Altria
Altria Client Services

October 21, 2014

Maxim Belushkin and Marco Esposito
Philip Morris International
Rue des Usines 90
CH-2000 Neuchatel

Dear Mr. Belushkin and Mr. Esposito:

In response to your request during our teleconference held on September 11, 2014, we are providing FDA Abbreviated Harmful and Potentially Harmful Constituent (HPHC) List smoke chemistry data for 31 Philip Morris USA (PM USA) conventional cigarette brands. These brands were tested in 2012 for reporting to the FDA and were used to demonstrate the feasibility of modeling HPHCs for reporting purposes. The data and requested information are presented in the enclosed Excel Document (2014-09-16 Philip Morris USA 2012 HPHC Test Results for 31 Products + 3R4F).

We understand that Philip Morris International ("PMI") will use the enclosed data on commercially marketed conventional cigarettes for comparison to aerosol chemistry data for the Tobacco Heating System 2.2 (THS 2.2) for purposes of obtaining FDA authorization to market THS 2.2. We provide this data in support of PMI's effort to obtain FDA authorization pursuant to the NGP License and Distribution Agreement between PMI and Altria Client Services Inc.

As you know, there are inherent limitations in the comparison of HPHC results, particularly when comparing results generated in different laboratories and/or using different analytical methods. There are also limitations even when testing is conducted within the same laboratory using the same analytical method, especially when testing is conducted at different points in time. As you are probably also aware, it is not reasonable to conclude that products differ in the yield of a compound on the basis of a two sample t-test or other similar statistical test, since that would not take lab-to-lab variation or long-term method variation into account.

Testing for the mainstream smoke abbreviated list HPHCs was distributed among two ISO 17025 accredited laboratories. The two laboratories were Enthalpy Analytical, Inc. (Durham, NC, USA) and Labstat International ULC (Kitchener, Ontario, CA). Enthalpy (Certificate #3198.01) is accredited by the American Association for Laboratory Accreditation (A2LA) while Labstat (Certificate #368) is accredited by the Standards Council of Canada (SCC). All analytical methods for the determination of the HPHCs were on the laboratories' ISO scope of accreditation at the time of testing. Testing was distributed between the two laboratories on a method basis and not a product basis. In other words, one lab tested all products for a given method. The testing was divided into five projects; identified as FDA12004 through FDA12008. The distribution of methods between the two laboratories is described in Table 1.

Table 1: HPHC Mainstream Smoke Constituents

Method Class	Mainstream Smoke Constituent	Testing Laboratory
TNCO	Nicotine, Carbon Monoxide, Tar, TPM, Puff count	Labstat
Carbonyls	Formaldehyde, Acetaldehyde, Acrolein, Crotonaldehyde	Labstat
PAH	Benzo[a]pyrene	Labstat
Aromatic Amines	1-Aminonapthalene, 2-Aminonapthalene, 4-Aminobiphenyl	Labstat
Ammonia	Ammonia	Enthalpy
Volatiles and Semi-Volatiles	1,3-Butadiene, Acrylonitrile, Benzene, Isoprene, Toluene	Enthalpy
Nitrosamines	NNK, NNN	Enthalpy

The University of Kentucky reference cigarette, 3R4F, was used as the reference product, and for method process control, for all mainstream smoke analyses. 3R4F was incorporated into each analytical sequence following the testing laboratories' normal testing procedure. Seven replicates were typically prepared and analyzed for all HPHCs with the exception of nicotine and carbon monoxide, in which 20 replicates were determined. In a few instances, nine replicates were carried out for carbonyl compounds. The HPHC results for 3R4F are included in the data set, and organized by project code.

Mainstream cigarette smoke (MS) was generated under both ISO and Canadian Intense (CI) machine smoking regimes using commercially available linear and rotary smoking machines. Cigarettes were conditioned before smoking in accordance with ISO 3402:1999. Mainstream cigarette smoke (MS) was generated and collected in basic accordance with ISO 3308:2012 and ISO 4387:2000. Deviations from the ISO standards were made when necessary in order to accommodate CI smoking and in order

to incorporate smoke traps for volatile or gas phase HPHCs. The methods used for the determination of the MS HPHC are described below. All methods were independently developed by the testing laboratory with the exception of the two Health Canada methods (carbonyls and tar, nicotine and carbon monoxide). Brief descriptions of the test methods are described below, with the exception of the two Health Canada methods.

Carbonyls in Mainstream Smoke:
Labstat determined carbonyls using Health Canada Official Method T-104, Determination of Selected Carbonyls in Mainstream Tobacco Smoke.

Tar, Nicotine and Carbon Monoxide (TNC) in Mainstream Smoke:
Labstat determined TNC using Health Canada Official Method T-115, Determination of "Tar", Nicotine and Carbon Monoxide in Mainstream Tobacco Smoke.

Benzo[a]pyrene (B[a]P) in Mainstream Smoke
Labstat determined B[a]P using Labstat method TMS-120. Cigarette mainstream smoke condensate is collected onto a 92mm filter pad. After the addition of internal standard, smoke condensate is extracted from the collection pad with methanol. The methanol extract is filtered and a portion of the filtered extract is diluted with water and passed through a C18 solid phase exchange cartridge. B[a]P is subsequently eluted with cyclohexane. Samples are analyzed on a GC-MS system consisting with a Mass Selective Detector (MSD). Separation is performed on a CP-SIL 5 CB low bleed/MS WCOT fused silica capillary column (15 m x 0.25 mm x 0.25 µm). The MSD was operated under automated EI (electron impact) mode, using selective ion monitoring (SIM) for quantification.

Aromatic Amines in Mainstream Smoke:
Labstat determined aromatic amines using Labstat method TMS-128. Conditioned cigarettes were smoked using a rotary smoking machine. The mainstream total particulate matter (TPM) was collected by passing the mainstream (MS) smoke through a conditioned, pre-weighed glass fiber filter disc (pad). The pad was quartered and placed in an Erlenmeyer flask with 100 mL of 5% hydrochloric acid solution. The flask was shaken for 30 minutes on a wrist-action shaker and the contents filtered into a 500 mL extraction vessel. The internal standards (d5-aniline, d9-o-toluidine, d7-o-anisidine, d9-4-aminobiphenyl) were spiked into the solution. The filtrate was washed with dichloromethane, made basic with sodium hydroxide solution and extracted with hexane. The hexane extract was dried with sodium sulphate, derivatized with pentafluoropropionic acid anhydride and trimethylamine and then passed through a florisil column. The aromatic amines in the hexane extract were then quantified by gas chromatography-mass spectrometry (GC/MS).

Volatile Organic Compounds (VOCs) in Mainstream Smoke
Enthalpy determined VOCs using Enthalpy method ENT 208. Cigarettes were smoked using an SM450 20-port linear analytical smoking machine following either ISO smoking or Canadian intense smoking procedures. During sample collection, the smoke was passed through a Cambridge filter pad followed by one impinger with 20 mL of methanol solution containing internal standards. The impinger was cooled by a dry ice/isopropanol bath to approximately -78 °C. After smoke collection was completed, the Cambridge pad was discarded. While still cold, an aliquot of the impinger solution was quickly transferred to a zero-headspace vial. The impinger solution was then analyzed by GC/MS for volatile organic compounds (1,3-butadiene, acrylonitrile, isoprene, benzene, and toluene).

Tobacco Specific Nitrosamines (TSNAs) in Mainstream Smoke
Enthalpy determined TSNAs using Enthalpy method ENT 211. Cigarettes were smoked using an SM450 20-port linear analytical smoking machine following either ISO smoking or Canadian intense smoking procedures. During sample collection, the smoke was passed through a Cambridge filter pad which was subsequently extracted in 10 mL of aqueous extraction solution containing internal standards. The solution was solvent-exchanged for methylene chloride and analyzed by GC/MS/MS for two nitrosamines, N-Nitrosonornicotine (NNN) and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Ammonia in Mainstream Smoke
Enthalpy determined ammonia using Enthalpy method ENT 304. Cigarettes were smoked using an SM450 20-port linear analytical smoking machine following either ISO smoking or Canadian intense smoking procedures. During sample collection, the smoke was passed through a Cambridge filter pad followed by one impinger with 40 mL of 40 mM aqueous sulfuric acid. After smoking, the filter pad was added to the impinger solution and mixed. The solution was filtered and analyzed by IC with a conductivity detector to determine the ammonia content.

Sincerely,

Karl Wagner, Ph.D.
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