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MEMORANDUM

Date:	July 14, 2017	
From:	Daniela Stricklin, PhD, MPH Division of Nonclinical Science, Office of Science, CTP	For Digitally signed by Philip Yeager -S Date: 2017.07.14 13:48:44 -04'00'
And:	Wanyoike Kang'ethe, PhD Division of Nonclinical Science, Office of Science, CTP	Digitally signed by Wanyoike W. Kangethe -S Date: 2017.07.14 13:50:06 -04'00'
Through:	Kimberly Benson, PhD Director Division of Nonclinical Science, Office of Science, CTP	Digitally signed by Kimberly A. Benson -S Date: 2017.07.17 10:00:05 -04'00'
To:	File	
Subject:	SE Review: Toxicological implications of Fire Standards Compliant (FSC) paper.	

1 PURPOSE

This memorandum summarizes the Division of Nonclinical Science's current thinking on the toxicological impact of Fire Standards Compliant (FSC)[1] (also referred to as low ignition propensity, LIP, or reduced ignition propensity, RIP) paper used in cigarettes.

2 BACKGROUND

Due to the fact that cigarettes and other combusted tobacco products have historically been a leading cause of fire deaths and fire-related injuries (Alpert et al., 2010), as of 2012 all states in the US have enacted laws requiring cigarettes to meet certain fire standards for self-extinction when not being smoked. In order to meet this fire standard, tobacco product manufacturers have used different cigarette paper designs to reduce the burn rate of the product. Various materials and design modifications have been subsequently incorporated to meet the required specifications. As a result, some SE Reports submitted to the FDA involve comparison between a new combusted tobacco product with FSC paper and a predicate combusted tobacco product with non-FSC paper where the only difference is the use of FSC paper in the new product.

3 FSC CIGARETTE PAPER

A brief description of FSC cigarette paper is provided below; in addition, a more detailed summary of FSC cigarette paper is available in a memorandum to file from the Division of Product Sciences (Gong and Eads, 2016).

Changes in the cigarette paper to meet FSC criteria typically include certain modifications of paper composition and application of extinguishing bands to the paper. The most common FSC cigarette paper design involves circumferential band material applied intermittently along the length of the paper of the rod. The bands restrict air flow through the paper to the burning ember and this slows the rate at which the

[1] FSC is sometimes referred to as fire safe cigarettes which is a misnomer since the cigarettes are not "fire safe" and can still remain a fire hazard if mishandled.

cigarette burns and causes the cigarette to extinguish if it is not smoked (World Health Organization, 2014). At present, common banding materials include cellulose, alginate, ethyl vinyl acetate (EVA), guar gum, citrate, and calcium carbonate. Other designs rely on longitudinal orientation in which some-level of double wrapping of cigarette paper or strips of reconstituted tobacco sheets to the interior of the wrapper are added to reduce the burn rate. Additional technologies may become available; if that occurs, this memorandum to file will be updated to address any new methods to achieve an FSC cigarette paper.

4 COMPARISON OF NON-FSC AND FSC PAPER

From a toxicological review perspective, the main concern with the use of FSC cigarette paper is whether the design and ingredient changes in the FSC paper increase the yield of harmful and potentially harmful constituents (HPHCs) in mainstream smoke and thus increase the health risks associated with the use of FSC cigarette paper when compared to non-FSC combusted tobacco products. The evidence available for evaluation of the potential health implications from FSC paper include (1) comparison of HPHC yields in mainstream smoke from cigarettes comprising non-FSC and FSC paper, (2) toxicology data from *in vitro* and *in vivo* nonclinical studies, and (3) human exposure studies comparing the effects of exposure to smoke from FSC and non-FSC cigarettes.

4.1 Changes in Mainstream HPHCs

Only a few studies have examined the difference in HPHC yields between FSC and non-FSC paper. An early study conducted by the National Institute of Standards and Technology (NIST) compared the tar, nicotine, and carbon monoxide (TNCO) yields from six brands using FSC paper with 14 bestselling cigarette brands as a group (Ohlemiller et al., 1993). Although no significant differences were observed between FSC and non-FSC cigarettes in this study, there were a number of design differences between the cigarettes tested which may have impacted the comparability of the results.

A more recent study by Connolly, et al. analyzed the HPHC yields from four brands, comparing FSC cigarettes sold in New York with non-FSC cigarettes of the same brand sold in Massachusetts (Connolly et al., 2005). The study did not specify whether the cigarettes tested had design modifications other than the FSC paper; however, it provided a comparison of actual marketed products with matched cigarette brands using FSC and non-FSC paper. The four matching brands were Marlboro Red Filter Hard Pack, Newport Menthol Kings Filter Soft Pack, Camel Filter Hard Pack, and Kool Filter Kings Soft Pack. In this comparison, the FSC cigarettes exhibited the following average increases in HPHC yields:

- Carbon monoxide (CO) yields (11.4%)
- Tar (3%)
- Naphthalene (13.9%)
- Fluorene (6.1%).

In one brand (Newport), polycyclic aromatic hydrocarbons (PAHs) were 11.3-19.9% higher in the FSC cigarettes, although the magnitude of the increases was in nanogram quantities.

FDA has had recent experience with SE Reports in which the only difference between a new cigarette product and its predicate product is a change to FSC paper. Tables 1 and 2 provide data from eleven new product/predicate product pairs under the ISO and CI machine smoking regimens. In all cases, tar, nicotine, and CO deliveries were increased in the cigarette products containing FSC paper. Although only TNCO was measured in the example below, other HPHCs, especially those whose concentration is dependent on combustion, may also increase.

Table 1. Example TNCO changes between new and predicate product pairs in which the only difference is the change to FSC paper (ISO Machine Smoking Regimen)

ISO		Mean Quantity with Standard Deviation (mg/cigarette)				
SE Report	Constituent	New Product	N	Predicate Product	N	% Change
(b) (4)	ar	16.2 (1.0)	10	13.7 (0.5)	10	+18
	icotine	0.957 (0.070)	10	0.843 (0.026)	10	+14
	arbon monoxide	20.1 (1.4)	10	15.1 (0.4)	10	+33
	ar	10.5 (0.9)	10	8.30 (0.68)	10	+27
	icotine	0.743 (0.055)	10	0.627 (0.038)	10	+19
	arbon monoxide	12.0 (1.0)	10	7.72 (0.63)	10	+55
	ar	9.42 (1.12)	10	7.71 (0.64)	10	+22
	icotine	0.693 (0.057)	10	0.585 (0.037)	10	+18
	arbon monoxide	10.7 (1.6)	10	7.07 (0.59)	10	+51
	ar	16.4 (0.7)	10	14.4 (0.5)	10	+14
	icotine	0.973 (0.065)	10	0.859 (0.045)	10	+13
	arbon monoxide	19.2 (0.6)	10	14.8 (0.6)	10	+30
	ar	9.86 (0.43)	10	7.66 (0.43)	10	+29
	icotine	0.722 (0.032)	10	0.592 (0.045)	10	+22
	arbon monoxide	10.4 (0.6)	10	6.97 (0.52)	10	+49
	ar	17.7 (0.8)	10	15.3 (0.4)	10	+16
	icotine	1.04 (0.05)	10	0.933 (0.027)	10	+11
	arbon monoxide	21.5 (1.2)	10	16.5 (0.7)	10	+30
	ar	12.1 (0.4)	10	10.6 (0.4)	10	+14
	icotine	0.868 (0.085)	10	0.756 (0.025)	10	+15
	arbon monoxide	13.2 (0.7)	10	10.1 (0.5)	10	+31
	ar	13.1 (0.6)	10	10.3 (0.4)	10	+27
	icotine	0.926 (0.031)	10	0.744 (0.034)	10	+24
	arbon monoxide	13.9 (0.9)	10	9.56 (0.50)	10	+45
	ar	17.9 (0.9)	10	14.9 (0.8)	10	+20
	icotine	1.06 (0.05)	10	0.956 (0.041)	10	+11
	arbon monoxide	21.3 (1.3)	10	15.7 (0.7)	10	+36
	ar	12.3 (0.8)	10	10.5 (0.5)	10	+17
	icotine	0.865 (0.077)	10	0.753 (0.025)	10	+15
	arbon monoxide	13.3 (0.7)	10	10.4 (0.5)	10	+28

Table 2. Example TNCO changes between new and predicate product pairs in which the only difference is the change to FSC paper (CI Machine Smoking Regimen)

CI		Mean Quantity with Standard Deviation (mg/cigarette)				
SE Report	Constituent	New Product	N	Predicate Product	N	% Change
(b) (4)	Tar	38.0 (2.0)	10	32.9 (1.6)	10	+16
	Nicotine	1.88 (0.07)	10	1.81 (0.08)	10	+4
	Carbon monoxide	36.0 (1.8)	10	31.3 (1.5)	10	+15
	Tar	38.5 (2.2)	10	34.5 (1.9)	10	+12
	Nicotine	2.00 (0.11)	10	1.86 (0.09)	10	+8
	Carbon monoxide	36.7 (2.1)	10	31.0 (0.8)	10	+18
	Tar	38.4 (1.9)	10	34.3 (1.7)	10	+12
	Nicotine	1.92 (0.11)	10	1.76 (0.07)	10	+9
	Carbon monoxide	35.8 (1.8)	10	29.8 (1.1)	10	+20
	Tar	39.4 (1.7)	10	34.4 (2.1)	10	+15
	Nicotine	1.98 (0.06)	10	1.78 (0.10)	10	+11
	Carbon monoxide	36.0 (1.4)	10	29.2 (1.8)	10	+23
	Tar	39.8 (2.2)	10	35.1 (2.3)	10	+13
	Nicotine	2.00 (0.10)	10	1.83 (0.11)	10	+9
	Carbon monoxide	39.7 (1.7)	10	30.9 (1.2)	10	+28
	Tar	41.7 (2.0)	10	36.3 (2.7)	10	+15
	Nicotine	2.21 (0.10)	10	2.02 (0.09)	10	+9
	Carbon monoxide	41.3 (2.2)	10	34.6 (1.6)	10	+19
	Tar	44.1 (2.9)	10	36.6 (2.4)	10	+20
	Nicotine	2.23 (0.11)	10	2.01 (0.10)	10	+11
	Carbon monoxide	42.9 (2.1)	10	34.9 (1.6)	10	+23
	Tar	41.0 (4.3)	10	37.5 (2.5)	10	+9
	Nicotine	2.37 (0.09)	10	2.13 (0.14)	10	+11
	Carbon monoxide	39.7 (1.7)	10	34.0 (2.0)	10	+17
	Tar	40.8 (1.8)	10	35.7 (2.6)	10	+14
	Nicotine	2.33 (0.16)	10	2.03 (0.10)	10	+15
	Carbon monoxide	40.3 (1.9)	10	32.9 (1.6)	10	+22
	Tar	41.8 (2.7)	10	36.9 (2.9)	10	+13
	Nicotine	2.23 (0.10)	10	2.02 (0.08)	10	+10
	Carbon monoxide	40.3 (2.4)	10	34.9 (1.0)	10	+15

4.2 Toxicology Studies

Only a few nonclinical studies on the comparative toxicity of FSC and non-FSC cigarettes are publically available and all were conducted by the tobacco industry (Theophilus et al., 2007a; Theophilus et al., 2007b; Werley et al., 2013). Although these studies do provide some limited information on the potential toxicological impact of FSC cigarettes compared to non-FSC cigarettes, they all normalized HPHC yields to total particulate matter (TPM) and did not control for design differences, which limits the quantitative comparability between the test and control cigarettes.

Several studies were conducted to evaluate changes in mainstream smoke composition, as well as *in vitro*, and *in vivo* toxicity of cigarettes using banded papers compared to non-FSC cigarettes (Theophilus et al., 2007a; Theophilus et al., 2007b). Detailed reviews of these two studies have been conducted internally and are only briefly presented here. Specifically, evaluation of mainstream smoke chemistry indicated that tar yield was increased in two of the three banded cigarettes tested (5.7 and 15.1% increase). CO was increased in all of the test banded cigarettes compared to non-banded control cigarettes (11.4-17.3%). The *in vitro* studies on mutagenicity and cytotoxicity showed no statistically significant differences in test and control cigarettes. A 30-week mouse tumor promotion study showed no consistent differences in tumor promotion potential between test and control cigarettes. Clinical signs and histopathology results from a 13-week subchronic inhalation study in rats also showed no consistent differences between test and control cigarettes. However, a significant dose-dependent increase in carboxyhemoglobin (COHb) was observed in animals exposed to the test cigarettes, and it was comparable to the increase in CO yields from the banded test cigarettes.

A series of studies were conducted to evaluate five different variables associated with banded FSC papers in comparison to five control cigarettes with similar design characteristics (Werley et al., 2013). Statistically significant increases in CO and benzo[a]pyrene (B[a]P) yields (15 and 11%) were observed in banded cigarettes as compared to non-banded controls; however, a few other constituents such as formaldehyde, NNN, and NNK exhibited statistically significant decreases (14, 8, and 8%). No differences in mutagenicity were observed. Although a small but statistically significant difference in cytotoxicity associated with for banded cigarettes was reported, the data was not included in the paper and could not be found in the supplemental material provided by the journal. No consistent differences in mean histopathology severity scores were observed in male rats exposed for 21 or 90 days to smoke from banded and non-banded cigarettes.

In each of these toxicology studies, banded and non-banded cigarettes indicate similar toxicological profiles; however, it is important to note that these studies have major methodological limitations, and the assays may lack the sensitivity to distinguish toxicological differences between exposures to FSC and non-FSC papers.

4.3 Human Exposure Studies

Two human exposure studies have examined differences in biomarkers of cigarette smoke exposure in smokers that used FSC cigarettes compared to those that smoked non-FSC cigarettes (June et al., 2011b; O'Connor et al., 2010). The study by O'Connor et al. used a cross-over design in which smokers of non-FSC were switched to FSC cigarettes for 14 days. This study also included a cohort that only smoked FSC cigarettes (O'Connor et al., 2010). The only statistically significant difference observed in FSC smokers was a significant increase in the metabolite levels of phenanthrene. The study by June et al. measured the exposure markers in smokers before and after FSC cigarettes were introduced in Canada and it reported non-significant increases in exhaled CO levels after FSC smoking (June et al., 2011b). In contrast, PAH urinary metabolites of fluorene, pyrene, and phenanthrene showed statistically significant increases after FSC smoking (22, 24, and 17%), although the increases were small in magnitude, on the order of ng/g creatinine. These increases correspond well with the small (ng/cig) increases in PAH exposures from the mainstream smoke from FSC cigarettes as referenced previously (Connolly et al., 2005). In both studies, some limitations of the epidemiological studies

are noted such as demographically different populations, limited sample sizes, limited number of study products, and the short-term duration of the study, which in turn limits the ability to extrapolate from the findings of these studies to other combusted tobacco products. In addition, although these two studies examined commercially available cigarettes and there was no indication whether any other design changes were included in the FSC cigarettes tested. Nevertheless, the studies provide some informative human exposure data from FSC versus non-FSC cigarette smoke exposures.

5 SUMMARY AND CONCLUSIONS

A number of studies confirm that the use of FSC cigarette paper in combusted tobacco products has served to decrease the incidence of fires and injuries resulting from cigarettes, supporting justification for the legislation requiring reduced ignition propensity paper (Alpert et al., 2014; Krasovsky, 2015; WHO, 2015; Yau and Marshall, 2014). Other studies, however, indicate that FSC paper may increase the yield of certain HPHC constituents in mainstream smoke, notably CO, a few PAHs (including naphthalene, fluorine and phenanthrene) and tar (Connolly et al., 2005; Ohlemiller et al., 1993; Theophilus et al., 2007b; Werley et al., 2013). Still the data available suggest that the overall amount HPHC increases, other than CO, appears to be in the ng/cig range (Connolly et al., 2005; Ohlemiller et al., 1993; Theophilus et al., 2007b; Werley et al., 2013). In addition, although some findings suggest that CO yield increased in FSC cigarettes, no corresponding statistically significant increases in exhaled CO were identified in persons who switched from non-FSC to FSC cigarettes (Connolly et al., 2005; June et al., 2011a; O'Connor et al., 2010). The toxicology studies that have been published to date have also not reported any profound differences in toxicity between non-FSC and FSC paper. However, these studies have significant limitations and cannot be used to adequately evaluate the potential toxicological differences between exposures to FSC and non-FSC papers. As more information from research becomes available this memorandum will be updated to reflect current understanding on the full impact of the switch to FSC paper may impact HPHC yields and associated human health risks.

A quantitative comparison of the risks associated with the increases in HPHCs and the reduction of fire-related injuries and deaths, both related to the use of FSC paper in cigarettes, would be needed to conclusively determine the overall risk benefit of conversion to FSC paper. However, due to the complexity of conducting such a comparative risk analysis and current limitations in available data, a quantitative comparison is not possible at this time. Given the information available on the changes that have been observed in HPHC yields from switching from non-FSC to FSC paper, the benefit of using FSC paper in cigarettes to reduce household fires is anticipated to outweigh any potential increased health risks from the small increases in HPHC exposures that may occur from the use of the FSC paper. Therefore, viewed from an overall public health perspective and based on the information available at this time, if the only change in a new combusted tobacco product is the change to FSC paper, the new product incorporating FSC paper is unlikely to raise different questions of public health as compared to the non-FSC predicate product.

6 TOXICOLOGY STUDIES ON FSC PAPER

Studies used in the toxicological review of FSC paper are provided in **Table 3**.

Table 3: Toxicology and Human Exposure Studies on FSC Paper.

Reference	Material Tested	Study Design	Study Results	Comments
Toxicology Studies				
(Theophilus et al., 2007a)	Two banded cigarette papers	13-week smoke inhalation in rats	No differences in histopathology between banded and non-banded cigarette exposures. COHb increases were observed in animals exposed to banded cig.	The study did not control for design changes and normalized results to TPM.
(Theophilus et al., 2007b)	Two banded cigarette papers	Evaluation of MS, in vitro geno- and cytotox., in vivo 13-wk rat, 30-wk dermal in mice	CO and B[a]P increases were observed in MS of banded cig. No consistent differences toxicological endpoints observed between test and control groups.	The study did not control for design changes and normalized results to TPM.
(Werley et al., 2013)	Banded cigarette papers	Smoke chemistry, in vitro mutagenicity and cytotoxicity, and inhalation studies with rats, were used to evaluate different band characteristics added to cigarette paper.	Differences in the amount of band material were associated with an increase in some metals in MS. No dose response to any band design parameter (base paper permeability, band width, band spacing, band chalk amount, or citrate) was observed. Some small differences were produced by different types of bands. There were no clear differences in	Insufficient details on experimental methods were provided. Based on results from previous studies, TPM concentrations used were too low to observe effects in rats. Smoke chemistry was performed on the cigarettes, but not on the test chamber atmosphere.

Reference	Material Tested	Study Design	Study Results	Comments
			toxicity.	Details to evaluate statistical assertions were not provided.
Human Biomarker Exposure Studies				
(O'Connor et al., 2010)	RIP (FSC) cigarettes	18-day switching study in smokers Biomarkers of exposure measured	NS changes in CO after RIP smoking Phenanthrene exp. increased significantly (20%) after RIP smoking.	Cotinine, pyrene, naphthalene, and fluorene were not increased. Mean expired CO was increased but NS after RIP. Study does not indicate or evaluate whether other design changes exits, but nevertheless, provides invaluable human health exposure data on FSC vs. non-FSC exposures.
(June et al., 2011b)	Pre- and Post-RIP cigarette	Smoker biomarker and topography pre- and post-RIP introduction	NS differences in smoking topography, expired CO, cotinine Metabolites of fluorene, pyrene, and phenanthrene were increased, 22, 24, 17%, respectively	Mean expired CO was increased but values were NS. Small (ng/g level) but significant increase in 3 PAH metabolites. Study does not indicate or evaluate whether other design changes exits, but nevertheless, provides invaluable human health exposure data on FSC vs. non-FSC exposures.

7 LIST OF ABBREVIATIONS

Abbreviation	Term
CO	Carbon monoxide
COHb	Carboxyhemoglobin
FSC	Fire standards compliant
HPHC	Harmful and potentially harmful constituents
LIP	Lower ignition propensity
MS	Mainstream smoke
NS	Not significant
PAH	Polycyclic aromatic hydrocarbon
RIP	Reduced ignition propensity
TNCO	Tar, nicotine, and carbon monoxide
TPM	Total particulate matter

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