Components in ZYN Cool Mint 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8	[redacted]				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										89.2					81.8
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[a]pyrene (ng/unit)	[redacted]	[redacted]				[redacted]				>99.9	[redacted]				NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Ethyl carbamate (ng/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				NA
Formaldehyde (µg/unit)										56.0					(49.9)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										70.0					14.5
Nicotine, batch average, free nicotine (mg/unit)										39.4					21.0
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.6					99.3
Polonium-210 (radioisotope) (Bq/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Cool Mint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Propylene Glycol (mg/unit)	(b) (4)									NA	(b) (4)				>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 52 Nicotine-Related Compounds in ZYN Cool Mint 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Cool Mint 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8				>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								98.2				98.7

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 53 Nicotine-Related Compounds in ZYN Cool Mint 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Cool Mint 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		Per Unit			Per Unit				Per Unit			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.6				99.3

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.12 Comparison of HPHCs in ZYN Fresh 3 mg to Those in CRP2.1 and General Snus

Table 54 HPHC Content and Relevant Snus Components in ZYN Fresh 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Fresh 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									90.0				91.2
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Fresh 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Cadmium (µg/g)	[redacted]								>96.5	[redacted]			>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									7.1				(52.5)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									90.8				27.6
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									65.5				53.2
Nitrite (µg/g)									>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Fresh 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)	[redacted]								>96.9	[redacted]			NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested for the SKUs ZYN Cinnamon 3 mg and 6 mg, ZYN Coffee 3 mg and 6 mg, ZYN Cool Mint 3 mg and 6 mg, ZYN Peppermint 3 mg and 6 mg, ZYN Spearmint 3 mg and 6 mg, and ZYN Wintergreen 3 mg and 6 mg. Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 55 HPHC Content and Relevant Snus Components in ZYN Fresh 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8	[redacted]				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										95.9					93.0
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[a]pyrene (ng/unit)	[redacted]									>99.9					NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Dibenzo[a,l]pyrene (ng/unit)	(b) (4)									NA	(b) (4)				NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										61.8					(30.4)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										96.2					21.5
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										86.1					60.5
Nicotine, batch average, free nicotine (mg/unit)										72.9					64.6
Nitrite (µg/unit)										97.2					64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
N-Nitrosonornicotine (µg/unit) (NNN)	[redacted]									NA					NA
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)[d]										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested for [redacted] olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 56 Nicotine-Related Compounds in ZYN Fresh 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Fresh 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 57 Nicotine-Related Compounds in ZYN Fresh 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Fresh 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation

9.1.13 Comparison of HPHCs in ZYN Fresh 6 mg to Those in CRP2.1 and General Snus

Table 58 HPHC Content and Relevant Snus Components in ZYN Fresh 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Fresh 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									88.1				89.5
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Fresh 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chromium (µg/g)	[redacted]								>82.3	[redacted]			>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									5.5				(55.2)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									90.5				25.9
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									29.7				4.5
Nitrite (µg/g)									>91.4				>44.1
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Fresh 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosonornicotine (µg/g) (NNN)	[redacted]								>99.8	[redacted]			>97.1
Nornicotine (µg/g as is)									98.7				99.1
Polonium-210 (radioisotope) (Bq/kg)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested for [redacted] olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 59 HPHC Content and Relevant Snus Components in ZYN Fresh 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										95.1					91.7
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoroanthene (ng/unit)	[redacted]									>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										61.2					(32.3)[b]

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Glycerol (mg/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										96.1					19.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										71.5					18.8
Nicotine, batch average, free nicotine (mg/unit)										43.9					26.9
Nitrite (µg/unit)										96.4					54.3
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)[d]										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Fresh 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	(b) (4)									NA	(b) (4)				NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested (b) (4) olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 60 Nicotine-Related Compounds in ZYN Fresh 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Fresh 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 61 Nicotine-Related Compounds in ZYN Fresh 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Fresh 6 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6				>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.14 Comparison of HPHCs in ZYN Peppermint 3 mg to Those in CRP2.1 and General Snus

Table 62 HPHC Content and Relevant Snus Components in ZYN Peppermint 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Peppermint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N					
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	(b) (4)								>99.6	(b) (4)			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									77.8				80.5
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Peppermint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Chrysene (ng/g)	(b) (4)								>99.9	(b) (4)			>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(1.6)[b]				(67.0)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									64.1				51.3
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)									NA				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Peppermint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Propylene glycol (%)	[redacted]								NA	[redacted]			>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 63 HPHC Content and Relevant Snus Components in ZYN Peppermint 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]	[redacted]				[redacted]				>99.8	[redacted]				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										89.6					82.4
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.0					>45.5
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoroanthene (ng/unit)		(b) (4)								>99.9	(b) (4)				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Formaldehyde (µg/unit)	[redacted]	[redacted]				[redacted]				58.2	[redacted]				(42.5)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										85.3					58.3
Nicotine, batch average, free nicotine (mg/unit)										74.1					66.2
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 3 mg Per Unit				CRP2.1 Per Unit				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs) Per Unit				% Reduction Compared to General Snus[a]
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Propylene Glycol (mg/unit)	(b) (4)									NA	(b) (4)				>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 64 Nicotine-Related Compounds in ZYN Peppermint 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Peppermint 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	[redacted]							>97.8	[redacted]			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

Table 65 Nicotine-Related Compounds in ZYN Peppermint 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Peppermint 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

9.1.15 Comparison of HPHCs in ZYN Peppermint 6 mg to Those in CRP2.1 and General Snus

Table 66 HPHC Content and Relevant Snus Components in ZYN Peppermint 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Peppermint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									74.9				78.0
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									99.9				46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Peppermint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Crotonaldehyde (µg/g)	[redacted]								NA	[redacted]			NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(6.6)[b]				(75.1)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									27.7				1.8
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									98.7				99.0
Polonium-210 (radioisotope) (Bq/kg)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Peppermint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Uranium-235 (Bq/kg)	(b) (4)								NA	(b) (4)			NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 67 HPHC Content and Relevant Snus Components in ZYN Peppermint 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8	[redacted]				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										89.7					82.6
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[a]pyrene-(ng/unit)	[redacted]	[redacted]				[redacted]				>99.9	[redacted]				NA
Benzo[b]fluoro-anthene (ng/unit)										>99.9					NA
Benzo[c]phena-nthrene (ng/unit)										>99.8					NA
Benzo[k]fluoro-anthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta [c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]py-rene (ng/unit)										NA					NA
Dibenzo[a,h]an-thracene (ng/unit)										>98.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Dibenzo[a,h]pyrene (ng/unit)	[redacted]									NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										56.5					(48.2)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										70.7					16.5
Nicotine, batch average, free nicotine (mg/unit)										44.6					27.8
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine										>98.7					NA

Analyte/ HPHC	Analytical Procedure	ZYN Peppermint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per-Unit				Per-Unit					Per-Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
(NDMA) (ng/unit)	[redacted]										[redacted]				
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.7					99.5
Polonium-210 (radioisotope) (Bq/unit)										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 68 Nicotine-Related Compounds in ZYN Peppermint 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Peppermint 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								98.7				99.0

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 69 Nicotine-Related Compounds in ZYN Peppermint 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Peppermint 6 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]	[redacted]						>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.8
Cotinine (µg/unit)								>99.8				>99.5
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.16 Comparison of HPHCs in ZYN Smooth 3 mg to Those in CRP2.1 and General Snus

Table 70 HPHC Content and Relevant Snus Components in ZYN Smooth 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Smooth 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									80.4				82.8
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Smooth 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Cadmium (µg/g)	[redacted]								>96.5	[redacted]			>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									7.5				(52.0)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									66.1				53.9
Nitrite (µg/g)									>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Smooth 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)			(b) (4)						>96.9	(b) (4)			NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested (b) (4) Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 71 HPHC Content and Relevant Snus Components in ZYN Smooth 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										91.9					86.3
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoranthene (ng/unit)	[redacted]									>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoranthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										61.7					(30.6)[b]

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Glycerol (mg/unit)	[redacted]	[redacted]				[redacted]				NA	[redacted]				NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										86.1					60.5
Nicotine, batch average, free nicotine (mg/unit)										72.1					63.6
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)[d]										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	[redacted]	[redacted]								NA	(b) (4)	[redacted]	[redacted]	[redacted]	NA
Uranium-238 (Bq/unit)										NA	(b) (4)	[redacted]	[redacted]	[redacted]	NA

Source: (b) (4) [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested (b) (4) [redacted] olonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 72 Nicotine-Related Compounds in ZYN Smooth 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Smooth 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

Table 73 Nicotine-Related Compounds in ZYN Smooth 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Smooth 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]	[redacted]						>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

9.1.17 Comparison of HPHCs in ZYN Smooth 6 mg to Those in CRP2.1 and General Snus

Table 74 HPHC Content and Relevant Snus Components in ZYN Smooth 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Smooth 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]								>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									84.4				86.3
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Smooth 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Crotonaldehyde (µg/g)	[redacted]								NA	[redacted]			NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									9.5				(48.8)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									30.9				6.1
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)[c]									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Smooth 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Uranium-235 (Bq/kg)	(b) (4)								NA	(b) (4)			NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] Polonium-210 was only tested (b) (4) Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 75 HPHC Content and Relevant Snus Components in ZYN Smooth 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										93.1					88.4
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										99.6					98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[c]phenanthrene (ng/unit)	[redacted]									>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										63.1					(26.0)[b]
Glycerol (mg/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Indeno[1,2,3-cd]pyrene (ng/unit)	[redacted]	[redacted]				[redacted]				>99.5	[redacted]				NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										72.0					20.3
Nicotine, batch average, free nicotine (mg/unit)										45.6					29.1
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA

Analyte/ HPHC	Analytical Procedure	ZYN Smooth 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Uranium-235 (Bq/unit)	[redacted]									NA	[redacted]				NA
Uranium-238 (Bq/unit)										NA					NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

[d] Polonium-210 was only tested [redacted]. Polonium-210 can be found as a contaminant in tobacco and the same source of nicotine was used for all SKUs.

Table 76 Nicotine-Related Compounds in ZYN Smooth 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Smooth 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N					
Anabasine (µg/g as is)	[redacted]							>97.8	[redacted]			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 77 Nicotine-Related Compounds in ZYN Smooth 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Smooth 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		Per Unit			Per Unit				Per Unit			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	(b) (4)							>99.6	(b) (4)			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.18 Comparison of HPHCs in ZYN Spearmint 3 mg to Those in CRP2.1 and General Snus

Table 78 HPHC Content and Relevant Snus Components in ZYN Spearmint 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Spearmint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]		[redacted]			[redacted]			>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									83.2				85.2
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Spearmint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Beryllium (µg/g)	[redacted]								NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									>97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(3.8)[b]				(70.5)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									64.5				51.8
Nitrite (µg/g)									>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Spearmint 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 79 HPHC Content and Relevant Snus Components in ZYN Spearmint 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8	[redacted]				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										93.1					88.3
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracesne (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[b]fluoranthene (ng/unit)	[redacted]									>99.9	[redacted]				NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoranthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]-pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA

Analyte/ HPHC	Analytic-al Procedu-re	ZYN Spearmint 3 mg				CRP2.1				% Reducti-on Compar-ed to CRP2.1[a]	General Snus (5 SKUs)				% Reduc-tion Comp-ared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Formaldehyde (µg/unit)	[redacted]									57.5	[redacted]				(44.8)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										85.5					58.8
Nicotine, batch average, free nicotine (mg/unit)										72.6					64.2
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethyla-mine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										>99.7					>99.5
Polonium-210 (radioisotope) (Bq/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Propylene Glycol (mg/unit)	[redacted]									NA	(b) (4)				>96.3
Selenium (µg/unit										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 80 Nicotine-Related Compounds in ZYN Spearmint 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Spearmint 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	[redacted]							>97.8	[redacted]			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								99.5				98.4
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

Table 81 Nicotine-Related Compounds in ZYN Spearmint 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Spearmint 3 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								99.9				99.0
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

9.1.19 Comparison of HPHCs in ZYN Spearmint 6 mg to Those in CRP2.1 and General Snus

Table 82 HPHC Content and Relevant Snus Components in ZYN Spearmint 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Spearmint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	(b) (4)								>99.6	(b) (4)			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									80.7				83.0
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Spearmint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Coumarin (µg/g)	[redacted]								>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(3.9)[b]				(70.7)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									28.2				2.5
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									97.4				98.1
Polonium-210 (radioisotope) (Bq/kg)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Spearmint 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Uranium-235 (Bq/kg)	(b) (4)								NA	(b) (4)			NA
Uranium-238 (Bq/kg)									NA				NA

Source: (b) (4)

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 83 HPHC Content and Relevant Snus Components in ZYN Spearmint 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										92.1					86.6
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Benzo[a]pyrene (ng/unit)	[redacted]	[redacted]				[redacted]				>99.9	[redacted]				NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA
Cadmium (µg/unit)										>98.5					>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Dibenzo[a,l]pyrene (ng/unit)	[redacted]									NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										57.5					(44.8)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										70.6					16.2
Nicotine, batch average, free nicotine (mg/unit)										40.6					22.5
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamine (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5

Analyte/ HPHC	Analytical Procedure	ZYN Spearmint 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Nornicotine (µg/unit)	[redacted]									99.5	[redacted]				98.9
Polonium-210 (radioisotope) (Bq/unit)										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/unit)										NA					NA
Uranium-238 (Bq/unit)										NA					NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 84 Nicotine-Related Compounds in ZYN Spearmint 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Spearmint 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	[redacted]							>97.8	[redacted]			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								98.6				95.4
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								97.4				98.1

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 85 Nicotine-Related Compounds in ZYN Spearmint 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Spearmint 6 mg Per Unit			CRP2.1 Per Unit			% Reduction Compared to CRP2.1	General Snus (5 SKUs) Per Unit			% Reduction Compared to General Snus
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								99.7				97.2
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.5				98.9

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

9.1.20 Comparison of HPHCs in ZYN Wintergreen 3 mg to Those in CRP2.1 and General Snus

Table 86 HPHC Content and Relevant Snus Components in ZYN Wintergreen 3 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Wintergreen 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]		[redacted]			[redacted]			>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									67.8				71.7
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Wintergreen 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Beryllium (µg/g)	[redacted]								NA				NA
Cadmium (µg/g)									>96.5				>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									(8.6)[b]				(78.4)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									63.8				50.9
Nitrite (µg/g)									>93.4				>57.3

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Wintergreen 3 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosodimethylamine (NDMA) (ng/g)	[redacted]								>96.9	[redacted]			NA
N-Nitrosonornicotine (µg/g) (NNN)									>99.8				>97.1
Nornicotine (µg/g as is)									>98.7				>99.1
Polonium-210 (radioisotope) (Bq/kg)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 87 HPHC Content and Relevant Snus Components in ZYN Wintergreen 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Wintergreen 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	[redacted]									>99.8					>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										86.8					77.7
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Wintergreen 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Cadmium (µg/unit)	[redacted]	[redacted]				[redacted]				>98.5	[redacted]				>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>98.1					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										55.5					(51.7)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										>85.2					>57.9

Analyte/ HPHC	Analytical Procedure	ZYN Wintergreen 3 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Nicotine, batch averag free nicotine (mg/unit		[redacted]				[redacted]				72.2	[redacted]				63.8
Nitrite (µg/unit)		[redacted]				[redacted]				>97.2	[redacted]				>64.4
N-Nitrosodimethylamin (NDMA) (ng/unit)		[redacted]				[redacted]				>98.7	[redacted]				NA
N-Nitrosonornicotine (µg/unit) (NNN)		[redacted]				[redacted]				>99.9	[redacted]				>97.5
Nornicotine (µg/unit)		[redacted]				[redacted]				>99.7	[redacted]				>99.5
Polonium-210 (radioisotope) (Bq/uni		[redacted]				[redacted]				NA	[redacted]				NA
Propylene Glycol (mg/unit)		[redacted]				[redacted]				NA	[redacted]				>96.3
Selenium (µg/unit)		[redacted]				[redacted]				>79.5	[redacted]				NA
Uranium-235 (Bq/uni		[redacted]				[redacted]				NA	[redacted]				NA
Uranium-238 (Bq/uni		[redacted]				[redacted]				NA	[redacted]				NA

(b) (4)

Source: (b) (4) [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 88 Nicotine-Related Compounds in ZYN Wintergreen 3 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Wintergreen 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	[redacted]							>97.8				>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								>98.7				>99.1

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

Table 89 Nicotine-Related Compounds in ZYN Wintergreen 3 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte	Analytical Procedure	ZYN Wintergreen 3 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		Per Unit			Per Unit				Per Unit			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								>99.7				>99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; SKU=stock keeping unit; SD=standard deviation.

9.1.21 Comparison of HPHCs in ZYN Wintergreen 6 mg to Those in CRP2.1 and General Snus

Table 90 HPHC Content and Relevant Snus Components in ZYN Wintergreen 6 mg Compared to CRP2.1 and General Snus on a Per Dry Weight Basis

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Wintergreen 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/g)	[redacted]		[redacted]						>99.6	[redacted]			>90.8
5-Methyl chrysene (ng/g)									NA				NA
Acetaldehyde (µg/g)									81.4				83.6
Acrolein (µg/g)									NA				NA
Acrylamide (ng/g)									>82.1				>93.0
Aflatoxin B1 (ng/g)									NA				NA
Ammonium ion (mg/g)									>90.9				>73.9
Anabasine (µg/g as is)									>97.8				>96.6
Arsenic (µg/g)									>65.5				>41.9
Benz[j]aceanthrylene (ng/g)									NA				NA
Benzo[a]anthracene (ng/g)									>99.9				>46.6
Benzo[a]pyrene (ng/g)									NA				NA
Benzo[a]pyrene (ng/g)									>99.8				NA
Benzo[b]fluoroanthene (ng/g)									>99.7				>18.6
Benzo[c]phenanthrene (ng/g)									>99.6				NA
Benzo[k]fluoroanthene (ng/g)									>99.3				NA
Beryllium (µg/g)									NA				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Wintergreen 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
Cadmium (µg/g)	[redacted]								>96.5	[redacted]			>89.4
Chromium (µg/g)									>82.3				>78.9
Chrysene (ng/g)									>99.9				>79.8
Coumarin (µg/g)									>95.4				NA
Crotonaldehyde (µg/g)									NA				NA
Cyclopenta[c,d]pyrene (ng/g)									>94.3				NA
Dibenzo[a,e]pyrene (ng/g)									NA				NA
Dibenzo[a,h]anthracene (ng/g)									97.4				NA
Dibenzo[a,h]pyrene (ng/g)									NA				NA
Dibenzo[a,i]pyrene (ng/g)									NA				NA
Dibenzo[a,l]pyrene (ng/g)									NA				NA
Ethyl carbamate (ng/g)									NA				NA
Formaldehyde (µg/g)									0.1				(64.2)[b]
Glycerol (%)									NA				NA
Indeno[1,2,3-cd]pyrene (ng/g)									>98.8				NA
Lead (µg/g)									>74.1				>61.2
Mercury (µg/g)									NA				NA
Naphthalene (ng/g)									>95.6				>65.3
Nickel (µg/g)									>93.1				>92.9
Nicotine (mg/g)									26.8				0.5
Nitrite (µg/g)									>93.4				>57.3
N-Nitrosodimethylamine (NDMA) (ng/g)									>96.9				NA

Analyte/HPHC	Analytical Procedure	LOQ	ZYN Wintergreen 6 mg			CRP2.1			% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)			% Reduction Compared to General Snus[a]
			Per Dry Weight			Per Dry Weight				Per Dry Weight			
			Mean	SD	N	Mean	SD	N		Mean	SD	N	
N-Nitrosonornicotine (µg/g) (NNN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	>99.8	[redacted]	[redacted]	[redacted]	>97.1
Nornicotine (µg/g as is)									97.6				98.3
Polonium-210 (radioisotope) (Bq/kg)									NA				NA
Propylene glycol (%)									NA				>95.2
Selenium (µg/g)									>48.6				>49.7
Uranium-235 (Bq/kg)									NA				NA
Uranium-238 (Bq/kg)									NA				NA

Source: [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD= standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

Table 91 HPHC Content and Relevant Snus Components in ZYN Wintergreen 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

Analyte/ HPHC	Analytical Procedure	ZYN Wintergreen 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK) (µg/unit)	(b) (4)									>99.8	(b) (4)				>92.2
5-Methylchrysene (ng/unit)										NA					NA
Acetaldehyde (µg/unit)										92.4					87.2
Acrolein (µg/unit)										NA					NA
Acrylamide (ng/unit)										>92.5					>93.9
Aflatoxin B1 (ng/unit)										NA					NA
Ammonium ion (mg/unit)										>99.6					>78.2
Anabasine (µg/unit)										>99.6					>98.2
Arsenic (µg/unit)										>85.5					>82.6
Benz[j]aceanthrylene (ng/unit)										NA					NA
Benzo[a]anthracene (ng/unit)										100.0					NA
Benzo[a]pyrene (ng/unit)										NA					NA
Benzo[a]pyrene (ng/unit)										>99.9					NA
Benzo[b]fluoroanthene (ng/unit)										>99.9					NA
Benzo[c]phenanthrene (ng/unit)										>99.8					NA
Benzo[k]fluoroanthene (ng/unit)										>99.7					NA
Beryllium (µg/unit)										NA					NA

Analyte/ HPHC	Analytical Procedure	ZYN Wintergreen 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Cadmium (µg/unit)	(b) (4)									>98.5	(b) (4)				>90.9
Chromium (µg/unit)										>92.6					>81.3
Chrysene (ng/unit)										100.0					>82.0
Coumarin (µg/unit)										>95.2					NA
Crotonaldehyde (µg/unit)										NA					NA
Cycolopenta[c,d]pyrene (ng/unit)										>97.6					NA
Dibenzo[a,e]pyrene (ng/unit)										NA					NA
Dibenzo[a,h]anthracene (ng/unit)										>98.9					NA
Dibenzo[a,h]pyrene (ng/unit)										NA					NA
Dibenzo[a,i]pyrene (ng/unit)										NA					NA
Dibenzo[a,l]pyrene (ng/unit)										NA					NA
Ethyl carbamate (ng/unit)										NA					NA
Formaldehyde (µg/unit)										59.4					(38.6)[b]
Glycerol (mg/unit)										NA					NA
Indeno[1,2,3-cd]pyrene (ng/unit)										>99.5					NA
Lead (µg/unit)										>89.1					>66.1
Mercury (µg/unit)										NA					NA
Naphthalene (ng/unit)										>98.1					>61.7
Nickel (µg/unit)										>97.1					>93.8
Nicotine (mg/unit)										69.9					14.4

Analyte/ HPHC	Analytical Procedure	ZYN Wintergreen 6 mg				CRP2.1				% Reduction Compared to CRP2.1[a]	General Snus (5 SKUs)				% Reduction Compared to General Snus[a]
		Per Unit				Per Unit					Per Unit				
		Mean	SD	N	LOQ	Mean	SD	N	LOQ		Mean	SD	N	LOQ	
Nicotine, batch average, free nicotine (mg/unit)		(b) (4)								42.2	[redacted]				24.6
Nitrite (µg/unit)										>97.2					>64.4
N-Nitrosodimethylamin (NDMA) (ng/unit)										>98.7					NA
N-Nitrosonornicotine (µg/unit) (NNN)										>99.9					>97.5
Nornicotine (µg/unit)										99.7					99.5
Polonium-210 (radioisotope) (Bq/un										NA					NA
Propylene Glycol (mg/unit)										NA					>96.3
Selenium (µg/unit)										>79.5					NA
Uranium-235 (Bq/uni										NA					NA
Uranium-238 (Bq/uni										NA					NA

Source: (b) (4) [redacted]

CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; DHHS=United States Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Note: The quantification of analytes were performed using accredited analyses with the exception of coumarin and acrylamide. In instances where averages were below the LOQ, data are shown as "< value of LOQ." For incidences where all replicate values were below LOQ, <LOQ was reported and the SD was not calculated. For incidences where individual replicate levels were below LOQ, the values were set to 50% of the LOQ for the mean and SD calculations. Where there are multiple LOQ, the highest LOQ value was shown. The group sizes reflect instances where analytical testing was not included at the time of testing or where less replicates than three were used.

[a] When analytes for only one product were found below LOQ, the percentage of reduction was calculated with the LOQ value. When analytes for both products were below the LOQ, no reduction can be calculated, and percentage of reduction is replaced by NA.

[b] Increase is noted in parentheses.

[c] The calculation can be found at USDHHS 2009.

Table 92 Nicotine-Related Compounds in ZYN Wintergreen 6 mg Compared to CRP2.1 and General Snus on an As Is Basis

Analyte	Analytical Procedure	ZYN Wintergreen 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		As Is			As Is				As Is			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/g as is)	(b) (4)							>97.8	(b) (4)			>96.6
Anatabine (µg/g as is)								>99.4				>99.3
Cotinine (µg/g as is)								>97.3				>97.4
Myosmine (µg/g as is)								>81.5				>80.3
Nicotine-N-oxide (µg/g as is)								>99.7				>98.9
β-Nicotyrine (µg/g as is)								>90.6				>82.1
Nornicotine (µg/g as is)								97.6				98.3

Source: (b) (4)

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

Table 93 Nicotine-Related Compounds in ZYN Wintergreen 6 mg Compared to CRP2.1 and General Snus Per Unit of Use

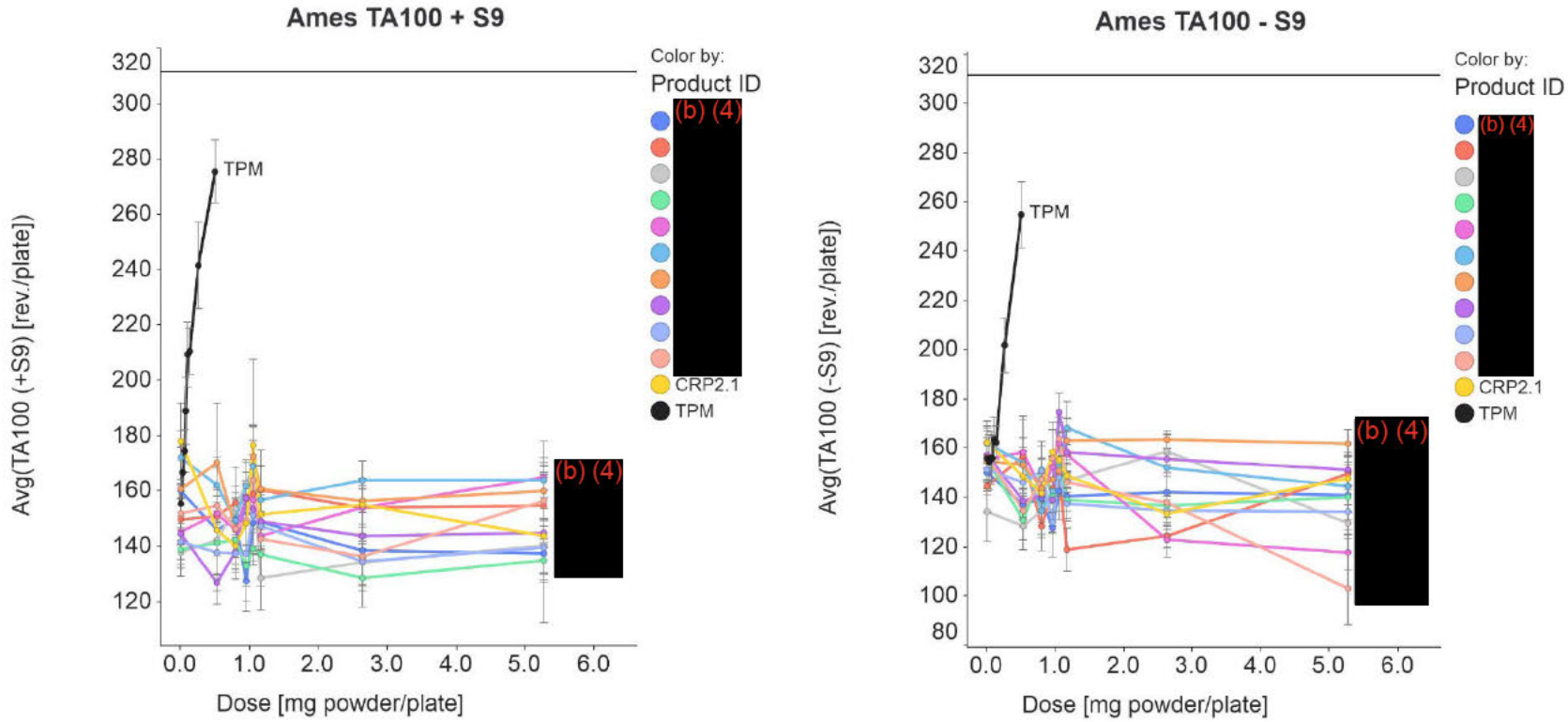
Analyte	Analytical Procedure	ZYN Wintergreen 6 mg			CRP2.1			% Reduction Compared to CRP2.1	General Snus (5 SKUs)			% Reduction Compared to General Snus
		Per Unit			Per Unit				Per Unit			
		Mean	SD	N	Mean	SD	N		Mean	SD	N	
Anabasine (µg/unit)	[redacted]							>99.6	[redacted]			>98.2
Anatabine (µg/unit)								>99.9				>99.6
Cotinine (µg/unit)								>99.5				>98.6
Myosmine (µg/unit)								>96.3				>89.4
Nicotine-N-oxide (µg/unit)								>99.9				>99.3
β-Nicotyrine (µg/unit)								>98.1				>92.1
Nornicotine (µg/unit)								99.7				99.5

Source: [redacted]

CRP=CORESTA Smokeless Tobacco Reference Product; N=group size; NA=not applicable; SKU=stock keeping unit; SD=standard deviation.

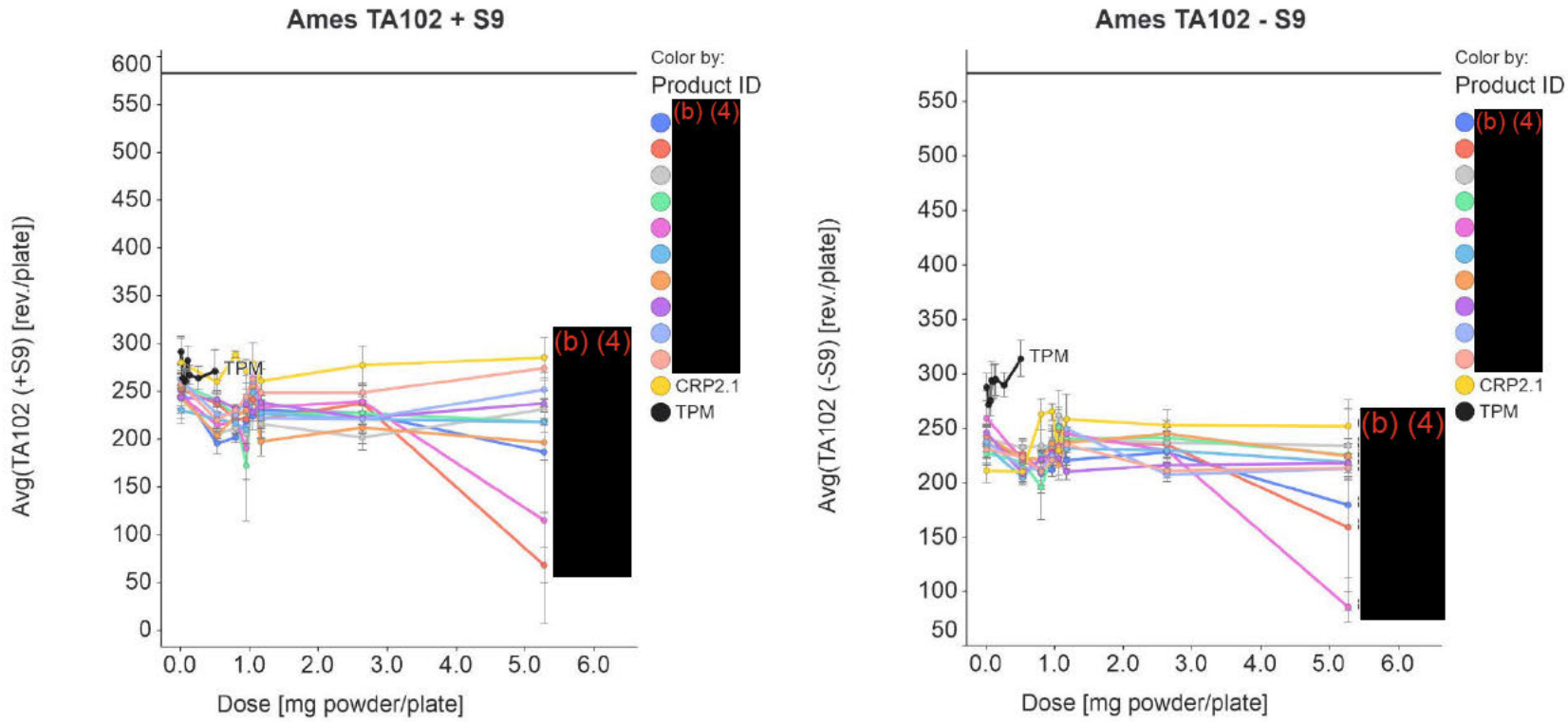
9.1.22 Supplemental Information for In Vitro Genotoxicity Testing of ZYN, CRP2.1 and Cigarette TPM

Figure 6 Ames Assay Data Strain TA100 With and Without Metabolic Activation for ZYN, CRP2.1 and Cigarette TPM



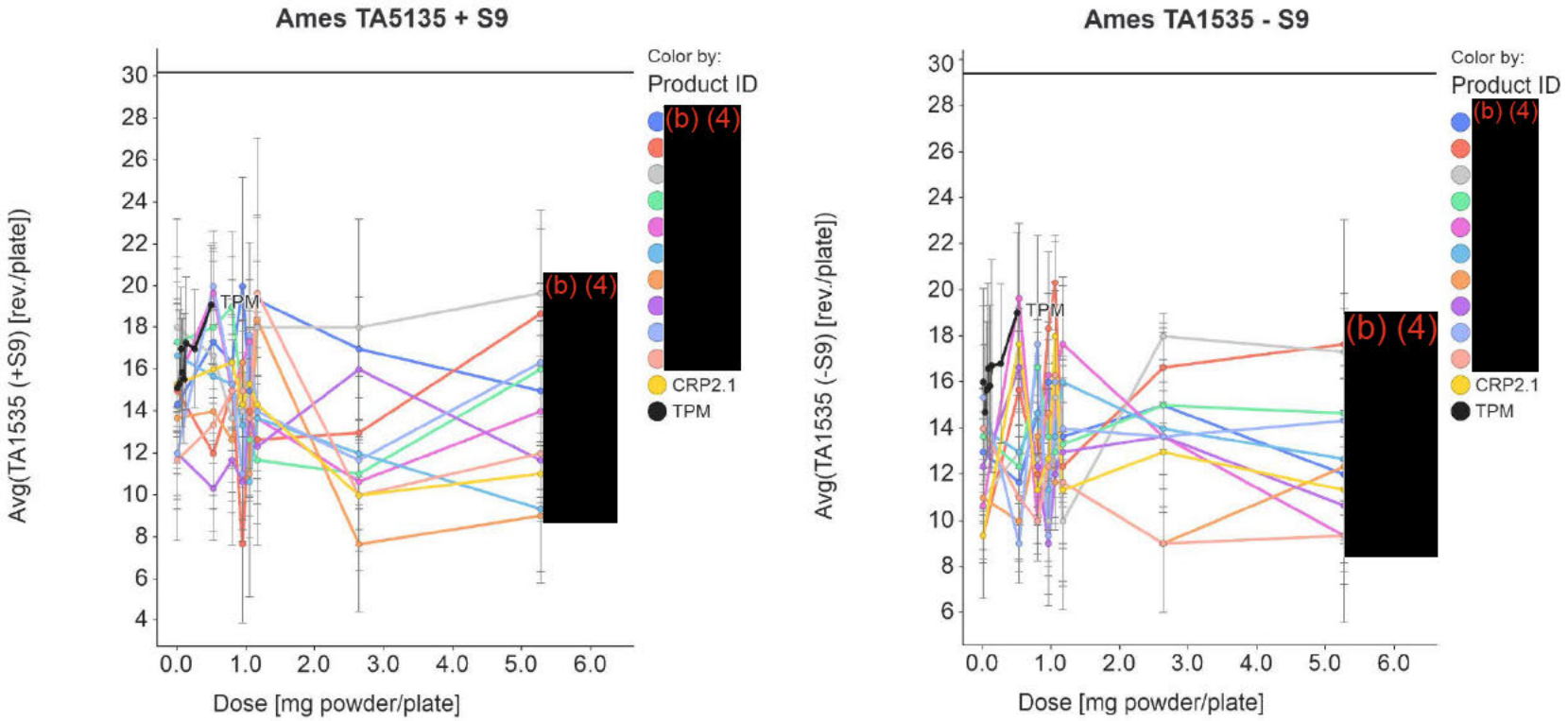
Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Left panel: Mean ± SD of revertants in strain TA98 with metabolic activation (+S9).
Right panel: Mean ± SD of revertants in strain TA98 without metabolic activation (-S9).
Replica 2 was selected as a representative replica for the test items. All tested concentrations included.
The horizontal line included for visualization represents 2-fold solvent control for TPM samples (b) (4) used for making mutagenicity call for reference TPM. For the overall mutagenic evaluation, the test items own solvent controls ((b) (4) were used.

Figure 7 Ames Assay Data Strain TA102 With and Without Metabolic Activation for ZYN, CRP2.1 and Cigarette TPM



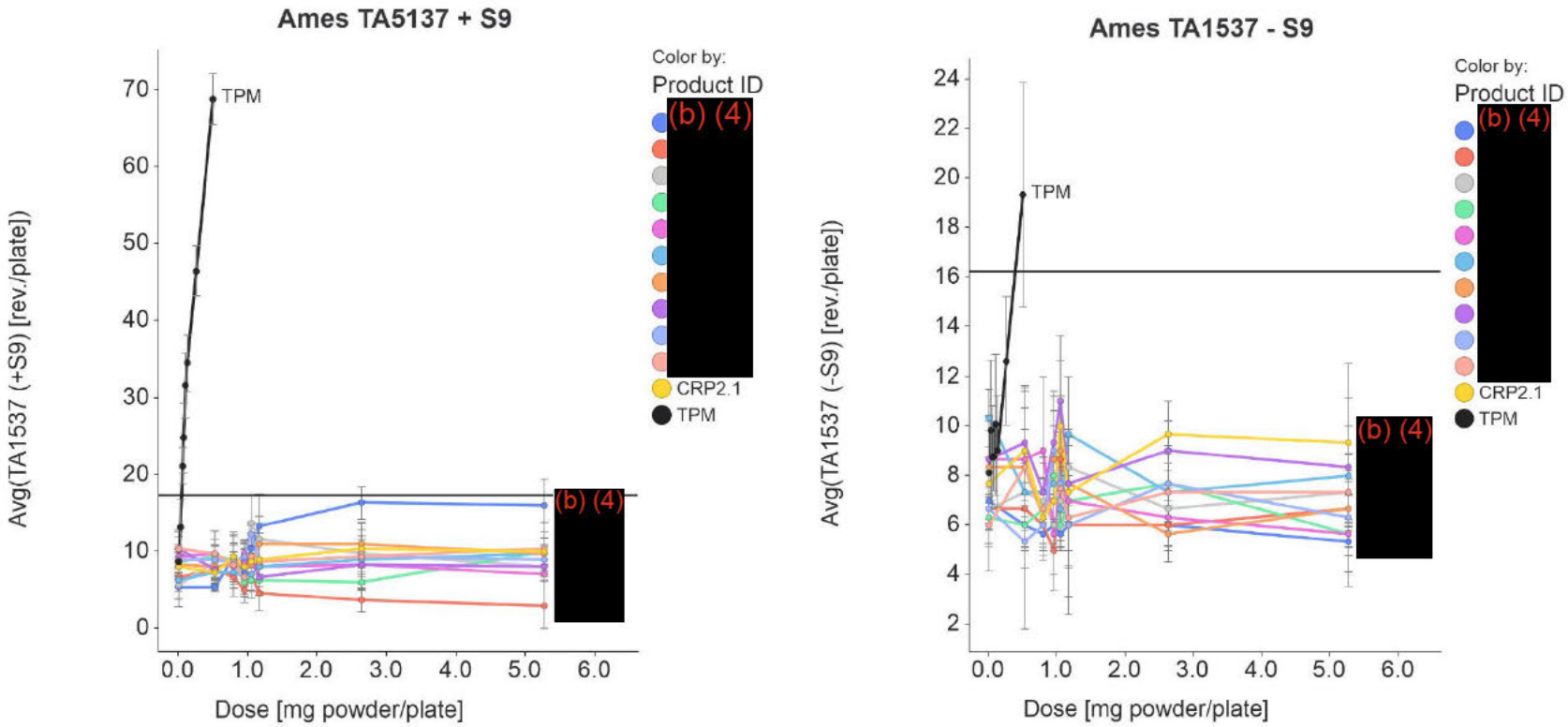
Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Left panel: Mean ± SD of revertants in strain TA98 with metabolic activation (+S9).
Right panel: Mean ± SD of revertants in strain TA98 without metabolic activation (-S9).
Replica 2 was selected as a representative replica for the test items. All tested concentrations included.
The horizontal line included for visualization represents 2-fold solvent control for TPM samples (b) (4) used for making mutagenicity call for reference TPM. For the overall mutagenic evaluation, the test items own solvent controls (b) (4)) were used.

Figure 8 Ames Assay Data Strain TA1535 With and Without Metabolic Activation for ZYN, CRP2.1 and Cigarette TPM



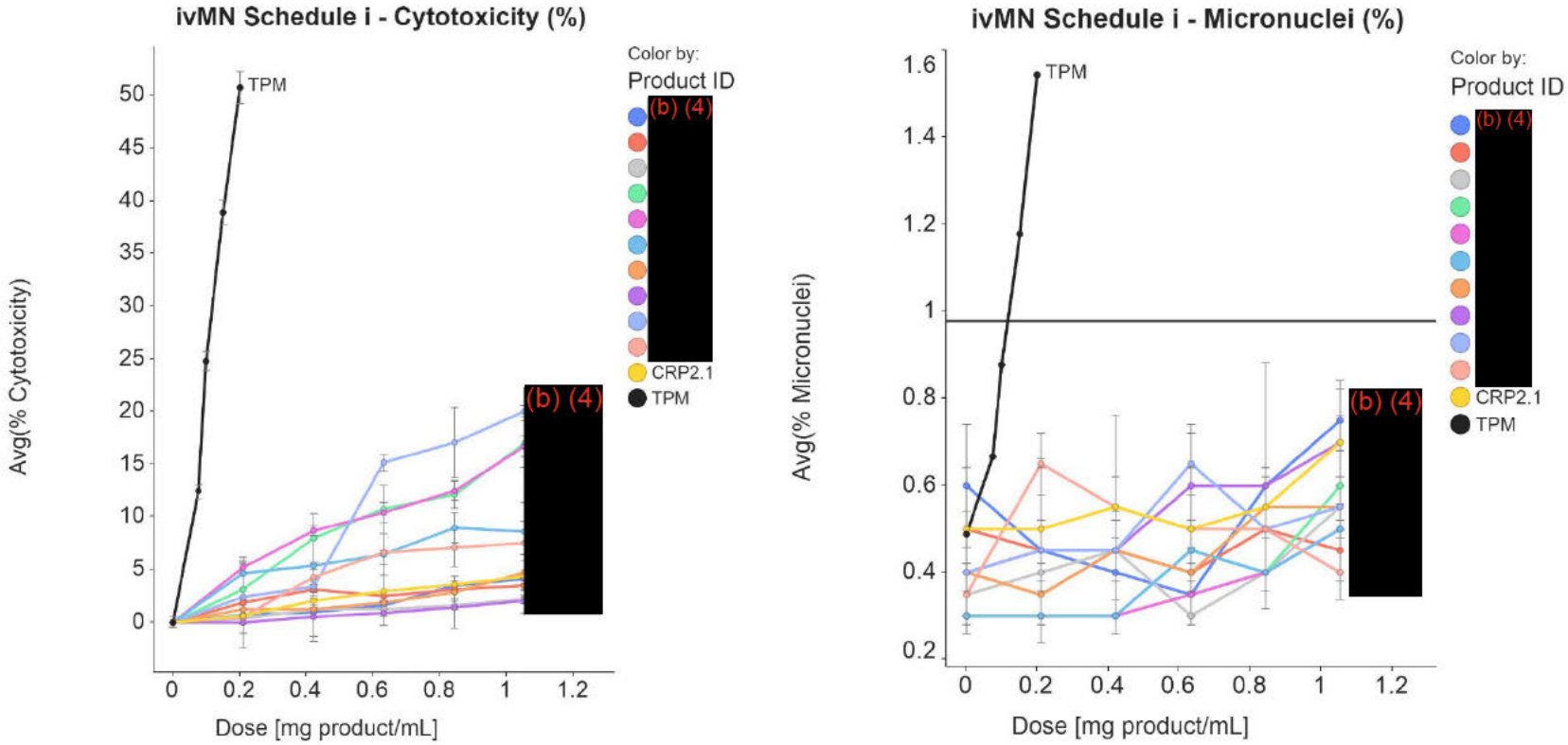
Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Left panel: Mean ± SD of revertants in strain TA98 with metabolic activation (+S9).
Right panel: Mean ± SD of revertants in strain TA98 without metabolic activation (-S9).
Replica 2 was selected as a representative replica for the test items. All tested concentrations included.
The horizontal line included for visualization represents 2-fold solvent control for TPM samples (b) (4) used for making mutagenicity call for reference TPM. For the overall mutagenic evaluation, the test items own solvent controls ((b) (4)) were used.

Figure 9 Ames Assay Data Strain TA1537 With and Without Metabolic Activation for ZYN, CRP2.1 and Cigarette TPM



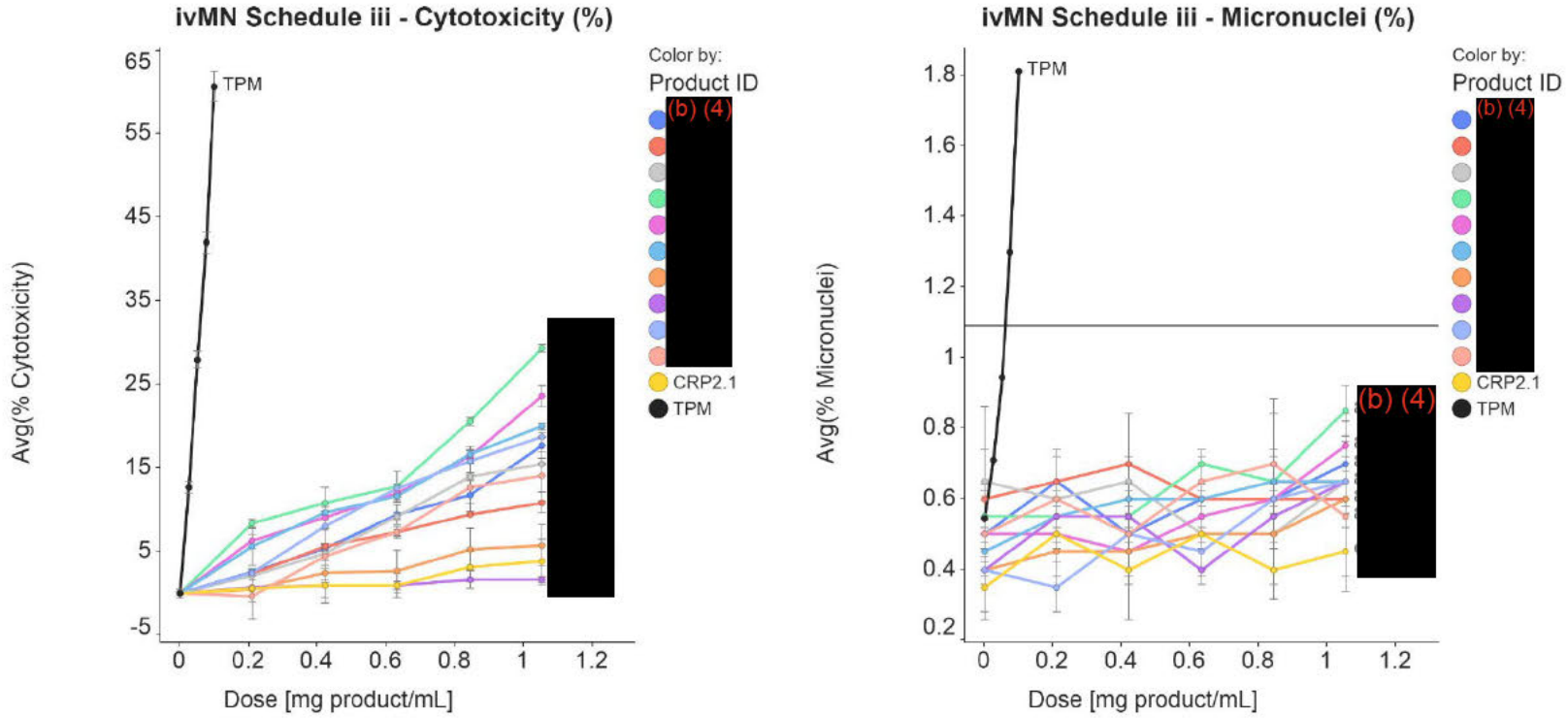
Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Left panel: Mean ± SD of revertants in strain TA98 with metabolic activation (+S9).
Right panel: Mean ± SD of revertants in strain TA98 without metabolic activation (-S9).
Replica 2 was selected as a representative replica for the test items. All tested concentrations included.
The horizontal line included for visualization represents 2-fold solvent control for TPM samples (b) (4) used for making mutagenicity call for reference TPM. For the overall mutagenic evaluation, the test items own solvent controls (b) (4)) were used.

Figure 10 In Vitro Micronucleus Assay Data for ZYN, CRP2.1 and Cigarette TPM, Short-term Treatment with Metabolic Activation (Schedule i)



Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Results from *in vitro* micronucleus assays in CHO-WBL cells using short term treatment without metabolic activation (-S9. Schedule i). Replicate 2 was selected as a representative replicate for the test items. All tested concentrations are included. 1,000 cells were counted per slide.
Left panel: Mean ± SD for cytotoxicity.
Right panel: Mean ± SD for %-micronuclei.
The horizontal line included for visualization represents the 2-fold increase over solvent control for TPM samples (b) (4) used for making genotoxicity call for reference TPM. For the overall genotoxic evaluation, the test items' own solvent controls ((b) (4) were used.

Figure 11 In Vitro Micronucleus Assay Data for ZYN, CRP2.1 and Cigarette TPM, Long-term Treatment Without Metabolic Activation (Schedule iii)



Source: Section H.2.3 Study (b) (4) Report
CRP2.1=CORESTA Smokeless Tobacco Reference Product 2.1; TPM=total particulate matter.
Note: Results from *in vitro* micronucleus assays in CHO-WBL cells using long-term treatment without metabolic activation (+S9, Schedule iii). Replicate 2 was selected as a representative replicate for the test items. All tested concentrations are included. 1,000 cells were counted per slide.
Left panel: Mean ± SD for cytotoxicity.
Right panel: Mean ± SD for %-micronuclei.
The horizontal line included for visualization represents a 2-fold increase over solvent control for TPM samples (b) (4) used for making the genotoxicity call for the reference TPM. For the overall genotoxic evaluation, the test items' own solvent controls ((b) (4)) were used.