
**Toxicology of Smokeless Tobacco Products:
In Vitro Micronucleus Assay**

***Labstat International ULC
Test Report***



***Prepared for
R.J. Reynolds Tobacco Corporation***

Project Code: M100

**Original Date: January 12, 2009
Revision 1 Date: November 3, 2009
Revision 2 Date: December 17, 2009
Revision 3 Date: April 23, 2010
Revision 5: December 22, 2010
Revision 7: February 4, 2011**

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1 Use of Labstat's¹ Analytical Reports²

Labstat International ULC is a recognized centre of analytical excellence related to tobacco and tobacco products. Our clients include major international tobacco manufacturers, various Governments and Government agencies such as the Canadian Federal Department of Health and the Massachusetts Department of Public Health, agricultural interests, university researchers and private research interests. Normally our contractual obligations extend **only** to the provision of data and related reports.

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¹ Labstat International ULC,
262 Manitou Drive, Kitchener, ON Canada N2C 1L3
Phone: (519) 748-5409; Fax: (519) 748-1654; Email: labstat@labstat.com

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³ *Unless superseded by a specific contractual obligation or other written agreement.*

2 Administrative Information⁴

2.1 Quotation Reference

Quotation Number: T2671 & T2672

Date of Quotation: October 6, 2008

Recipient's Name: Dr. Suzana Theophilus

2.2 Client Identification

R.J. Reynolds Tobacco Corporation
950 Reynolds Boulevard
Winston-Salem NC 27102-1487
USA

2.3 Date of Sample Receipt

The samples to be tested for M100 were received on September 16, 2008 and October 21, 2008 via UPS.

2.4 Sample Characteristics

The shipment received on September 16, 2008 consisted of one Ziploc bag of one product, one plastic container for each of 2 products, 91 boxes of one product and 20 tins of one product. Additional product of one brand was received on October 21, 2008 and consisted of 90 tins. There was no physical damage to the containers, bag or tins. Individual pouches, sticks and strips were normal in appearance.

2.5 Test Article Identification

The following sample codes have been used to identify the products associated with the results in each of the tables that are part of this report.

Sample ID	Sample Description
084394	Camel SNUS Frost
084395	2S3 Research Moist smokeless tobacco
084396	Kentucky Reference 2R4F
084454	Fresh Strips

Sample ID	Sample Description
084455	Mellow Sticks
084456	Copenhagen Long Cut
084457	Ariva Wintergreen
084458	Fresh Orbs

2.6 Special Instructions

Some of the products required for testing were removed from inventory remaining from Projects M97, M78L and M78M. Labstat International ULC supplied the "Kentucky Reference 2R4F" (Sample ID 084396).

2.7 Date of Test Report

Original: January 12, 2009

Revision 1: November 3, 2009

Revision 2: December 17, 2009

Revision 3: April 23, 2010

Revision 5: December 22, 2010

⁴ Provided in accord with International Standard ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories" Section 5.10

Revision 7: February 4, 2011

2.8 Revision History

2.8.1 Revision 1

This revision was required due to client request for re-analysis and additional information following the submission of the original report and subsequent conference calls with the client regarding specific data analysis methodologies to be used (client CRO # 2009-003).

2.8.2 Revision 2

This revision was required due to an inquiry from the client (client inquiry number CRO 2009-008-M100-MN).

2.8.3 Revision 3

This revision was required due to an inquiry from the client (client inquiry number CRO 2010-003-M100-MN).

2.8.4 Revision 5⁵

This revision was required due to a client request for additional analysis on a 'unit of use' basis for the smokeless tobacco products tested (client CRO # 2010-014-Smokeless-R1) and for alternative calculations of the measure of cytotoxicity.

2.8.5 Revision 7⁶

This revision was required due to a client request for additional comparative analysis of the data using pairwise t-tests when the within-sample standard deviations differ by more than a factor of 15. This revision also separates the analysis results from the 'unit of use' basis into a separate report. In addition, all micronucleus assay reporting on a nicotine dose basis was converted from 'mg/mL' to 'µg/mL'.

⁵ Revision 4 was only applied to the Neutral Red Uptake (NRU) report that is also part of the M100 project.

⁶ Revision 6 was only applied to the Neutral Red Uptake (NRU) report that is also part of the M100 project.

3 Accreditation

3.1 Scope (refer to [appendix A](#))

Labstat International ULC has been accredited by the Standards Council of Canada to International Standard ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories" with a scope that includes all of the mandated tobacco-related Health Canada methods (see Tobacco Reporting Regulations dated 26 June 2000, Canada Gazette Part II, Vol. 134, No. 15 Schedules 1, 2 and 3 pages 1780 – 1785). The testing included in this report is within the scope of this accreditation, unless otherwise noted in Section 4.



Accredited LAB 368
(SCC Accreditation & Design Mark is an Official Mark of the Standards Council of Canada, used under license)

3.2 International Recognition of Tests

Our accrediting organization, Standards Council of Canada, is one of a number of such member bodies participating in a global mutual recognition agreement (MRA), known as the ILAC (International Laboratory Accreditation Cooperation) Arrangement. The arrangement, effective January 31, 2001, requires acceptance of technical test data from accredited laboratories by member bodies in numerous international economies.

4 Methods

4.1 General References

The test method for the *in vitro* micronucleus assay of mainstream tobacco smoke is referenced in the table below and was practiced as written unless otherwise indicated (see "[Method Deviations](#)").

OFFICIAL METHOD FOR ASSAYS OF MAINSTREAM TOBACCO SMOKE⁷

Assay	Official Method
<i>In Vitro</i> Micronucleus (MN)	Health Canada Official Method T-503, <i>In Vitro</i> Micronucleus Assay for Mainstream Tobacco Smoke

4.2 Preparation of Solutions and Media

(b) (4)

⁷ Canadian Regulations Amending the Tobacco Reporting Regulations: 2005-06-29 *Canada Gazette Part II*, Vol. 139, No. 13, Part 3.1: Toxicity of Cigarette Emissions. Test method number refers to Health Canada methodologies, which may be obtained by contacting Health Canada.

4.3 Preparation of CHO-WBL Cell Culture Suspension

(b) (4)

4.4 Collection of Total Particulate Matter (TPM)⁸

(b) (4)

4.4.1 Processing of TPM

(b) (4)

4.4.2 Test Method Deviations

(b) (4)

4.5 Smokeless Tobacco Sample Preparation

(b) (4)

⁸ See International Standard ISO 4387 Cigarettes – Determination of total and nicotine-free dry particulate matter using a routine analytical smoking machine (Reference number ISO4387:2000:E)

⁹ Health Canada 100% Vent Blocking Method

6(b)(iii) all ventilation holes must be blocked by placing over them a strip of Mylar adhesive tape, Scotch Brand product no. 600 Transparent Tape, and the tape must be cut so that it covers the circumference and is tightly secured from the end of the filter to the tipping overwrap seam, or by another method of equivalent efficiency.

¹⁰ DMSO is the most useful solvent for cell toxicity assays because it dissolves a wide range of chemicals, is relatively non-toxic to the cells and to the microsomal S9 enzymes.

4.6 Clastogenicity/Genotoxicity Testing

4.6.1 Preparation of CHO-WBL Cells and Exposure to Test Articles

(b) (4)

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4.6.2 Harvesting and Counting of Cells

(b) (4)

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4.6.3 Micronucleus Staining and Scoring

(b) (4)

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4.7 Method Deviations

(b) (4)

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5 Results

5.1 Data Files

Individual results and the corresponding sample statistics may be found on the compact disk (CD) that accompanies this report. The data files have been labeled *M100_mn_tpm_dataCF.xls* (micronucleus assay results for TPM of tobacco brand 084396), *M100_mn_wt_dataCF.xls* (micronucleus assay results for smokeless tobacco products) and *M100_chem_dataCF.xls* (nicotine analysis results for smoked and smokeless tobacco products).

5.1.1 Moisture-Corrected and Nicotine Doses

(b) (4)



5.2 Quality Control

5.2.1 Chemicals and Media

5.2.1.1 Requirement

As per section 13.1 of T-503, the sterility of all media, reagents and solutions must be verified and recorded. (b) (4)



5.2.1.2 Conclusion

No bacterial growth was detected on any of the nutrient agar plates used to check the sterility of the media, reagents and solutions. No turbidity was noted in any of the media preparations used throughout this project.

5.2.2 Cell Culture Maintenance

5.2.2.1 Requirement

(b) (4)



5.2.2.2 Conclusion

No changes in cell morphology or adhesive properties were noted. Mycoplasma contamination was absent in all cases.

5.2.3 Evaluation of Negative Controls

5.2.3.1 Acceptance Criteria for Negative Controls

(b) (4)

5.2.3.2 Conclusion

Treatment Schedule	Assay Date	Flask 1		Flask 2	
		% MN	QC Result	% MN	QC Result
Schedule (i)	28-Nov-08	0.500	< 2.5% MN	0.500	< 2.5% MN
Schedule (i)	28-Nov-08	0.600	< 2.5% MN	0.500	< 2.5% MN
Schedule (i)	28-Nov-08	0.500	< 2.5% MN	0.700	< 2.5% MN
Schedule (i)	28-Nov-08	0.500	< 2.5% MN	0.600	< 2.5% MN
Schedule (i)	04-Dec-08	0.600	< 2.5% MN	0.700	< 2.5% MN
Schedule (i)	04-Dec-08	0.500	< 2.5% MN	0.500	< 2.5% MN
Schedule (i)	04-Dec-08	0.600	< 2.5% MN	0.600	< 2.5% MN
Schedule (i)	04-Dec-08	0.600	< 2.5% MN	0.400	< 2.5% MN
Schedule (i)	05-Dec-08	0.400	< 2.5% MN	0.400	< 2.5% MN
Schedule (i)	05-Dec-08	0.600	< 2.5% MN	0.700	< 2.5% MN
Schedule (i)	05-Dec-08	0.500	< 2.5% MN	0.600	< 2.5% MN
Schedule (i)	05-Dec-08	0.600	< 2.5% MN	0.500	< 2.5% MN
Schedule (ii)	11-Dec-08	0.700	< 2.5% MN	0.600	< 2.5% MN
Schedule (ii)	11-Dec-08	0.700	< 2.5% MN	0.600	< 2.5% MN
Schedule (ii)	11-Dec-08	0.500	< 2.5% MN	0.700	< 2.5% MN
Schedule (ii)	11-Dec-08	0.400	< 2.5% MN	0.700	< 2.5% MN
Schedule (ii)	12-Dec-08	0.600	< 2.5% MN	0.600	< 2.5% MN
Schedule (ii)	12-Dec-08	0.600	< 2.5% MN	0.700	< 2.5% MN
Schedule (ii)	12-Dec-08	0.500	< 2.5% MN	0.600	< 2.5% MN
Schedule (ii)	12-Dec-08	0.600	< 2.5% MN	0.700	< 2.5% MN
Schedule (ii)	17-Dec-08	0.600	< 2.5% MN	0.600	< 2.5% MN
Schedule (ii)	17-Dec-08	0.500	< 2.5% MN	0.600	< 2.5% MN
Schedule (ii)	17-Dec-08	0.700	< 2.5% MN	0.500	< 2.5% MN
Schedule (ii)	17-Dec-08	0.500	< 2.5% MN	0.700	< 2.5% MN

All negative control assay results that are part of this report were found to be acceptable in regards to the above requirement. See the ["Control Summary"](#) sheet in the *M100_mn_Labstat Internal Controls.xls* data file for evaluation results.

5.2.4 Evaluation of Cell Proliferation

5.2.4.1 Acceptance Criteria for Cell Proliferation

(b) (4)

5.2.4.2 Conclusion

All negative control assay results that are part of this report were found to be acceptable in regards to the above requirements for cell proliferation. See the ["Assay Info"](#) sheet in the *M100_mn_Labstat Internal Controls.xls* data file for evaluation results.

5.2.5 Evaluation of Positive Controls

5.2.5.1 Acceptance Criteria for Positive Controls¹¹

(b) (4)

5.2.5.2 Conclusion

Treatment Schedule	Assay Date	Positive Control	[Conc] [µg/mL]	Expected		Flask 1 Observed		Flask 2 Observed	
				(% MN)	SD	(% MN)	p-value	(% MN)	p-value
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	17.5	0.868	18.3	0.243
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	18.7	0.067	17.9	0.617
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	17.5	0.868	17.3	0.617
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	18.5	0.134	17.7	0.868
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	18.7	0.067	17.8	0.739
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	18.4	0.182	18.2	0.317
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	17.3	0.617	17.8	0.739
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	17.3	0.617	17.8	0.739
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.4	0.182	18.1	0.405
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.2	0.317	17.7	0.868
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.1	0.405	17.8	0.739
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.4	0.182	18.1	0.405
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	9.5	0.046	10.3	1.000
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	10.8	0.211	10.4	0.803
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	10.1	0.617	10.0	0.453
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	10.4	0.803	10.3	1.000
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	10.3	1.000	10.7	0.317
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	10.2	0.803	10.2	0.803
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	9.4	0.024	9.8	0.211
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	10.0	0.453	10.3	1.000
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	9.6	0.080	10.2	0.803

¹¹ Acceptance criteria have not been defined in the Official Health Canada Test Method T-503

Treatment Schedule	Assay Date	Positive Control	[Conc] [µg/mL]	Expected		Flask 1 Observed		Flask 2 Observed	
				(% MN)	SD	(% MN)	p-value	(% MN)	p-value
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	10.1	0.617	9.8	0.211
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	9.9	0.317	10.0	0.453
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	10.0	0.453	10.2	0.803
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.5	0.617	3.5	0.617
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.6	0.317
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.4	1.000	3.6	0.317
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.1	0.134
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.4	1.000	3.3	0.617
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.4	1.000
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.5	0.617
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.4	1.000
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.2	0.317
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.3	0.617	3.5	0.617
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.5	0.617	3.3	0.617
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.4	1.000	3.2	0.317

All positive control assay results that are part of this report were found to be acceptable in regards to the above requirements for positive control results. See the "Control Summary" sheet in the *M100_mn_Labstat Internal Controls.xls* data file for evaluation results.

5.2.6 Evaluation of Laboratory Controls (Kentucky Reference 3R4F)

5.2.6.1 Acceptance Criteria for Clastogenicity/Genotoxicity

(b) (4)

5.2.6.2 Conclusion

Treatment Schedule	Assay Date	Target (%MN per mg TPM/mL)		Observed (%MN / mg TPM/mL)	Z Score	P Value
		Average	Std Dev			
Schedule (i)	28-Nov-08	5.10	0.50	5.13	-0.051	0.959
Schedule (i)	28-Nov-08	5.10	0.50	5.87	-1.531	0.126
Schedule (i)	04-Dec-08	5.10	0.50	4.85	0.515	0.607
Schedule (i)	04-Dec-08	5.10	0.50	6.20	-2.184	0.029
Schedule (i)	05-Dec-08	5.10	0.50	5.35	-0.487	0.627
Schedule (i)	05-Dec-08	5.10	0.50	5.33	-0.443	0.658
Schedule (ii)	11-Dec-08	4.15	0.49	3.93	0.436	0.663
Schedule (ii)	11-Dec-08	4.15	0.49	3.43	1.452	0.146
Schedule (ii)	12-Dec-08	4.15	0.49	3.30	1.718	0.086

¹² A minimum of 30 results is normally required for the purpose of this comparison.

Treatment Schedule	Assay Date	Target (%MN per mg TPM/mL)		Observed (%MN / mg TPM/mL)	Z Score	P Value
		Average	Std Dev			
Schedule (ii)	12-Dec-08	4.15	0.49	3.09	2.160	0.031
Schedule (ii)	17-Dec-08	4.15	0.49	3.67	0.966	0.334
Schedule (ii)	17-Dec-08	4.15	0.49	4.50	-0.713	0.476

The results of the Kentucky Reference 3R4F assays necessitated by section 13.3.1 of T-503 were acceptable in regards to the criteria defined in section 5.2.6.1 of this report. Thus, it is reasonable to assume that the results reported for the test samples are reflective of the characteristics of the products as received and tested as described in section 4 of this report. See the "Assay Acceptance Criteria" sheet in the *M100_mn_Labstat Internal Controls.xls* data file for evaluation results.

5.2.7 Cytotoxicity

5.2.7.1 Requirement

(b) (4)

5.2.7.2 Conclusions

% cytotoxicity (by RICC) was calculated for all test sample and control sample assay cultures that are part of this report. See the "Summary Data" sheet in the test sample data files and Labstat Internal Control data file for evaluation results.

6 Genotoxicity Comparisons

6.1 Data Files

Data files containing calculated specific activities (slope of the linear portion of the dose-response curve) may be found on the compact disk (CD) that accompanies this report. The data files have been labeled *M100_mn_tpm_stats.xls* (dose-response curve analysis results for TPM of tobacco brand 084396), *M100_mn_wt_stats_ST.xls* (dose-response curve analysis results for smokeless tobacco products on a 'mg extracted smokeless tobacco in DMSO/mL' dose basis), *M100_mn_wt_stats_ST-H2O.xls* (dose-response curve analysis results for smokeless tobacco products on a 'mg extracted moisture-corrected smokeless tobacco in DMSO/mL' dose basis) and *M100_mn_wt_stats_Nicotine.xls* (dose-response curve analysis results for smokeless tobacco products on a 'µg extracted Nicotine in DMSO/mL' dose basis).

6.2 Methodology

1. (b) (4)

2.

¹³ www.oecd.org/env/testguidelines

3. (b) (4)

4.

5.

6.

6.3 Specific Activity Determinations

(b) (4)

6.4 Comparisons among Smokeless Tobacco Products

6.4.1 Individual Replicate Slopes and Slope Statistics

Tables of results were obtained for the individual replicate slope estimates and the summary statistics over the three replicate slopes for each smokeless tobacco test sample under both treatment schedules.

6.4.1.1 % micronucleated cells (% MNC)/[mg 'Extracted Smokeless Tobacco in DMSO'/mL]

		Replicate Slope Analysis [%MNC/(mg 'ST'/mL)]								
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'ST' Dose (mg/mL)	slope	'ST' Dose (mg/mL)	slope	'ST' Dose (mg/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 2.22	0.264	0 - 2.22	0.268	0 - 2.22	0.254	0.262	0.004	0.244 - 0.28
Schedule (i)	084395	0 - 2.22	0.277	0 - 2.22	0.231	0 - 2.22	0.254	0.254	0.013	0.197 - 0.311
Schedule (i)	084454	0 - 2.22	0.356	0 - 2.22	0.391	0 - 2.22	0.326	0.358	0.019	0.276 - 0.439
Schedule (i)	084455	0 - 2.22	0.393	0 - 2.22	0.341	0 - 2.22	0.312	0.349	0.024	0.247 - 0.451
Schedule (i)	084456	0 - 2.22	0.326	0 - 2.22	0.343	0 - 2.22	0.221	0.297	0.038	0.132 - 0.461
Schedule (i)	084457	0 - 2.22	0.514	0 - 2.22	0.360	0 - 2.22	0.285	0.386	0.067	0.096 - 0.676
Schedule (i)	084458	0 - 2.22	0.500	0 - 2.22	0.352	0 - 2.22	0.361	0.404	0.048	0.198 - 0.61
Schedule (ii)	084394	0 - 2.22	0.160	0 - 2.22	0.238	0 - 2.22	0.223	0.207	0.024	0.105 - 0.309
Schedule (ii)	084395	0 - 2.22	0.188	0 - 2.22	0.156	0 - 2.22	0.212	0.185	0.016	0.115 - 0.256
Schedule (ii)	084454	0 - 2.22	0.251	0 - 2.22	0.246	0 - 2.22	0.244	0.247	0.002	0.237 - 0.257
Schedule (ii)	084455	0 - 2.22	0.181	0 - 2.22	0.231	0 - 2.22	0.267	0.226	0.025	0.119 - 0.334
Schedule (ii)	084456	0 - 2.22	0.195	0 - 2.22	0.184	0 - 2.22	0.178	0.185	0.005	0.165 - 0.206
Schedule (ii)	084457	0 - 2.22	0.178	0 - 2.22	0.273	0 - 2.22	0.290	0.247	0.035	0.097 - 0.396
Schedule (ii)	084458	0 - 2.22	0.380	0 - 2.22	0.301	0 - 2.22	0.319	0.333	0.024	0.231 - 0.435

6.4.1.2 % micronucleated cells (% MNC)/[mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL]

		Replicate Slope Analysis [%MNC/(mg 'ST-H ₂ O'/mL)]								
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'ST-H ₂ O' Dose (mg/mL)	slope	'ST-H ₂ O' Dose (mg/mL)	slope	'ST-H ₂ O' Dose (mg/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 1.52	0.387	0 - 1.52	0.393	0 - 1.52	0.372	0.384	0.006	0.358 - 0.410
Schedule (i)	084395	0 - 1.02	0.602	0 - 1.02	0.502	0 - 1.02	0.553	0.552	0.029	0.428 - 0.676
Schedule (i)	084454	0 - 1.98	0.400	0 - 1.98	0.440	0 - 1.98	0.366	0.402	0.021	0.311 - 0.494
Schedule (i)	084455	0 - 2.09	0.418	0 - 2.09	0.363	0 - 2.09	0.332	0.371	0.025	0.263 - 0.480
Schedule (i)	084456	0 - 0.992	0.730	0 - 0.992	0.769	0 - 0.992	0.495	0.665	0.086	0.297 - 1.03
Schedule (i)	084457	0 - 2.14	0.533	0 - 2.14	0.374	0 - 2.14	0.296	0.401	0.070	0.100 - 0.702
Schedule (i)	084458	0 - 2.11	0.527	0 - 2.11	0.371	0 - 2.11	0.380	0.426	0.051	0.209 - 0.643
Schedule (ii)	084394	0 - 1.52	0.235	0 - 1.52	0.348	0 - 1.52	0.326	0.303	0.035	0.154 - 0.453
Schedule (ii)	084395	0 - 1.02	0.408	0 - 1.02	0.338	0 - 1.02	0.461	0.403	0.036	0.249 - 0.556
Schedule (ii)	084454	0 - 1.98	0.283	0 - 1.98	0.277	0 - 1.98	0.274	0.278	0.003	0.267 - 0.289
Schedule (ii)	084455	0 - 2.09	0.193	0 - 2.09	0.246	0 - 2.09	0.284	0.241	0.027	0.126 - 0.355
Schedule (ii)	084456	0 - 0.992	0.436	0 - 0.992	0.412	0 - 0.992	0.399	0.416	0.011	0.369 - 0.462
Schedule (ii)	084457	0 - 2.14	0.185	0 - 2.14	0.283	0 - 2.14	0.301	0.256	0.036	0.101 - 0.411
Schedule (ii)	084458	0 - 2.11	0.400	0 - 2.11	0.317	0 - 2.11	0.336	0.351	0.025	0.243 - 0.459

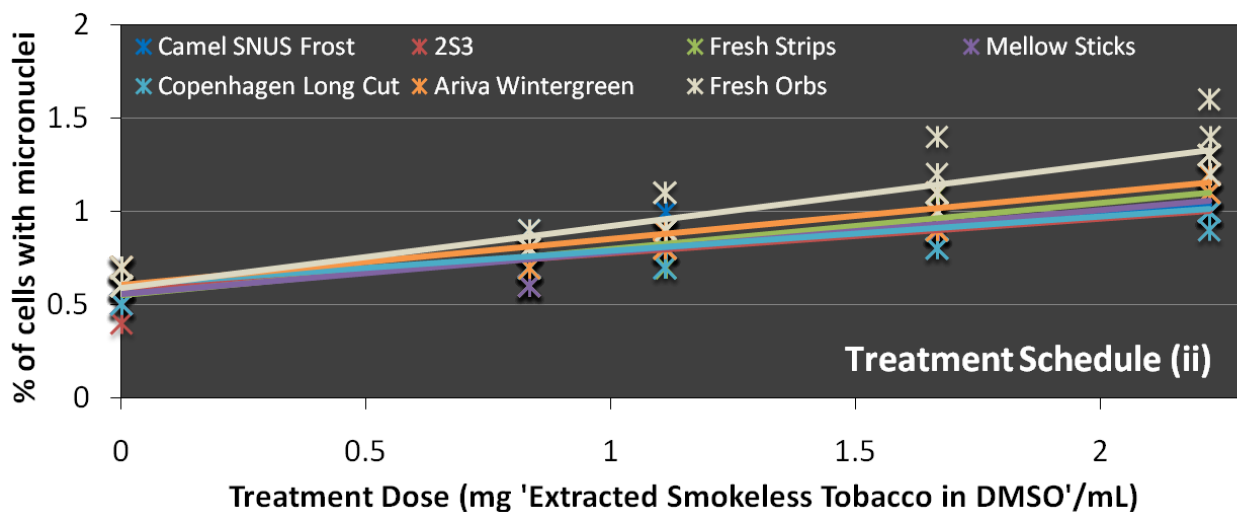
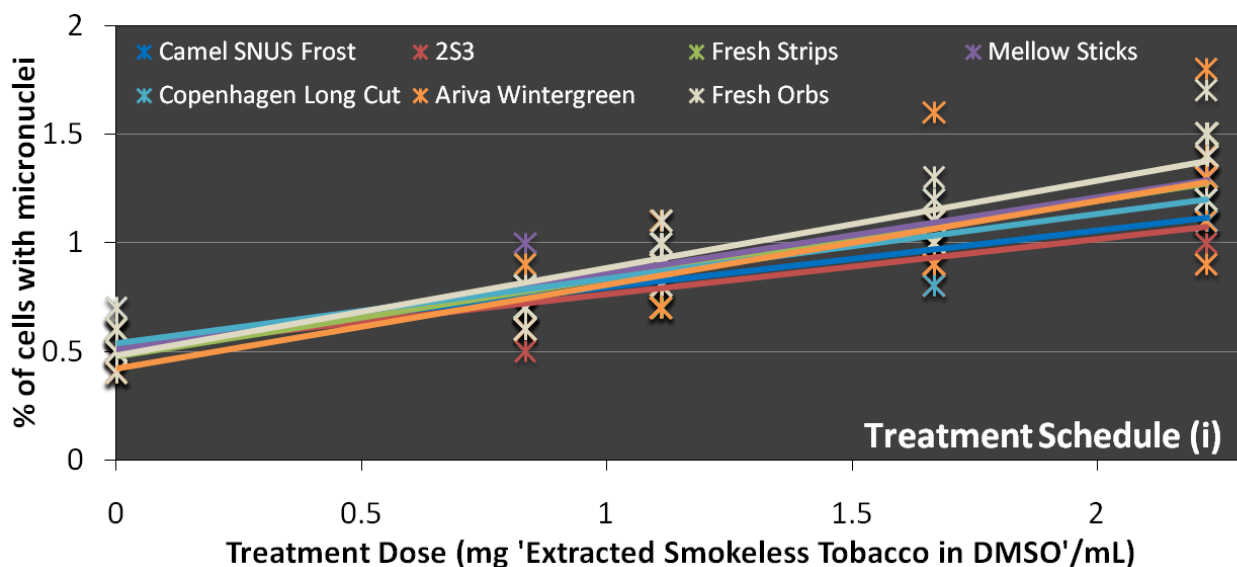
6.4.1.3 % micronucleated cells (% MNC)/[μg 'Extracted Nicotine in DMSO'/mL]

		Replicate Slope Analysis [%MNC/(μg 'Nic.'/mL)]								
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'Nic' Dose (μg/mL)	slope	'Nic' Dose (μg/mL)	slope	'Nic' Dose (μg/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 27.8	0.021	0 - 28.7	0.021	0 - 29.5	0.019	0.020	0.001	0.018 - 0.023
Schedule (i)	084395	0 - 30.0	0.021	0 - 29.4	0.017	0 - 31.4	0.018	0.019	0.001	0.015 - 0.023
Schedule (i)	084454	0 - 8.22	0.096	0 - 8.00	0.109	0 - 7.66	0.094	0.100	0.004	0.081 - 0.119
Schedule (i)	084455	0 - 8.83	0.099	0 - 10.7	0.071	0 - 8.07	0.086	0.085	0.008	0.050 - 0.120
Schedule (i)	084456	0 - 28.3	0.026	0 - 27.4	0.028	0 - 27.2	0.018	0.024	0.003	0.011 - 0.037
Schedule (i)	084457	0 - 12.5	0.091	0 - 12.5	0.064	0 - 12.5	0.051	0.069	0.012	0.017 - 0.120
Schedule (i)	084458	0 - 4.63	0.240	0 - 5.23	0.150	0 - 4.94	0.162	0.184	0.028	0.062 - 0.305
Schedule (ii)	084394	0 - 27.8	0.013	0 - 28.7	0.018	0 - 29.5	0.017	0.016	0.002	0.009 - 0.023
Schedule (ii)	084395	0 - 30.0	0.014	0 - 29.4	0.012	0 - 31.4	0.015	0.014	0.001	0.009 - 0.018
Schedule (ii)	084454	0 - 8.22	0.068	0 - 8.00	0.068	0 - 7.66	0.071	0.069	0.001	0.066 - 0.073
Schedule (ii)	084455	0 - 8.83	0.046	0 - 10.7	0.048	0 - 8.07	0.074	0.056	0.009	0.017 - 0.094
Schedule (ii)	084456	0 - 28.3	0.015	0 - 27.4	0.015	0 - 27.2	0.015	0.015	0.000	0.014 - 0.016
Schedule (ii)	084457	0 - 12.5	0.032	0 - 12.5	0.049	0 - 12.5	0.052	0.044	0.006	0.017 - 0.071
Schedule (ii)	084458	0 - 4.63	0.182	0 - 5.23	0.128	0 - 4.94	0.143	0.151	0.016	0.082 - 0.221

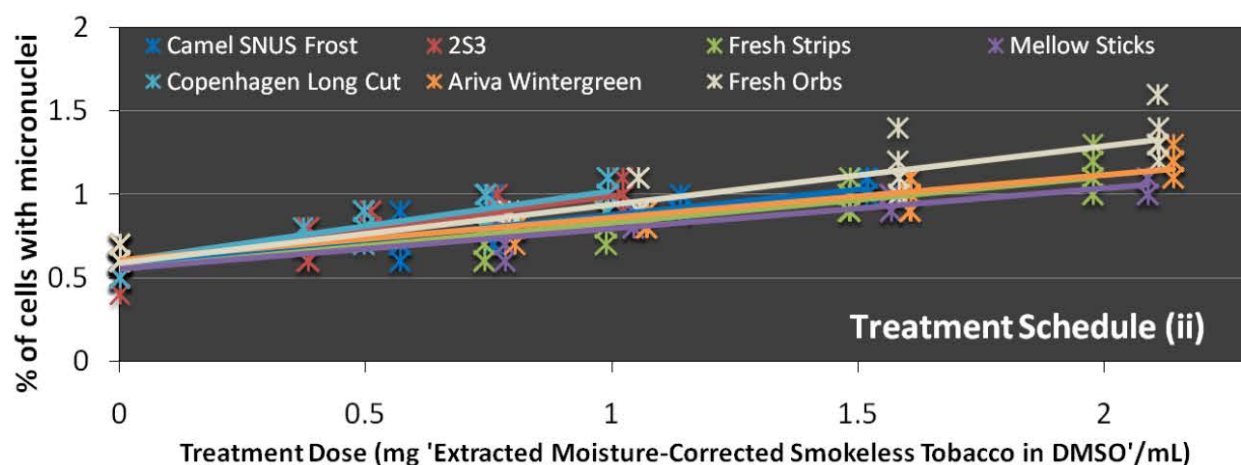
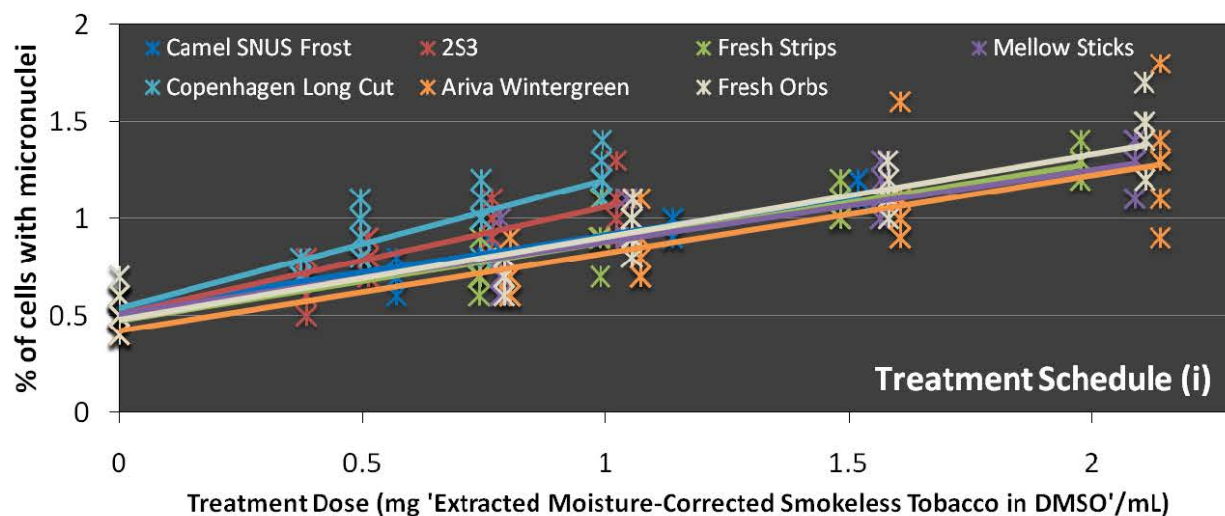
6.4.2 Data Plots

Plots of all replicate smokeless tobacco test samples can be found in the files *M100_mn_wt_stats_ST.xls*, *M100_mn_wt_stats_ST-H2O.xls* and *M100_mn_wt_stats_Nicotine.xls* on the CD that accompanies this report. Box-and-Whisker plots of the calculated specific activities can also be found on the CD that accompanies this report.

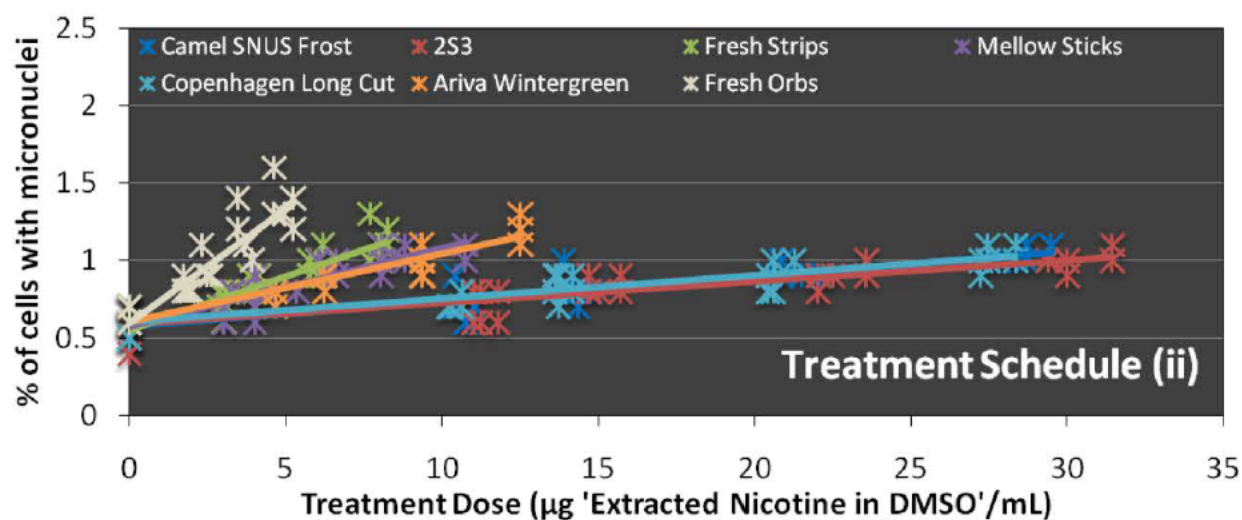
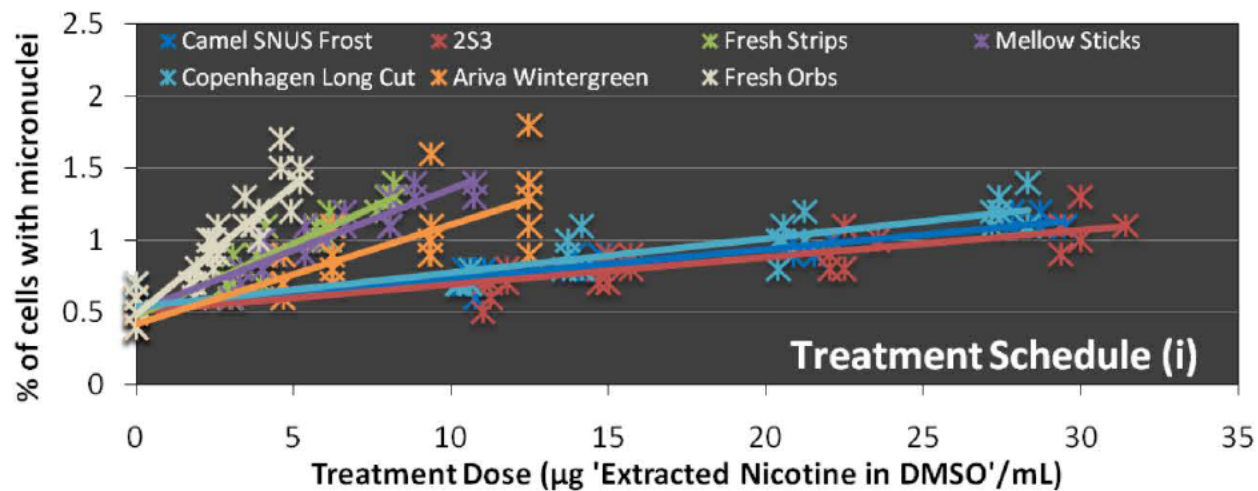
6.4.2.1 % micronucleated cells vs. [mg 'Extracted Smokeless Tobacco in DMSO']/mL



6.4.2.2 % micronucleated cells vs. [mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL]



6.4.2.3 % micronucleated cells vs. [μg 'Extracted Nicotine in DMSO'/mL]



6.4.3 One-Way ANOVA Results

One-way ANOVA comparisons of mean 'extracted smokeless tobacco', 'extracted moisture-corrected smokeless tobacco' and extracted nicotine' slope estimates among smokeless tobacco test samples yielded the following:

6.4.3.1 'Extracted Smokeless Tobacco in DMSO'

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	0.064	6	0.011	2.640	0.063
	Within Samples	0.056	14	0.004		
	Total	0.120	20			
Treatment Schedule (ii)	Among Samples	0.047	6	0.008	5.621	0.004
	Within Samples	0.020	14	0.001		
	Total	0.067	20			

One-way ANOVA analysis indicates significant differences, at $\alpha = 0.05$, among mean '% micronucleated cells/(mg 'Extracted Smokeless Tobacco in DMSO'/mL)' slope estimates for smokeless tobacco test samples assayed under treatment schedule (ii) only.

6.4.3.2 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	0.216	6	0.036	5.027	0.006
	Within Samples	0.100	14	0.007		
	Total	0.316	20			
Treatment Schedule (ii)	Among Samples	0.088	6	0.015	6.529	0.002
	Within Samples	0.031	14	0.002		
	Total	0.119	20			

One-way ANOVA analysis indicates significant differences, at $\alpha = 0.05$, among mean '% micronucleated cells/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL)' slope estimates for smokeless tobacco test samples assayed under both treatment schedules (i) and (ii).

6.4.3.3 'Extracted Nicotine in DMSO'

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	0.0640	6	0.0107	24.00	< 0.001
	Within Samples	0.0062	14	0.0004		
	Total	0.0702	20			
Treatment Schedule (ii)	Among Samples	0.0431	6	0.0072	43.66	< 0.001
	Within Samples	0.0023	14	0.0002		
	Total	0.0454	20			

One-way ANOVA analysis indicates significant differences, at $\alpha = 0.05$, among mean '% micronucleated cells/(μ g 'Extracted Nicotine in DMSO'/mL)' slope estimates for smokeless tobacco test samples assayed under both treatment schedules (i) and (ii).

6.4.4 Contrasts of Interest

(b) (4)

6.4.4.1 % micronucleated cells/(mg 'Extracted Smokeless Tobacco in DMSO'/mL)

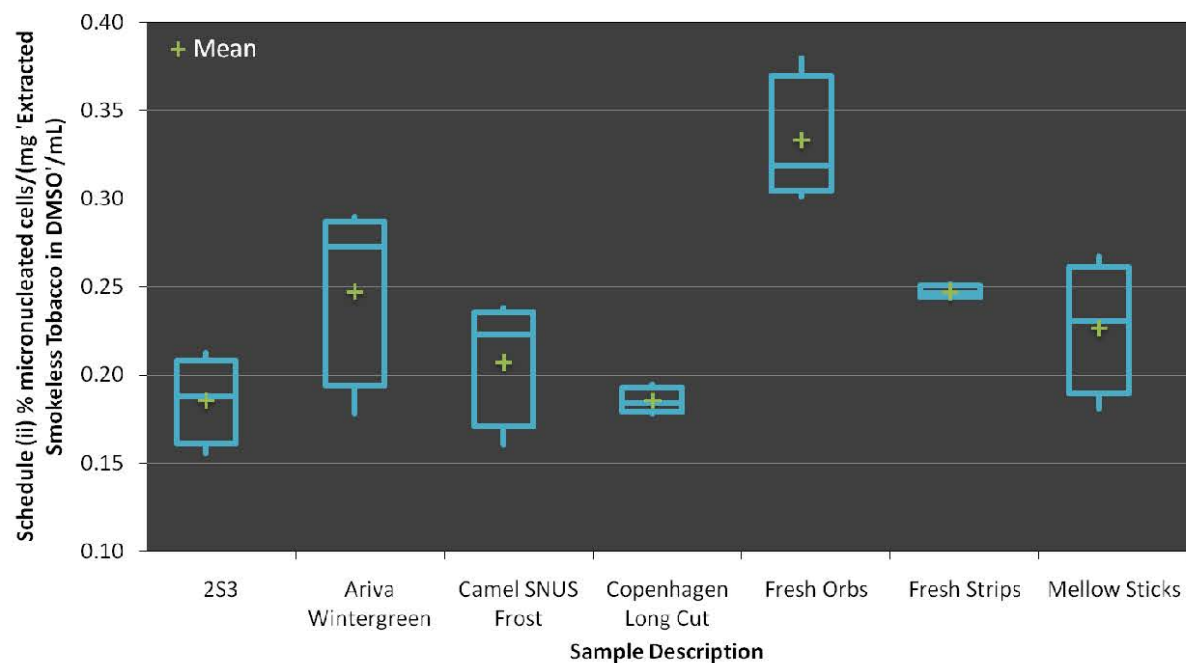
Method Applied for Contrasts

(b) (4)

Contrasts of Interest

	Treatment Schedule (i)			Treatment Schedule (ii)		
Contrast of Interest	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.5856	0.5896	not significant	0.7573	0.4910	not significant
084394 vs. 084454	4.9378	0.0078	not significant	1.6827	0.1677	not significant
084394 vs. 084455	3.6074	0.0226	not significant	0.5584	0.6063	not significant
084394 vs. 084456	0.9008	0.4186	not significant	0.8882	0.4246	not significant
084394 vs. 084457	1.8376	0.1400	not significant	0.9474	0.3971	not significant
084394 vs. 084458	2.9552	0.0418	not significant	3.7577	0.0198	not significant
084395 vs. 084454	4.4884	0.0109	not significant	3.7376	0.0202	not significant
084395 vs. 084455	3.4941	0.0250	not significant	1.3739	0.2414	not significant
084395 vs. 084456	1.0571	0.3501	not significant	0.0198	0.9851	not significant
084395 vs. 084457	1.9248	0.1266	not significant	1.6054	0.1837	not significant
084395 vs. 084458	3.0222	0.0391	not significant	5.1231	0.0069	not significant
084454 vs. 084455	0.2899	0.7863	not significant	0.8307	0.4528	not significant
084454 vs. 084456	1.4288	0.2263	not significant	11.4848	0.0003	significant
084454 vs. 084457	0.4076	0.7044	not significant	0.0065	0.9951	not significant
084454 vs. 084458	0.9061	0.4161	not significant	3.6050	0.0227	not significant
084455 vs. 084456	1.1594	0.3108	not significant	1.6000	0.1848	not significant
084455 vs. 084457	0.5224	0.6290	not significant	0.4817	0.6552	not significant
084455 vs. 084458	1.0374	0.3581	not significant	3.1005	0.0362	not significant
084456 vs. 084457	1.1546	0.3126	not significant	1.7486	0.1553	not significant
084456 vs. 084458	1.7551	0.1541	not significant	6.0843	0.0037	not significant
084457 vs. 084458	0.2197	0.8369	not significant	2.0505	0.1096	not significant

Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted smokeless tobacco' slope were detected between **Fresh Strips (084454)** and **Copenhagen Long Cut (084456)** under treatment schedule (ii).



6.4.4.2 % micronucleated cells/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL)

Method Applied for Contrasts

Treatment Schedule	Std. Dev. Ratio (Max ÷ Min)	Type of Comparison
Schedule (i)	14.2	ANOVA (equal variance)
Schedule (ii)	14.3	ANOVA (equal variance)

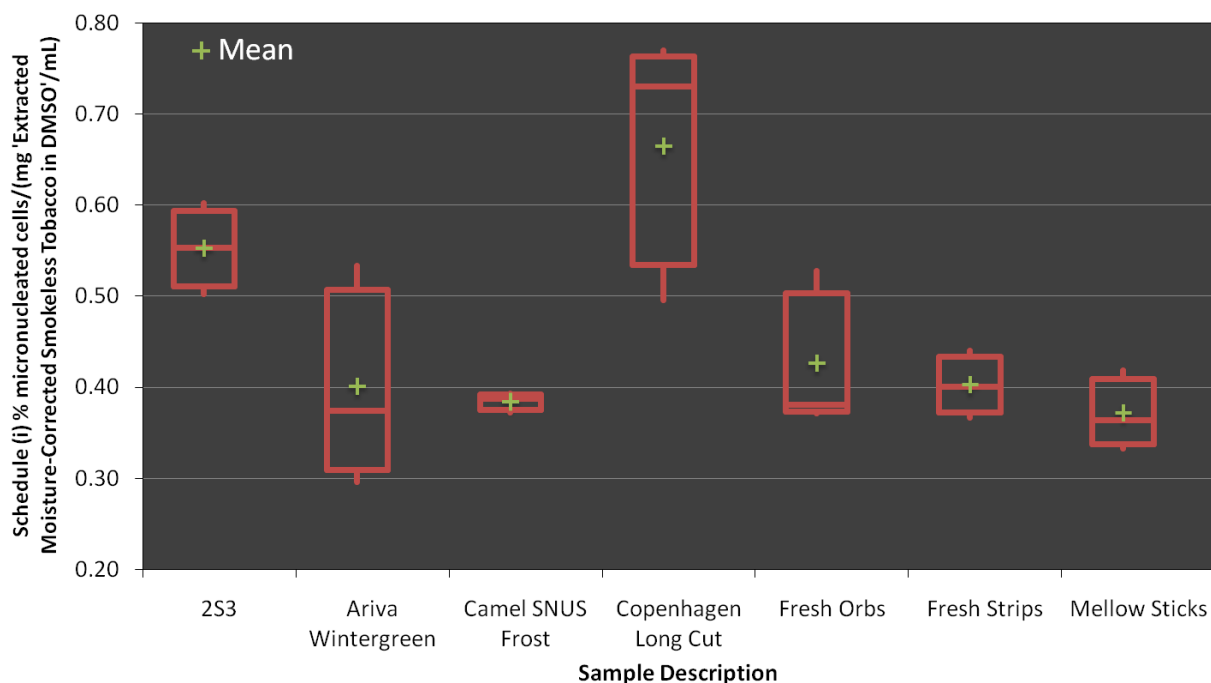
Contrasts of Interest

Contrast of Interest	Treatment Schedule (i)			Treatment Schedule (ii)		
	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	5.9387	0.0288	not significant	6.6128	0.0222	not significant
084394 vs. 084454	0.0705	0.7945	not significant	0.4261	0.5245	not significant
084394 vs. 084455	0.0329	0.8586	not significant	2.5946	0.1295	not significant
084394 vs. 084456	16.5154	0.0012	significant	8.4440	0.0115	not significant
084394 vs. 084457	0.0600	0.8100	not significant	1.4706	0.2453	not significant
084394 vs. 084458	0.3741	0.5506	not significant	1.5407	0.2349	not significant
084395 vs. 084454	4.7151	0.0476	not significant	10.3961	0.0061	not significant
084395 vs. 084455	6.8558	0.0202	not significant	17.4916	0.0009	significant
084395 vs. 084456	2.6470	0.1260	not significant	0.1118	0.7431	not significant
084395 vs. 084457	4.8044	0.0458	not significant	14.3204	0.0020	significant
084395 vs. 084458	3.3318	0.0894	not significant	1.7696	0.2047	not significant
084454 vs. 084455	0.1998	0.6618	not significant	0.9178	0.3543	not significant
084454 vs. 084456	14.4278	0.0020	significant	12.6638	0.0031	not significant
084454 vs. 084457	0.0004	0.9840	not significant	0.3135	0.5844	not significant
084454 vs. 084458	0.1198	0.7344	not significant	3.5874	0.0791	not significant
084455 vs. 084456	18.0229	0.0008	significant	20.3999	0.0005	significant
084455 vs. 084457	0.1819	0.6762	not significant	0.1585	0.6966	not significant
084455 vs. 084458	0.6289	0.4410	not significant	8.1341	0.0128	not significant
084456 vs. 084457	14.5837	0.0019	significant	16.9625	0.0010	significant
084456 vs. 084458	11.9183	0.0039	not significant	2.7709	0.1182	not significant
084457 vs. 084458	0.1344	0.7194	not significant	6.0219	0.0278	not significant

ANOVA-Based Homogenous Groupings and Pairwise T-Test Results: Treatment Schedule (i)

Sample ID	Sample Description	Mean Slope	ANOVA-based Homogenous Groups
084455	Mellow Sticks	0.371	X
084394	Camel SNUS Frost	0.384	X
084457	Ariva Wintergreen	0.401	X
084454	Fresh Strips	0.402	X
084458	Fresh Orbs	0.426	X X
084395	2S3	0.552	X X
084456	Copenhagen Long Cut	0.665	X

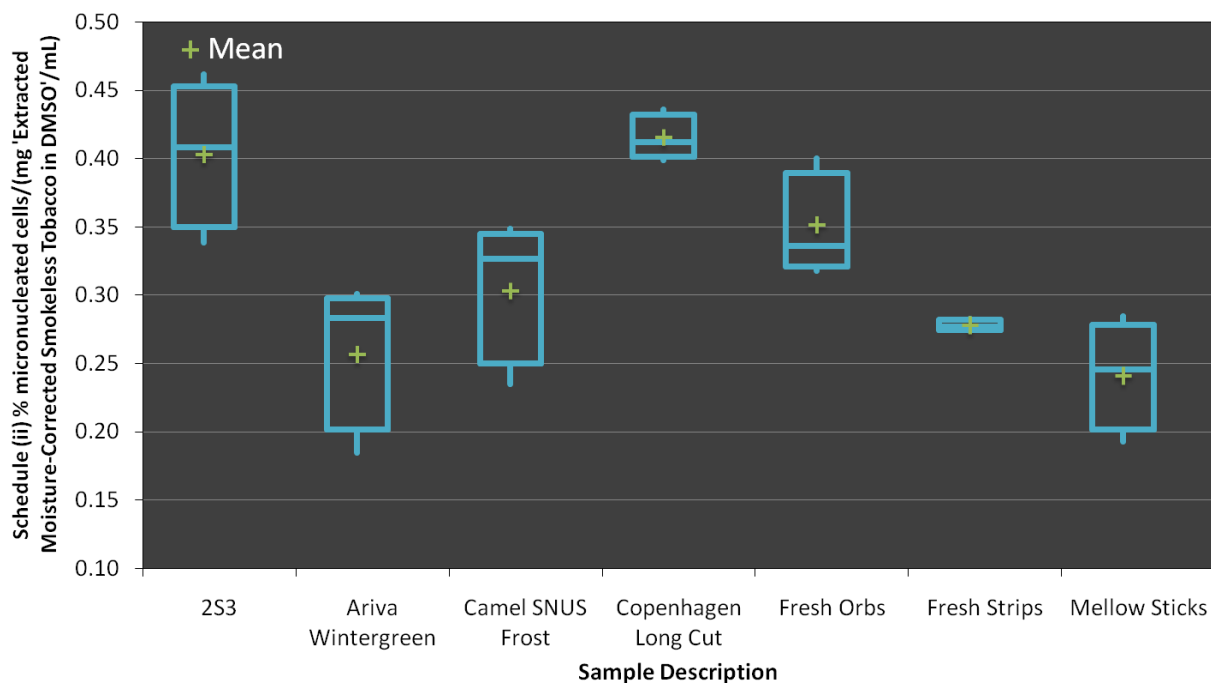
ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean specific activity slope were detected under treatment schedule (i) between **Copenhagen Long Cut (084456)** and each of {**Camel SNUS Frost (084394)**, **Fresh Strips (084454)**, **Mellow Sticks (084455)**, **Ariva Wintergreen (084457)**}.



ANOVA-Based Homogenous Groupings and Pairwise T-Test Results: Treatment Schedule (ii)

Sample ID	Sample Description	Mean Slope	ANOVA-based Homogenous Groups
084455	Mellow Sticks	0.241	X
084457	Ariva Wintergreen	0.256	X
084454	Fresh Strips	0.278	X X
084394	Camel SNUS Frost	0.303	X X
084458	Fresh Orbs	0.351	X X
084395	2S3	0.403	X
084456	Copenhagen Long Cut	0.416	X

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean specific activity slope were detected under treatment schedule (ii) between **2S3 Research Moist Snuff (084395)** as well as **Copenhagen Long Cut (084456)** and each of {**Mellow Sticks (084455)**, **Ariva Wintergreen (084457)**}.



6.4.4.3 % micronucleated cells/(μ g 'Extracted Nicotine in DMSO'/mL)

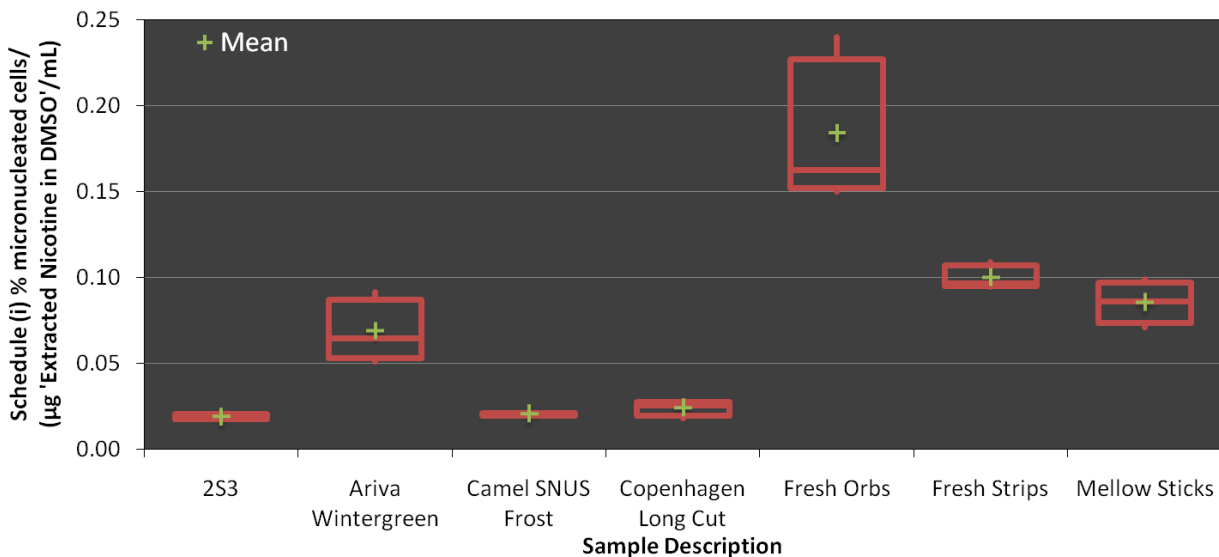
Method Applied for Contrasts

(b) (4)

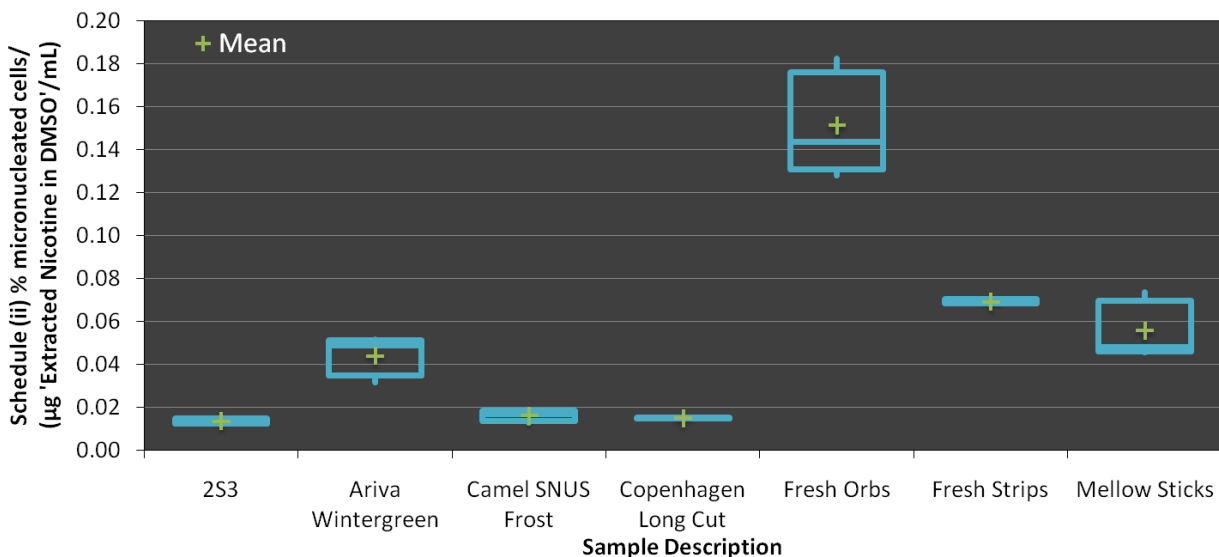
Contrasts of Interest

Contrast of Interest	Treatment Schedule (i)			Treatment Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	1.5251	0.2019	not significant	1.2809	0.2694	not significant
084394 vs. 084454	17.6871	0.0001	significant	28.6353	0.0000	significant
084394 vs. 084455	7.9215	0.0014	significant	4.3368	0.0123	not significant
084394 vs. 084456	1.1533	0.3130	not significant	0.6601	0.5453	not significant
084394 vs. 084457	4.0422	0.0156	not significant	4.3490	0.0122	not significant
084394 vs. 084458	5.7918	0.0044	not significant	8.3381	0.0011	significant
084395 vs. 084454	17.8315	0.0001	significant	44.2041	0.0000	significant
084395 vs. 084455	8.0967	0.0013	significant	4.6572	0.0096	not significant
084395 vs. 084456	1.6687	0.1705	not significant	1.3813	0.2393	not significant
084395 vs. 084457	4.1762	0.0140	not significant	4.8412	0.0084	not significant
084395 vs. 084458	5.8499	0.0043	not significant	8.5194	0.0010	significant
084454 vs. 084455	1.5699	0.1915	not significant	1.4844	0.2119	not significant
084454 vs. 084456	14.2264	0.0001	significant	64.1162	0.0000	significant
084454 vs. 084457	2.4412	0.0711	not significant	4.0132	0.0160	not significant
084454 vs. 084458	2.9429	0.0423	not significant	5.0881	0.0070	not significant
084455 vs. 084456	7.0704	0.0021	significant	4.5321	0.0106	not significant
084455 vs. 084457	1.1416	0.3173	not significant	1.0725	0.3439	not significant
084455 vs. 084458	3.3587	0.0283	not significant	5.1759	0.0066	not significant
084456 vs. 084457	3.6470	0.0218	not significant	4.6780	0.0095	not significant
084456 vs. 084458	5.6395	0.0049	not significant	8.4500	0.0011	significant
084457 vs. 084458	3.7588	0.0198	not significant	6.2079	0.0034	not significant

Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were detected between **Fresh Strips (084454)** as well as **Mellow Sticks (084455)** and each of {**Camel SNUS Frost (084394)**, **2S3 Research Moist Snuff (084395)**, **Copenhagen Long Cut (084456)**} under treatment schedule (i).



Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were detected between **Fresh Strips (084454)** as well as **Fresh Orbs (084458)** and each of {**Camel SNUS Frost (084394)**, **2S3 Research Moist Snuff (084395)**, **Copenhagen Long Cut (084456)**} under treatment schedule (ii).



6.5 Comparisons between Smoked and Smokeless Tobacco Products

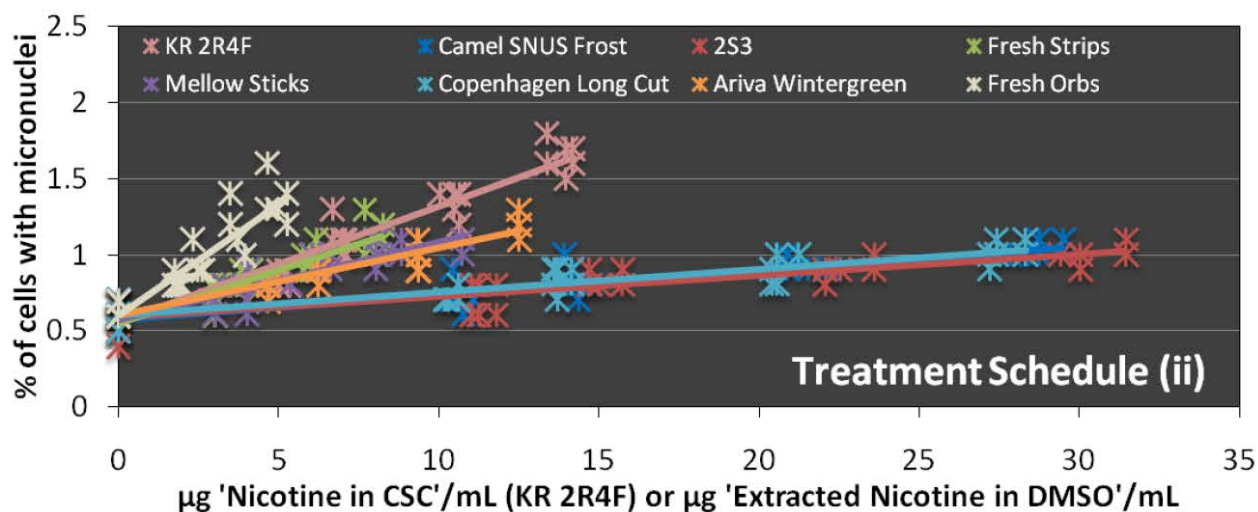
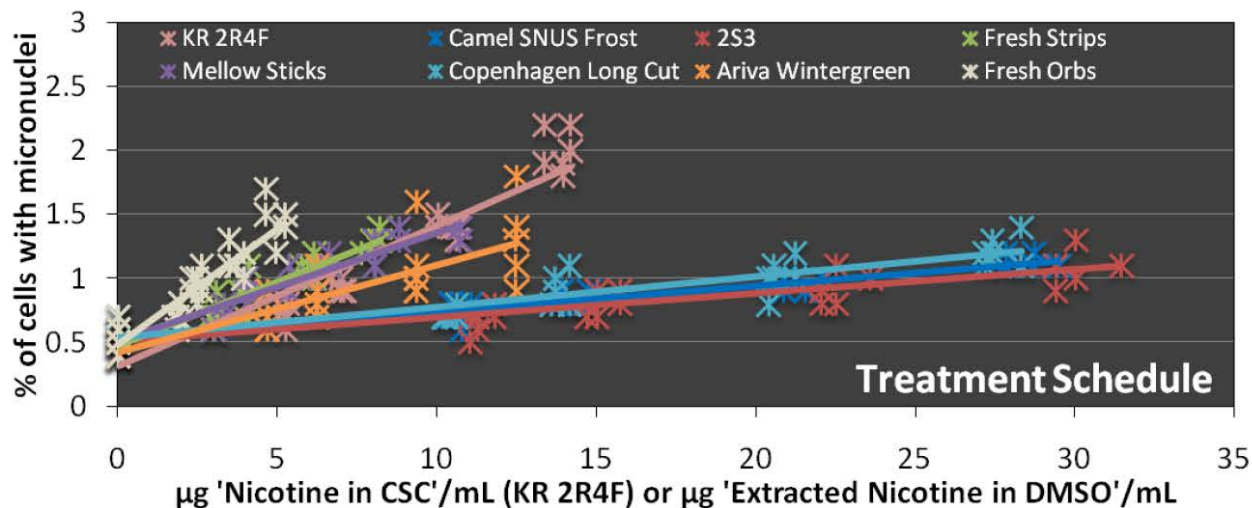
6.5.1 Individual Replicate Slopes and Slope Statistics

Tables of results were obtained for the individual replicate slope estimates, and the summary statistics, on a 'Nicotine' dose basis over the three replicate slopes for each smoked and smokeless tobacco test sample under both treatment schedules. The file *M100_mn_tpm+wt_stats_Nicotine.xls* gives tables of results for all the smokeless tobacco samples plus the tobacco smoke CSC of the KR 2R4F (084396) samples on an 'extracted nicotine in DMSO' and 'Nicotine in CSC' dose basis, respectively.

		Replicate Slope Analysis [%MNC/(μ g 'Nic./mL)]						Slope Statistics		
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3				
Schedule	ID	'Nic' Dose (μ g/mL)	slope	'Nic' Dose (μ g/mL)	slope	'Nic' Dose (μ g/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 27.8	0.021	0 - 28.7	0.021	0 - 29.5	0.019	0.020	0.001	0.018 - 0.023
Schedule (i)	084395	0 - 30.0	0.021	0 - 29.4	0.017	0 - 31.4	0.018	0.019	0.001	0.015 - 0.023
Schedule (i)	084396	0 - 13.4	0.120	0 - 14.2	0.108	0 - 14.0	0.104	0.111	0.005	0.090 - 0.132
Schedule (i)	084454	0 - 8.22	0.096	0 - 8.00	0.109	0 - 7.66	0.094	0.100	0.004	0.081 - 0.119
Schedule (i)	084455	0 - 8.83	0.099	0 - 10.7	0.071	0 - 8.07	0.086	0.085	0.008	0.050 - 0.120
Schedule (i)	084456	0 - 28.3	0.026	0 - 27.4	0.028	0 - 27.2	0.018	0.024	0.003	0.011 - 0.037
Schedule (i)	084457	0 - 12.5	0.091	0 - 12.5	0.064	0 - 12.5	0.051	0.069	0.012	0.017 - 0.120
Schedule (i)	084458	0 - 4.63	0.240	0 - 5.23	0.150	0 - 4.94	0.162	0.184	0.028	0.062 - 0.305
Schedule (ii)	084394	0 - 27.8	0.013	0 - 28.7	0.018	0 - 29.5	0.017	0.016	0.002	0.009 - 0.023
Schedule (ii)	084395	0 - 30.0	0.014	0 - 29.4	0.012	0 - 31.4	0.015	0.014	0.001	0.009 - 0.018
Schedule (ii)	084396	0 - 13.4	0.081	0 - 14.2	0.075	0 - 14.0	0.073	0.077	0.002	0.066 - 0.087
Schedule (ii)	084454	0 - 8.22	0.068	0 - 8.00	0.068	0 - 7.66	0.071	0.069	0.001	0.066 - 0.073
Schedule (ii)	084455	0 - 8.83	0.046	0 - 10.7	0.048	0 - 8.07	0.074	0.056	0.009	0.017 - 0.094
Schedule (ii)	084456	0 - 28.3	0.015	0 - 27.4	0.015	0 - 27.2	0.015	0.015	0.000	0.014 - 0.016
Schedule (ii)	084457	0 - 12.5	0.032	0 - 12.5	0.049	0 - 12.5	0.052	0.044	0.006	0.017 - 0.071
Schedule (ii)	084458	0 - 4.63	0.182	0 - 5.23	0.128	0 - 4.94	0.143	0.151	0.016	0.082 - 0.221

6.5.2 Data Plots

Plots of all replicate smoked and smokeless tobacco test samples expressed on a 'Nicotine' dose basis can be found in the file *M100_mn_tpm+wt_stats_Nicotine.xls* on the CD that accompanies this report. Box-and-Whisker plots of the calculated specific activities can also be found on the CD that accompanies this report.



6.5.3 One-Way ANOVA Results

One-way ANOVA comparisons of mean 'extracted nicotine' and 'nicotine in CSC' slope estimates among all 7 smokeless and one smoked tobacco test sample yielded the following:

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	0.0680	7	0.0097	24.42	< 0.001
	Within Samples	0.0064	16	0.0004		
	Total	0.0744	23			
Treatment Schedule (ii)	Among Samples	0.0446	7	0.0064	43.69	< 0.001
	Within Samples	0.0023	16	0.0001		
	Total	0.0470	23			

One-way ANOVA analysis indicates significant differences, at $\alpha = 0.05$, among mean 'Nicotine' slope estimates for smoked and smokeless tobacco samples assayed under both treatment schedules (i) and (ii).

6.5.4 Contrasts of Interest

(b) (4)

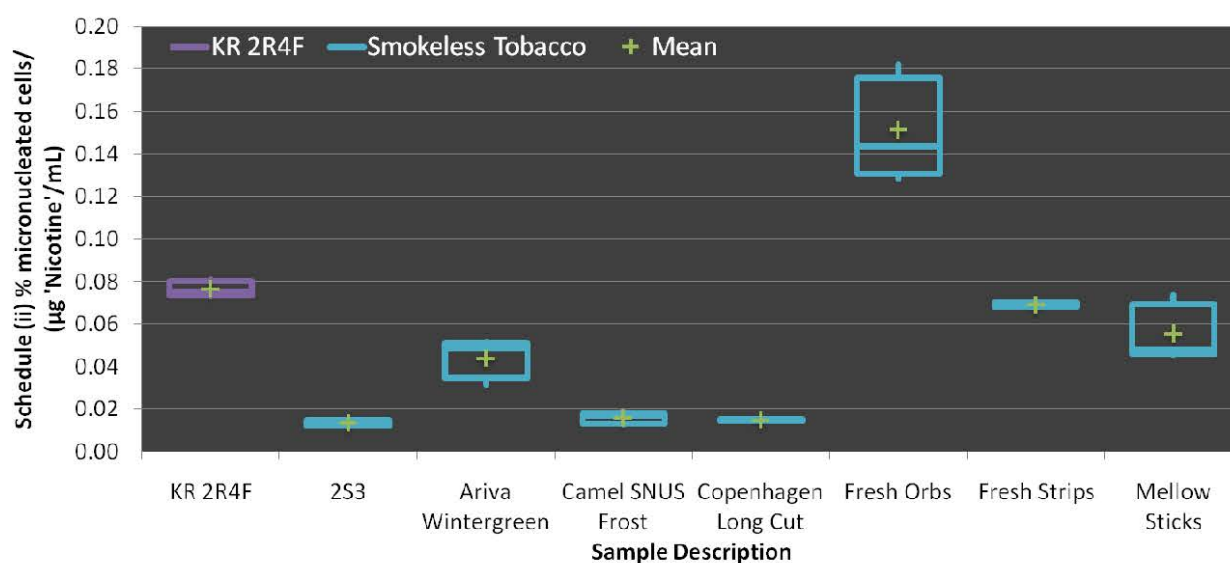
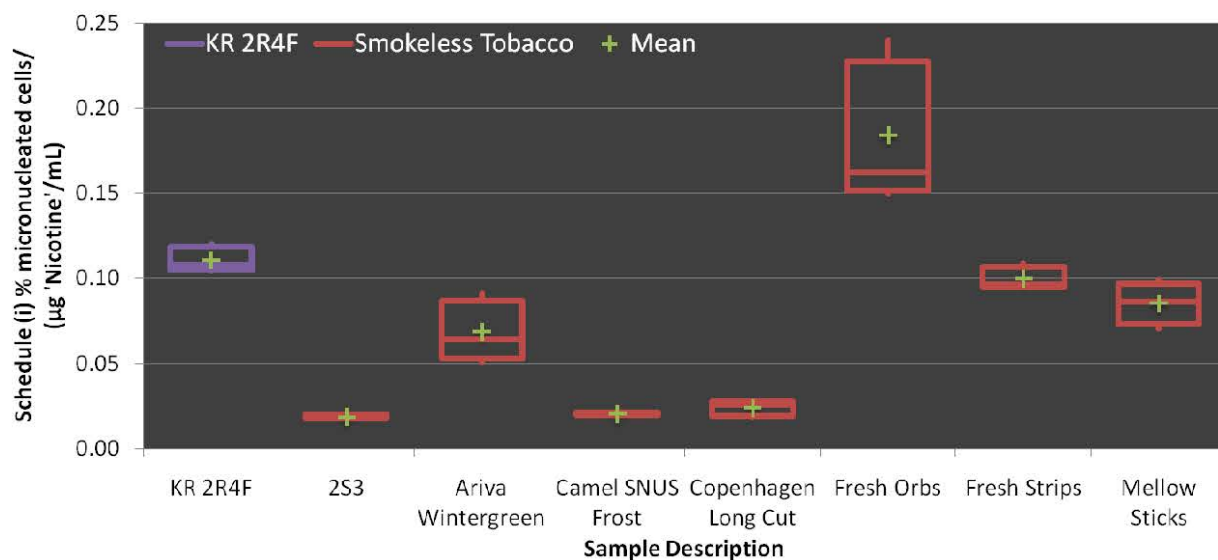
Method Applied for Contrasts

(b) (4)

Contrasts of Interest

	Treatment Schedule (i)			Treatment Schedule (ii)		
Contrast of Interest	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	18.2889	5.3E-05	significant	20.9526	3.1E-05	significant
084395 vs. 084396	18.4326	5.1E-05	significant	24.7207	1.6E-05	significant
084454 vs. 084396	1.6324	0.1779	not significant	2.9980	0.0400	not significant
084455 vs. 084396	2.6682	0.0559	not significant	2.2482	0.0878	not significant
084456 vs. 084396	15.1765	1.1E-04	significant	25.9795	1.3E-05	significant
084457 vs. 084396	3.2476	0.0314	not significant	4.9121	0.0080	not significant
084458 vs. 084396	2.5583	0.0628	not significant	4.5810	0.0102	not significant

Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under both treatment schedules (i) and (ii), significant differences in mean specific activity slope were detected between the cigarette smoke condensate of KR 2R4F (084396) and the following smokeless tobacco extracts on a 'Nicotine' dose basis: {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)}.



7 Summary

Based on the results obtained in this study and the corresponding analysis of the toxicological data, the following summarizes the findings in regards to genotoxicity as measured with the *in vitro* micronucleus assay.

- The mg 'extracted moisture-corrected smokeless tobacco in DMSO'/mL ('ST-H₂O') dose base appeared to be able to differentiate brands by specific activity slope better than the mg 'extracted smokeless tobacco in DMSO'/mL ('ST') dose base.
- The µg 'extracted nicotine in DMSO'/mL ('nicotine') dose base appeared to be able to differentiate brands by specific activity slope better than the mg 'extracted moisture-corrected smokeless tobacco in DMSO'/mL ('ST-H₂O') dose base.
- Under both treatment schedules, the CSC of KR 2R4F test samples on a nicotine dose basis was significantly more genotoxic than the extracts of smokeless tobacco test samples {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)}.

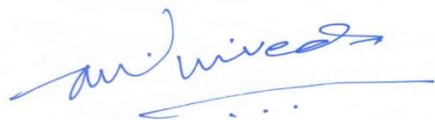
8 Attribution

8.1 Original

8.1.1 Technical Director (Toxicology)

This report has been reviewed by me and is certified, to the best of my knowledge, to be a true and accurate description of the procedures, protocols and test methods used to arrive at the data and/or findings that accompany this report.

Dated: January 12, 2009

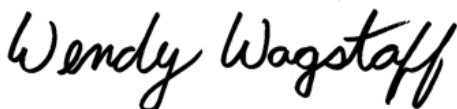


Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.1.2 Senior Statistician

This report has been prepared by me and is certified, to the best of my knowledge, to be a true and accurate description of the statistical methods used to arrive at the findings that accompany this report.

Dated: January 12, 2009

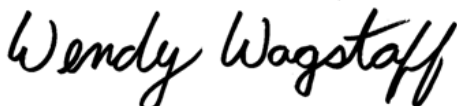


Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.2 Revision 1

This report has been prepared by me and is certified, to the best of my knowledge, to be a true and accurate description of the statistical methods used to arrive at the findings that accompany this report.

Dated: November 3, 2009



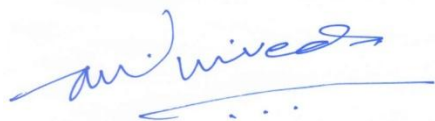
Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.3 Revision 2

8.3.1 Technical Director (Toxicology)

This report has been reviewed by me and is certified, to the best of my knowledge, to be a true and accurate description of the procedures, protocols and test methods used to arrive at the data and/or findings that accompany this report.

Dated: December 17, 2009

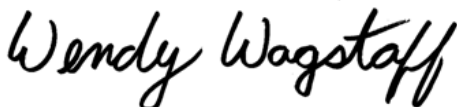


Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.3.2 Senior Statistician

This report has been prepared by me and is certified, to the best of my knowledge, to be a true and accurate description of the statistical methods used to arrive at the findings that accompany this report.

Dated: December 17, 2009



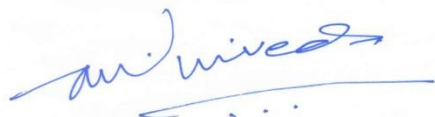
Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.4 Revision 3

8.4.1 Technical Director (Toxicology)

This report has been reviewed by me and is certified, to the best of my knowledge, to be a true and accurate description of the procedures, protocols and test methods used to arrive at the data and/or findings that accompany this report.

Dated: April 23, 2010



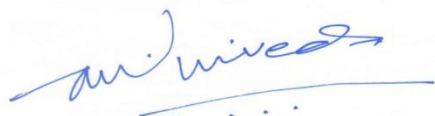
Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.5 Revision 5

8.5.1 Technical Director (Toxicology)

This report has been reviewed by me and is certified, to the best of my knowledge, to be a true and accurate description of the procedures, protocols and test methods used to arrive at the data and/or findings that accompany this report.

Dated: December 22, 2010

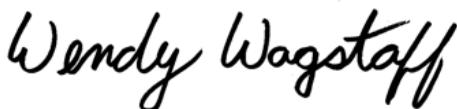


Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.5.2 Senior Statistician

This report has been prepared by me and is certified, to the best of my knowledge, to be a true and accurate description of the statistical methods used to arrive at the findings that accompany this report.

Dated: December 22, 2010



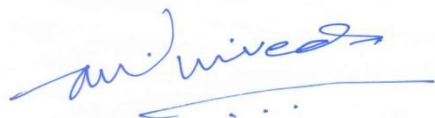
Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.6 Revision 7

8.6.1 Technical Director (Toxicology)

This report has been reviewed by me and is certified, to the best of my knowledge, to be a true and accurate description of the procedures, protocols and test methods used to arrive at the data and/or findings that accompany this report.

Dated: February 4, 2011

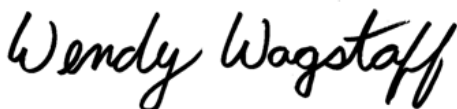
A handwritten signature in blue ink, reading 'Amit Trivedi', with a horizontal line underneath.

Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.6.2 Senior Statistician

This report has been prepared by me and is certified, to the best of my knowledge, to be a true and accurate description of the statistical methods used to arrive at the findings that accompany this report.

Dated: February 4, 2011

A handwritten signature in black ink, reading 'Wendy Wagstaff'.

Wendy Wagstaff
Senior Statistician
Labstat International ULC

Appendix A

Scope of Accreditation



Standards Council of Canada
Conseil canadien des normes

200-270, rue Albert St.
Ottawa, ON (Canada)
K1P 6N7

Canada

Tel.: +1 613 238 3222

Fax: +1 613 569 7808

E-mail/Courriel: info@scc.ca

Internet: <http://www.scc.ca>

SCOPE OF ACCREDITATION

LABSTAT INTERNATIONAL ULC
262 Manitou Drive, Unit 5
Kitchener, ON
N2C 1L3

Accredited Laboratory No. 368
(Conforms with requirements of CAN-P-4E (ISO/IEC 17025:2005))

CONTACT: Mr. Lucian Hirtie
TEL: (519) 748-5409
FAX: (519) 748-1654
EMAIL: lhirtie@labstat.com

CLIENTS SERVED: All interested parties

FIELDS OF TESTING: Biological, Chemical/Physical

ISSUED ON: 2008-10-06

VALID TO: 2012-01-22

Remarque: La présente portée d'accréditation existe également en français, sous la forme d'un document distinct.

Note: This scope of accreditation is also available in French as a separately issued document.

ANIMAL AND PLANTS (AGRICULTURE)

Agricultural products: (except food and chemicals)

Tobacco

AOAC 966.02	Moisture in Tobacco
ASTM E2187	Standard Test Method for Measuring the Ignition Strength of Cigarettes
ISO 10315	Cigarettes – Determination of Nicotine in Smoke Condensates Gas-Chromatographic Method
ISO 10362-1	Cigarettes – Determination of Water in Smoke Condensates – Part 1:

The approved and most recent version of this document can be viewed on the SCC website at <http://palcan.scc.ca/SpecsSearch/GLSearchForm.do>

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	Gas-Chromatographic Method
ISO 15592-2	Fine-cut Tobacco and smoking articles made from it – Methods of sampling, conditioning and analysis – Part 2: Atmosphere for conditioning and testing
ISO 15592-3	Fine-cut Tobacco and smoking articles made from it – Methods of sampling, conditioning and analysis – Part 3: Determination of total particulate matter of smoking articles using a routine analytical smoking machine, preparation for the determination of water and nicotine, and calculation of nicotine-free dry particulate matter
ISO 3308	Routine Analytical Cigarette-Smoking Machine– Definitions and Standard Conditions
ISO 3402	Tobacco and Tobacco Products – Atmosphere for Conditioning and Testing
ISO 4387	Cigarettes – Determination of Total and Nicotine-Free Dry Particulate Matter Using a Routine Analytical Smoking Machine
ISO 6565	Tobacco and Tobacco Products – Draw Resistance of Cigarettes and Pressure Drop of Filter Rods–Standard Conditions and Measurement
ISO 8454	Cigarettes – Determination of Carbon Monoxide in the Vapour Phase of Cigarette Smoke – NDIR method
TMS-118	Determination of Volatile Nitrosamines in Mainstream Tobacco Smoke
TMS-120	Determination of Selected Polynuclear Aromatic Hydrocarbons (PAHs) in Mainstream Tobacco Smoke
TMS-124	Determination of Vinyl Chloride, 1,3-Butadiene, Isoprene, Acrylonitrile, Benzene, Toluene, Styrene and Acetamide in Mainstream Tobacco Smoke (Expanded List)
TMS-127	Determination of Selected Polynuclear Aromatic Hydrocarbons (PAHs) And Aza-Arenes in the Particulate Phase of Mainstream Tobacco Smoke
TMS-128	Determination of Aromatic Amines in Mainstream Tobacco smoke (Expanded list: Aniline, o-Toluidine, m-Toluidine, p-Toluidine, o-Anisidine, 1- and 2-Aminonaphthalene and 3- and 4-Aminobiphenyl)
TMS-132	Determination of Gas Phase and Particulate Phase Free Radicals in Mainstream Tobacco Smoke
TMS-133	Determination of Selected Heterocyclic Aromatic Amines (HAAs) in Mainstream Tobacco Smoke
TMS-135	Determination of Tobacco Specific Nitrosamines in Mainstream Tobacco Smoke by Liquid Chromatography–Tandem Mass Spectrometry
TMS-137	Determination of Acetamide and Acrylamide in Mainstream Tobacco Smoke
TSS-219	Determination of Selected Polynuclear Aromatic Hydrocarbons (PAHs) in Sidestream Tobacco Smoke
TSS-222	Determination of Sidestream Tobacco Smoke pH
TWT-303	Determination of Carbonyls in Tobacco Samples
TWT-320	Determination of 1- and 2- Aminonaphthalene and 3- and 4-Aminobiphenyl in Tobacco Samples
TWT-321	

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	Determination Of Nicotine Alkaloids And Reducing Sugars In Tobacco Samples
TWT-324	Determination of Nicotine in Tobacco Samples (CDC method)
TWT-332	Determination of Volatile Nitrosamines in Tobacco Samples
TWT-333	Determination of Tobacco Specific Nitrosamines in Tobacco Samples by Liquid Chromatography–Tandem Mass Spectrometry
TWT-334	Determination of Chloride in Tobacco Samples
TWT-335	Determination of Selected Polycyclic Aromatic Hydrocarbons (PAHs) in Tobacco Samples
TWT-336	Determination of Acrylamide in Tobacco Samples by Liquid Chromatography – Tandem Mass Spectrometry
TWT-337	Determination of 1,3-Butadiene and Benzene in Tobacco Samples

(Health Canada Tobacco Reporting Regulations Official Methods)

T-101	Determination of Ammonia in Mainstream Tobacco Smoke
T-102	Determination of 1- and 2- Aminonaphthalene and 3- and 4- Aminobiphenyl in Mainstream Tobacco Smoke
T-103	Determination of Benzo[a]pyrene in Mainstream Tobacco Smoke
T-104	Determination of Selected Carbonyls in Mainstream Tobacco Smoke
T-105	Determination of Eugenol in Mainstream Tobacco Smoke
T-106	Determination of Filter Efficiency in Mainstream Tobacco Smoke
T-107	Determination of Hydrogen Cyanide in Mainstream Tobacco Smoke
T-108	Determination of Mercury in Mainstream Tobacco Smoke
T-109	Determination of Ni, Pb, Cd, Cr, As and Se in Mainstream Tobacco Smoke
T-110	Determination of Oxides of Nitrogen in Mainstream Tobacco Smoke
T-111	Determination of Nitrosamines in Mainstream Tobacco Smoke
T-112	Determination of Pyridine, Quinoline and Styrene in Mainstream Tobacco Smoke
T-113	Determination of Mainstream Tobacco Smoke pH
T-114	Determination of Phenolic Compounds in Mainstream Tobacco Smoke
T-115	Determination of Tar, Nicotine and Carbon Monoxide in Mainstream Tobacco Smoke
T-116	Determination of 1,3- Butadiene, Isoprene, Acrylonitrile, Benzene and Toluene in Mainstream Tobacco Smoke
T-201	Determination of Ammonia in Sidestream Tobacco Smoke
T-202	Determination of 1- and 2- Aminonaphthalene and 3- and 4- Aminobiphenyl in Sidestream Tobacco Smoke
T-203	Determination of Benzo[a]pyrene in Sidestream Tobacco Smoke
T-203A	Determination of Benzo[a]pyrene in Sidestream Tobacco Smoke (GC/MS)
T-204	Determination of Selected Carbonyls in Sidestream Tobacco Smoke
T-205	Determination of Hydrogen Cyanide in Sidestream Tobacco Smoke
T-206	Determination of Mercury in Sidestream Tobacco Smoke
T-207	Determination of Toxic Trace Metals in Sidestream Smoke

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T-208	Determination of Oxides of Nitrogen in Sidestream Tobacco Smoke
T-209	Determination of Nitrosamines in Sidestream Tobacco Smoke
T-210	Determination of Pyridine and Quinoline in Sidestream Tobacco Smoke
T-211	Determination of Phenolic Compounds in Sidestream Tobacco Smoke
T-212	Determination of "Tar" and Nicotine in Sidestream Tobacco Smoke
T-213	Determination of 1,3 Butadiene, Isoprene, Acrylonitrile, Benzene, Toluene and Styrene in Sidestream Tobacco Smoke
T-214	Determination of Carbon Monoxide (CO) in Sidestream Tobacco Smoke
T-301	Determination of Alkaloids in Whole Tobacco
T-302	Determination of Ammonia in Whole Tobacco
T-304	Determination of Humectants in Whole Tobacco
T-306	Determination of Ni, Pb, Cd, Cr, As, Se and Hg in Whole Tobacco
T-307	Determination of Benzo[a]pyrene in Whole Tobacco
T-308	Determination of Nitrate from Whole Tobacco
T-309	Determination of Nitrosamines in Whole Tobacco
T-310	Determination of Whole Tobacco pH
T-311	Determination of Triacetin in Whole Tobacco
T-312	Determination of Sodium Propionate in Whole Tobacco
T-313	Determination of Sorbic Acid in Whole Tobacco
T-314	Determination of Eugenol in Whole Tobacco
T-401	Preparation of Cigarettes from Packaged Leaf Tobacco for Testing
T-402	Preparation of Cigarettes, Cigarette Tobacco, Cigars, Kreteks, Bidis, Packaged Leaf Tobacco, Pipe Tobacco and Smokeless Tobacco for testing

(Microbiology Tests)

T-501	Bacterial Reverse Mutation Assay for Mainstream Tobacco Smoke
T-502	Neutral Red Uptake Assay for Mainstream Tobacco Smoke
T-503	In Vitro Micronucleus Assay for Mainstream Tobacco Smoke
TBA-504	<i>In vitro</i> Sister Chromatid Exchange (SCE) Assay for Mainstream Tobacco Smoke

(Other: Measures of Exposure)

TME-001	Determination of Nicotine, Cotinine and Caffeine in Physiological Fluid Samples
TME-002	Determination of Creatinine in Urine
TME-003	Determination of 3-Hydroxycotinine in Physiological Fluid Samples
TME-004	<i>Salmonella Typhimurium</i> Reverse Mutation Assay: Microsuspension Method For Testing Urine Mutagenicity
TME-005	Determination of Nicotine and its Major Metabolites in Urine by Liquid Chromatography – Tandem Mass Spectrometry

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TME-006	Determination of S-Phenylmercapturic Acid (S-PMA) in Urine by Liquid Chromatography – Tandem Mass Spectrometry
TME-007	Determination of 8-Hydroxy-2'-Deoxyguanosine (8-OHdG) in Urine by Liquid Chromatography – Tandem Mass Spectrometry
TME-008	Determination of 1-Hydroxypyrene (1-HOP) in Urine by Liquid Chromatography – Tandem Mass Spectrometry
TME-009	Determination of 4-(Methyl-Nitrosamino)-1-(3-Pyridyl)-1-Butanol (NNAL) and its Glucuronides in Urine by Liquid Chromatography – Tandem Mass Spectrometry
TME-010	Determination of 1,3-Butadiene Urinary Metabolites by Liquid Chromatography – Tandem Mass Spectrometry
TME-011	Determination of 3-Hydroxypropylmercapturic Acid (3-HPMA) in Urine by Liquid Chromatography – Tandem Mass Spectrometry
TME-012	Determination of Selected Arylamines in Urine by Gas Chromatography – Mass Spectrometry (GC-MS)

Notes:

AOAC: Association of Official Analytical Chemists

ASTM: American Society for Testing and Materials

CAN-P-4E (ISO/IEC 17025): General Requirements for the Competence of Testing and Calibration Laboratories (ISO/IEC 17025-2005)

CDC: Centers for Disease Control and Prevention

ISO: International Organization for Standardization

T: Health Canada Tobacco Reporting Regulations Official Methods

TBA: Test Method, Biological Activity

TME: Test Method, Measures of Exposure

TMS: Test method, Mainstream Smoke

TSS: Test method, Sidestream Smoke

TWT: Test method, Whole Tobacco

P. Paladino, P. Eng., Director, Conformity Assessment

Date: 2008-10-06

Number of Scope Listings: 93
SCC 1003-15/420

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Partner File #0

Partner: None

Appendix B

“Raw” Data and Analysis Results (See Enclosed CD)

Use of Labstat's¹ Analytical Reports²

Labstat International ULC is a recognized centre of analytical excellence related to tobacco and tobacco products. Our clients include major international tobacco manufacturers, various Governments and Government agencies such as the Canadian Federal Department of Health and the Massachusetts Department of Public Health, agricultural interests, university researchers and private research interests. Normally our contractual obligations extend **only** to the provision of data and related reports.

It should be noted³, in this regard, that

All analytical data and reports, provided by Labstat International ULC, are for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the data, the report nor the name of the laboratory (Labstat International ULC) nor any member of its staff may be used in connection with the advertising or sale of any product or process without written authorization from the CEO of the company or his designate. Labstat International ULC is not responsible for unauthorized use of test reports.

The following also applies to reported data.

All Labstat reports on testing relate only to the sample received and tested by it at the time of testing. Labstat warrants that all samples submitted were tested in accordance with its standard test procedures. Except as stated herein, there is no warranty expressed or implied, statutory or otherwise, as to the results of Labstat tests. Labstat does not warrant or guarantee the fitness of the materials from which the samples have been drawn for any particular purpose including without limitation for consumption as cigarettes, cigars, smokeless tobacco or any other form of tobacco or tobacco-related product.

¹. Labstat International ULC,
262 Manitou Drive, Kitchener, ON Canada N2C 1L3
Phone: (519) 748-5409; Fax: (519) 748-1654; Email: labstat@labstat.com

². This document may not be reproduced, in whole or in part in any form, without the written consent of the author(s) on behalf of Labstat International ULC

³. Unless superseded by a specific contractual obligation or other written agreement.

Attribution Policy

Labstat International ULC ("Labstat") is a private independent analytical laboratory whose services are generally limited to the analysis of tobacco and tobacco related products ("product") provided by clients. Neither Labstat, as a company, nor its personnel, as individuals, participate in product development, product preparation or the design of experiments related to product characteristics. It is for this reason that the company does not allow the use of its name (Labstat International ULC), any part of its name, its address (262 Manitou Drive, Kitchener, Ontario Canada), or any part of its address, its logo (as shown below) or the name of any of its employees to be used in either indirect or direct product marketing or advertising including but not limited to press releases, advertisements in the print media, or public statements regarding product attributes based on test results.



Sample ID	Sample Description
084394	Camel SNUS Frost
084395	2S3 Research Moist smokeless tobacco
084396	Kentucky Reference 2R4F
084454	Fresh Strips
084455	Mellow Sticks
084456	Copenhagen Long Cut
084457	Ariva Wintergreen
084458	Fresh Orbs
control	Kentucky Reference 3R4F

**Nicotine Extracted from Processed Tobacco
('As Received' Basis)**

Sample ID	Nicotine [mg/g]
084394	12.5
084394	12.9
084394	13.3
Average	12.9
Std. Dev.	0.4
Coeff. Var.	2.9
084395	13.5
084395	13.2
084395	14.1
Average	13.6
Std. Dev.	0.5
Coeff. Var.	3.5
084454	3.69
084454	3.60
084454	3.45
Average	3.58
Std. Dev.	0.12
Coeff. Var.	3.5
084455	3.97
084455	3.63
084455	4.83
Average	3.80
Std. Dev.	0.24
Coeff. Var.	6.3
084456	12.7
084456	12.3
084456	12.2
Average	12.4
Std. Dev.	0.3
Coeff. Var.	2.1

**Nicotine Extracted from Processed Tobacco
('As Received' Basis)**

Sample ID	Nicotine [mg/g]
084457	5.63
084457	5.61
084457	5.62
Average	5.62
Std. Dev.	0.01
Coeff. Var.	0.1
084458	2.08
084458	2.35
084458	2.22
Average	2.22
Std. Dev.	0.13
Coeff. Var.	6.1

**Yields of Nicotine in Mainstream Tobacco Smoke:
'FTC' Conditions ***

Set Number	Run Number	Sample ID	Weight [mg/cig]	Puff Count [per cig]	MS TPM [mg/cig]	Nicotine [mg/cig]
1	1	control	1037	8.5	9.17	0.655
2	1	control	1038	8.5	9.37	0.763
3	3	control	1046	8.8	9.33	0.669
		Average	1040	8.6	9.29	0.695
		Std. Dev.	5	0.2	0.11	0.059
		Coeff. Var.	0.5	2.0	1.2	8.5
1	2	084396	1045	8.9	10.6	0.919
2	2	084396	1043	8.9	11.4	0.767
3	2	084396	1043	8.9	11.2	0.780
		Average	1044	8.9	11.1	0.822
		Std. Dev.	1	0.0	0.4	0.084
		Coeff. Var.	0.1	0.4	4.0	10.3

* puff volume, 35mL; interval, 60 sec; duration, 2 sec; vent blocking, 0%.
See text for additional details.

**Yields of Nicotine in Mainstream Tobacco Smoke:
'FTC' Conditions ***

Set Number	Run Number	Sample ID	Weight [mg/cig]	Puff Count [per cig]	MS TPM [mg/cig]	Nicotine [mg/cig]
1	2	084396	1045	8.8	11.0	0.734
1	3	084396	1036	9.1	10.8	0.767
1	4	084396	1038	8.7	10.5	0.731
Average			1039	8.9	10.7	0.744
Std. Dev.			5	0.2	0.3	0.020
Coeff. Var.			0.5	2.1	2.5	2.7

* puff volume, 35mL; interval, 60 sec; duration, 2 sec; vent blocking, 0%.
See text for additional details.

LABSTAT INTERNATIONAL ULC

262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

Period: November 6, 2008

Smoking Data[†] for *In Vitro* Micronucleus Assay analysis**TPM and Nicotine Dose Data for *In Vitro* MN Assay**

Set Number	Run Number	Sample ID	Replicate Number	Smoking Date	Cigarettes Smoked	Puff Count (per cig)	MS TPM (mg/cig) ¹	Nicotine (mg/cig)	Smoking Machine	TPM Dose (mg/mL media)					Nicotine Dose (µg/mL media)				
										1	2	3	4	5	1	2	3	4	5
1	2	084396	1	6-Nov-08	20	8.8	11.0	0.734	Borgwaldt Rotary	0	0.075	0.100	0.150	0.200	0	5.02	6.69	10.0	13.4
1	3	084396	2	6-Nov-08	20	9.1	10.8	0.767	Borgwaldt Rotary	0	0.075	0.100	0.150	0.200	0	5.32	7.09	10.6	14.2
1	4	084396	3	6-Nov-08	20	8.7	10.5	0.731	Borgwaldt Rotary	0	0.075	0.100	0.150	0.200	0	5.24	6.99	10.5	14.0

[†] Samples generated under 'ISO' smoking conditions:

35mL puff volume; 60 second interval; 2 second duration; no vent blocking.

1. Samples extracted in DMSO to give a final concentration of 10.0 mg/mL.

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation**
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	TPM (mg/mL)	Nicotine (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
									Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
1	2	084396	1	Schedule (i)	0	0	3	-S9	0	0	0	0.50	0.50	0.50
1	2	084396	1	Schedule (i)	0.075	5.02	3	-S9	19.0	12.7	15.8	0.80	0.80	0.80
1	2	084396	1	Schedule (i)	0.100	6.69	3	-S9	27.7	26.1	26.9	1.20	1.10	1.15
1	2	084396	1	Schedule (i)	0.150	10.0	3	-S9	48.9	51.5	50.2	1.50	1.50	1.50
1	2	084396	1	Schedule (i)	0.200	13.4	3	-S9	81.8	77.6	79.7	2.20	2.40	2.30
1	3	084396	2	Schedule (i)	0	0	3	-S9	0	0	0	0.70	0.50	0.60
1	3	084396	2	Schedule (i)	0.075	5.32	3	-S9	19.8	20.7	20.3	0.80	0.70	0.75
1	3	084396	2	Schedule (i)	0.100	7.09	3	-S9	31.5	42.2	36.9	1.00	0.90	0.95
1	3	084396	2	Schedule (i)	0.150	10.6	3	-S9	62.2	57.8	60.0	1.40	1.50	1.45
1	3	084396	2	Schedule (i)	0.200	14.2	3	-S9	83.8	89.7	86.7	2.10	2.30	2.20
1	4	084396	3	Schedule (i)	0	0	3	-S9	0	0	0	0.40	0.50	0.45
1	4	084396	3	Schedule (i)	0.075	5.24	3	-S9	10.4	12.0	11.2	0.60	0.80	0.70
1	4	084396	3	Schedule (i)	0.100	6.99	3	-S9	31.2	30.7	30.9	1.00	1.10	1.05
1	4	084396	3	Schedule (i)	0.150	10.5	3	-S9	50.6	53.3	52.0	1.40	1.50	1.45
1	4	084396	3	Schedule (i)	0.200	14.0	3	-S9	81.8	86.0	83.9	1.80	2.00	1.90
1	2	084396	1	Schedule (ii)	0	0	3	+S9	0	0	0	0.70	0.70	0.70
1	2	084396	1	Schedule (ii)	0.075	5.02	3	+S9	5.3	5.4	5.4	0.90	0.90	0.90
1	2	084396	1	Schedule (ii)	0.100	6.69	3	+S9	12.9	10.1	11.5	1.30	1.20	1.25
1	2	084396	1	Schedule (ii)	0.150	10.0	3	+S9	25.0	24.0	24.5	1.60	1.40	1.50
1	2	084396	1	Schedule (ii)	0.200	13.4	3	+S9	35.6	38.8	37.2	1.90	1.70	1.80
1	3	084396	2	Schedule (ii)	0	0	3	+S9	0	0	0	0.60	0.60	0.60
1	3	084396	2	Schedule (ii)	0.075	5.32	3	+S9	15.8	10.1	12.9	0.90	0.80	0.85
1	3	084396	2	Schedule (ii)	0.100	7.09	3	+S9	22.6	17.3	19.9	1.10	1.10	1.10
1	3	084396	2	Schedule (ii)	0.150	10.6	3	+S9	32.9	32.4	32.6	1.30	1.40	1.35
1	3	084396	2	Schedule (ii)	0.200	14.2	3	+S9	41.8	41.0	41.4	1.60	1.70	1.65
1	4	084396	3	Schedule (ii)	0	0	3	+S9	0	0	0	0.60	0.60	0.60
1	4	084396	3	Schedule (ii)	0.075	5.24	3	+S9	16.9	17.2	17.1	1.00	0.90	0.95
1	4	084396	3	Schedule (ii)	0.100	6.99	3	+S9	29.2	25.0	27.1	1.10	1.10	1.10
1	4	084396	3	Schedule (ii)	0.150	10.5	3	+S9	36.2	35.9	36.0	1.50	1.30	1.40
1	4	084396	3	Schedule (ii)	0.200	14.0	3	+S9	43.8	41.4	42.6	1.70	1.50	1.60

LABSTAT INTERNATIONAL ULC

262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

Period: November 28 - December 17, 2008

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(Assay Information)**

Sample ID	Replicate Number	Assay Date	Treatment Schedule	Metabolic Activation	Treatment (hours)	Recovery (hours)	Before Treatment (Cells (x10 ⁵) per mL)		Negative Control (Cells (x10 ⁵) per mL)		Increase > 90%	
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1	Flask 2
084396	1	28-Nov-08	Schedule (i)	-S9	3	27	1.96	2.00	7.44	7.36	≥ 90%	≥ 90%
084396	2	04-Dec-08	Schedule (i)	-S9	3	27	1.96	2.00	6.40	6.64	≥ 90%	≥ 90%
084396	3	05-Dec-08	Schedule (i)	-S9	3	27	2.04	2.08	8.20	8.08	≥ 90%	≥ 90%
084396	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.08	7.36	7.24	≥ 90%	≥ 90%
084396	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.08	7.92	7.64	≥ 90%	≥ 90%
084396	3	17-Dec-08	Schedule (ii)	+S9	3	27	1.96	1.96	7.16	7.08	≥ 90%	≥ 90%

LABSTAT INTERNATIONAL ULC

262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

Period: November 13 - 19, 2008

Sample Generation Data for *In Vitro* Micronucleus Assay

Set-Run	Sample ID	Replicate Number	Extraction Date	Tobacco Weight (g)	Volume (mL) ¹	mg Tobacco per mL	Dry Matter (%)	Nicotine (mg/g)	mg (Tobacco-H ₂ O) per mL	Calculated Nicotine in
										Extraction Solution (mg/mL)
3-4	084394	1	19-Nov-08	2.5013	22.5	111.169	68.27	12.5	75.900	1.39
3-6	084394	2	19-Nov-08	2.5002	22.5	111.120		12.9	75.867	1.44
3-13	084394	3	19-Nov-08	2.5018	22.5	111.191		13.3	75.916	1.47
3-9	084395	1	19-Nov-08	2.5008	22.5	111.147	45.98	13.5	51.108	1.50
3-11	084395	2	19-Nov-08	2.5005	22.5	111.133		13.2	51.102	1.47
3-15	084395	3	19-Nov-08	2.5014	22.5	111.173		14.1	51.121	1.57
3-2	084454	1	19-Nov-08	2.5018	22.5	111.191	88.90	3.69	98.845	0.411
3-10	084454	2	19-Nov-08	2.5016	22.5	111.182		3.60	98.837	0.400
3-12	084454	3	19-Nov-08	2.5006	22.5	111.138		3.45	98.798	0.383
3-1	084455	1	19-Nov-08	2.5017	22.5	111.187	93.93	3.97	104.434	0.442
3-3	084455	2	19-Nov-08	2.5015	22.5	111.178		4.83	104.426	0.537
3-7	084455	3	19-Nov-08	2.5003	22.5	111.124		3.63	104.375	0.403
2-7	084456	1	13-Nov-08	2.5011	22.5	111.160	44.63	12.7	49.614	1.42
2-9	084456	2	13-Nov-08	2.5000	22.5	111.111		12.3	49.592	1.37
2-10	084456	3	13-Nov-08	2.5012	22.5	111.164		12.2	49.616	1.36
2-3	084457	1	13-Nov-08	2.5004	22.5	111.129	96.32	5.63	107.044	0.625
2-5	084457	2	13-Nov-08	2.5004	22.5	111.129		5.61	107.044	0.624
2-6	084457	3	13-Nov-08	2.5002	22.5	111.120		5.62	107.036	0.625
2-2	084458	1	13-Nov-08	2.5000	22.5	111.111	94.86	2.08	105.400	0.231
2-4	084458	2	13-Nov-08	2.5019	22.5	111.196		2.35	105.480	0.262
2-8	084458	3	13-Nov-08	2.5014	22.5	111.173		2.22	105.459	0.247

1. Samples extracted in appropriate solvent control to give a final concentration of 10.0 mg/mL

**Extracted Smokeless Tobacco, Moisture-Corrected Smokeless Tobacco and
Nicotine in Smokeless Tobacco Dosing Data**

Set- Run	Sample ID	Replicate Number	mg Extracted Smokeless Tobacco/mL media					mg Extracted Moisture-Corrected Smokeless Tobacco /mL media				
			1	2	3	4	5	1	2	3	4	5
3-4	084394	1	0	0.834	1.11	1.67	2.22	0	0.569	0.759	1.14	1.52
3-6	084394	2	0	0.833	1.11	1.67	2.22	0	0.569	0.759	1.14	1.52
3-13	084394	3	0	0.834	1.11	1.67	2.22	0	0.569	0.759	1.14	1.52
3-9	084395	1	0	0.834	1.11	1.67	2.22	0	0.383	0.511	0.767	1.02
3-11	084395	2	0	0.834	1.11	1.67	2.22	0	0.383	0.511	0.767	1.02
3-15	084395	3	0	0.834	1.11	1.67	2.22	0	0.383	0.511	0.767	1.02
3-2	084454	1	0	0.834	1.11	1.67	2.22	0	0.741	0.988	1.48	1.98
3-10	084454	2	0	0.834	1.11	1.67	2.22	0	0.741	0.988	1.48	1.98
3-12	084454	3	0	0.834	1.11	1.67	2.22	0	0.741	0.988	1.48	1.98
3-1	084455	1	0	0.834	1.11	1.67	2.22	0	0.783	1.04	1.57	2.09
3-3	084455	2	0	0.834	1.11	1.67	2.22	0	0.783	1.04	1.57	2.09
3-7	084455	3	0	0.833	1.11	1.67	2.22	0	0.783	1.04	1.57	2.09
2-7	084456	1	0	0.834	1.11	1.67	2.22	0	0.372	0.496	0.744	0.992
2-9	084456	2	0	0.833	1.11	1.67	2.22	0	0.372	0.496	0.744	0.992
2-10	084456	3	0	0.834	1.11	1.67	2.22	0	0.372	0.496	0.744	0.992
2-3	084457	1	0	0.833	1.11	1.67	2.22	0	0.803	1.07	1.61	2.14
2-5	084457	2	0	0.833	1.11	1.67	2.22	0	0.803	1.07	1.61	2.14
2-6	084457	3	0	0.833	1.11	1.67	2.22	0	0.803	1.07	1.61	2.14
2-2	084458	1	0	0.833	1.11	1.67	2.22	0	0.790	1.05	1.58	2.11
2-4	084458	2	0	0.834	1.11	1.67	2.22	0	0.791	1.05	1.58	2.11
2-8	084458	3	0	0.834	1.11	1.67	2.22	0	0.791	1.05	1.58	2.11

Tobacco Extract in Solvent (µL/mL media)				
1	2	3	4	5
0	7.5	10	15	20

Set- Run	Sample ID	Replicate Number	µg Nicotine in Smokeless Tobacco/mL media				
			1	2	3	4	5
3-4	084394	1	0	10.4	13.9	20.9	27.8
3-6	084394	2	0	10.8	14.4	21.5	28.7
3-13	084394	3	0	11.1	14.7	22.1	29.5
3-9	084395	1	0	11.3	15.0	22.5	30.0
3-11	084395	2	0	11.0	14.7	22.0	29.4
3-15	084395	3	0	11.8	15.7	23.6	31.4
3-2	084454	1	0	3.08	4.11	6.16	8.22
3-10	084454	2	0	3.00	4.00	6.00	8.00
3-12	084454	3	0	2.87	3.83	5.75	7.66
3-1	084455	1	0	3.31	4.42	6.62	8.83
3-3	084455	2	0	4.02	5.37	8.05	10.7
3-7	084455	3	0	3.03	4.03	6.05	8.07
2-7	084456	1	0	10.6	14.2	21.2	28.3
2-9	084456	2	0	10.3	13.7	20.6	27.4
2-10	084456	3	0	10.2	13.6	20.4	27.2
2-3	084457	1	0	4.69	6.25	9.38	12.5
2-5	084457	2	0	4.68	6.24	9.35	12.5
2-6	084457	3	0	4.68	6.25	9.37	12.5
2-2	084458	1	0	1.74	2.31	3.47	4.63
2-4	084458	2	0	1.96	2.62	3.92	5.23
2-8	084458	3	0	1.85	2.47	3.71	4.94

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))**

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	4	084394	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.50	0.55
3	4	084394	1	Schedule (i)	0.834	0.569	10.4	3	-S9	13.0	13.4	13.2	0.80	0.70	0.75
3	4	084394	1	Schedule (i)	1.11	0.759	13.9	3	-S9	24.6	26.1	25.3	0.90	0.80	0.85
3	4	084394	1	Schedule (i)	1.67	1.14	20.9	3	-S9	39.9	45.8	42.8	1.00	1.00	1.00
3	4	084394	1	Schedule (i)	2.22	1.52	27.8	3	-S9	58.0	54.2	56.1	1.10	1.30	1.20
3	6	084394	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.60	0.60
3	6	084394	2	Schedule (i)	0.833	0.569	10.8	3	-S9	13.8	10.9	12.4	0.70	0.60	0.65
3	6	084394	2	Schedule (i)	1.11	0.759	14.4	3	-S9	28.3	27.3	27.8	0.90	0.80	0.85
3	6	084394	2	Schedule (i)	1.67	1.14	21.5	3	-S9	45.7	39.8	42.7	1.10	0.90	1.00
3	6	084394	2	Schedule (i)	2.22	1.52	28.7	3	-S9	60.9	55.5	58.2	1.20	1.20	1.20
3	13	084394	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.50	0.55
3	13	084394	3	Schedule (i)	0.834	0.569	11.1	3	-S9	5.2	8.7	7.0	0.80	0.70	0.75
3	13	084394	3	Schedule (i)	1.11	0.759	14.7	3	-S9	9.3	16.0	12.7	0.90	0.80	0.85
3	13	084394	3	Schedule (i)	1.67	1.14	22.1	3	-S9	30.1	27.7	28.9	1.00	1.00	1.00
3	13	084394	3	Schedule (i)	2.22	1.52	29.5	3	-S9	43.0	38.3	40.7	1.30	1.10	1.20
3	9	084395	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.60	0.55
3	9	084395	1	Schedule (i)	0.834	0.383	11.3	3	-S9	23.4	20.0	21.7	0.60	0.80	0.70
3	9	084395	1	Schedule (i)	1.11	0.511	15.0	3	-S9	33.1	37.1	35.1	0.80	0.90	0.85
3	9	084395	1	Schedule (i)	1.67	0.767	22.5	3	-S9	46.2	47.1	46.7	1.00	1.10	1.05
3	9	084395	1	Schedule (i)	2.22	1.02	30.0	3	-S9	57.9	55.0	56.5	1.10	1.40	1.25
3	11	084395	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.40	0.50
3	11	084395	2	Schedule (i)	0.834	0.383	11.0	3	-S9	9.6	10.1	9.8	0.80	0.50	0.65
3	11	084395	2	Schedule (i)	1.11	0.511	14.7	3	-S9	14.7	19.5	17.1	0.80	0.80	0.80
3	11	084395	2	Schedule (i)	1.67	0.767	22.0	3	-S9	26.9	24.5	25.7	1.00	0.90	0.95
3	11	084395	2	Schedule (i)	2.22	1.02	29.4	3	-S9	35.9	35.2	35.6	1.10	1.00	1.05
3	15	084395	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.50	0.55
3	15	084395	3	Schedule (i)	0.834	0.383	11.8	3	-S9	8.2	5.7	6.9	0.70	0.80	0.75
3	15	084395	3	Schedule (i)	1.11	0.511	15.7	3	-S9	11.4	6.9	9.1	0.80	0.90	0.85
3	15	084395	3	Schedule (i)	1.67	0.767	23.6	3	-S9	17.4	17.1	17.3	1.10	1.00	1.05
3	15	084395	3	Schedule (i)	2.22	1.02	31.4	3	-S9	26.6	32.0	29.3	1.10	1.10	1.10
3	2	084454	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.70	0.60
3	2	084454	1	Schedule (i)	0.834	0.741	3.08	3	-S9	22.8	22.4	22.6	0.70	1.00	0.85
3	2	084454	1	Schedule (i)	1.11	0.988	4.11	3	-S9	36.6	34.7	35.6	0.90	1.20	1.05
3	2	084454	1	Schedule (i)	1.67	1.48	6.16	3	-S9	46.9	50.3	48.6	1.10	1.20	1.15
3	2	084454	1	Schedule (i)	2.22	1.98	8.22	3	-S9	64.1	70.1	67.1	1.40	1.50	1.45

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation**
 (% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	10	084454	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.50	0.50
3	10	084454	2	Schedule (i)	0.834	0.741	3.00	3	-S9	6.9	10.7	8.8	0.70	0.70	0.70
3	10	084454	2	Schedule (i)	1.11	0.988	4.00	3	-S9	16.0	20.8	18.4	0.90	1.00	0.95
3	10	084454	2	Schedule (i)	1.67	1.48	6.00	3	-S9	26.4	26.8	26.6	1.10	1.20	1.15
3	10	084454	2	Schedule (i)	2.22	1.98	8.00	3	-S9	34.7	39.6	37.2	1.30	1.50	1.40
3	12	084454	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.60	0.55
3	12	084454	3	Schedule (i)	0.834	0.741	2.87	3	-S9	6.2	7.2	6.7	0.70	0.80	0.75
3	12	084454	3	Schedule (i)	1.11	0.988	3.83	3	-S9	13.8	10.8	12.3	0.90	0.90	0.90
3	12	084454	3	Schedule (i)	1.67	1.48	5.75	3	-S9	22.6	20.0	21.3	1.20	1.20	1.20
3	12	084454	3	Schedule (i)	2.22	1.98	7.66	3	-S9	29.2	26.7	27.9	1.40	1.30	1.35
3	1	084455	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.50	0.55
3	1	084455	1	Schedule (i)	0.834	0.783	3.31	3	-S9	17.1	23.9	20.5	0.80	0.80	0.80
3	1	084455	1	Schedule (i)	1.11	1.04	4.42	3	-S9	35.7	34.5	35.1	1.00	0.90	0.95
3	1	084455	1	Schedule (i)	1.67	1.57	6.62	3	-S9	54.3	50.7	52.5	1.20	1.30	1.25
3	1	084455	1	Schedule (i)	2.22	2.09	8.83	3	-S9	63.6	69.7	66.6	1.50	1.40	1.45
3	3	084455	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.70	0.65
3	3	084455	2	Schedule (i)	0.834	0.783	4.02	3	-S9	15.7	14.0	14.8	0.80	1.00	0.90
3	3	084455	2	Schedule (i)	1.11	1.04	5.37	3	-S9	36.4	33.1	34.8	1.00	1.10	1.05
3	3	084455	2	Schedule (i)	1.67	1.57	8.05	3	-S9	44.3	45.6	44.9	1.10	1.30	1.20
3	3	084455	2	Schedule (i)	2.22	2.09	10.7	3	-S9	64.3	64.7	64.5	1.40	1.40	1.40
3	7	084455	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.40	0.50	0.45
3	7	084455	3	Schedule (i)	0.833	0.783	3.03	3	-S9	6.7	9.4	8.1	0.60	0.70	0.65
3	7	084455	3	Schedule (i)	1.11	1.04	4.03	3	-S9	17.1	19.3	18.2	1.00	0.90	0.95
3	7	084455	3	Schedule (i)	1.67	1.57	6.05	3	-S9	28.1	28.8	28.4	1.00	1.00	1.00
3	7	084455	3	Schedule (i)	2.22	2.09	8.07	3	-S9	37.1	34.4	35.8	1.10	1.20	1.15
2	7	084456	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.50	0.55
2	7	084456	1	Schedule (i)	0.834	0.372	10.6	3	-S9	22.8	26.0	24.4	0.90	0.80	0.85
2	7	084456	1	Schedule (i)	1.11	0.496	14.2	3	-S9	31.7	34.9	33.3	1.10	0.90	1.00
2	7	084456	1	Schedule (i)	1.67	0.744	21.2	3	-S9	44.8	41.8	43.3	1.20	1.00	1.10
2	7	084456	1	Schedule (i)	2.22	0.992	28.3	3	-S9	60.0	58.2	59.1	1.40	1.30	1.35
2	9	084456	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.50	0.50
2	9	084456	2	Schedule (i)	0.833	0.372	10.3	3	-S9	17.9	16.4	17.1	0.70	0.80	0.75
2	9	084456	2	Schedule (i)	1.11	0.496	13.7	3	-S9	28.5	22.4	25.4	1.10	1.00	1.05
2	9	084456	2	Schedule (i)	1.67	0.744	20.6	3	-S9	32.5	31.9	32.2	1.20	1.10	1.15
2	9	084456	2	Schedule (i)	2.22	0.992	27.4	3	-S9	47.2	42.2	44.7	1.30	1.20	1.25

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation**
 (% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
2	10	084456	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.70	0.65
2	10	084456	3	Schedule (i)	0.834	0.372	10.2	3	-S9	12.3	11.2	11.7	0.70	0.80	0.75
2	10	084456	3	Schedule (i)	1.11	0.496	13.6	3	-S9	19.6	15.5	17.6	0.80	0.90	0.85
2	10	084456	3	Schedule (i)	1.67	0.744	20.4	3	-S9	27.0	24.2	25.6	1.00	1.10	1.05
2	10	084456	3	Schedule (i)	2.22	0.992	27.2	3	-S9	31.3	32.3	31.8	1.20	1.20	1.20
2	3	084457	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.50	0.55
2	3	084457	1	Schedule (i)	0.833	0.803	4.69	3	-S9	17.1	15.8	16.5	0.90	0.80	0.85
2	3	084457	1	Schedule (i)	1.11	1.07	6.25	3	-S9	27.1	28.6	27.9	1.10	1.00	1.05
2	3	084457	1	Schedule (i)	1.67	1.61	9.38	3	-S9	45.0	41.4	43.2	1.60	1.20	1.40
2	3	084457	1	Schedule (i)	2.22	2.14	12.5	3	-S9	54.3	50.4	52.3	1.90	1.40	1.65
2	5	084457	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.50	0.50
2	5	084457	2	Schedule (i)	0.833	0.803	4.68	3	-S9	9.7	19.8	14.8	0.70	0.60	0.65
2	5	084457	2	Schedule (i)	1.11	1.07	6.24	3	-S9	29.2	28.9	29.1	0.80	0.80	0.80
2	5	084457	2	Schedule (i)	1.67	1.61	9.35	3	-S9	38.9	38.8	38.9	1.00	1.00	1.00
2	5	084457	2	Schedule (i)	2.22	2.14	12.5	3	-S9	46.9	52.1	49.5	1.40	1.40	1.40
2	6	084457	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.40	0.40	0.40
2	6	084457	3	Schedule (i)	0.833	0.803	4.68	3	-S9	12.2	10.5	11.3	0.70	0.60	0.65
2	6	084457	3	Schedule (i)	1.11	1.07	6.25	3	-S9	21.8	21.6	21.7	0.80	0.80	0.80
2	6	084457	3	Schedule (i)	1.67	1.61	9.37	3	-S9	34.0	32.7	33.3	0.90	1.00	0.95
2	6	084457	3	Schedule (i)	2.22	2.14	12.5	3	-S9	44.9	41.2	43.0	1.10	1.10	1.10
2	2	084458	1	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.50	0.50
2	2	084458	1	Schedule (i)	0.833	0.790	1.74	3	-S9	9.7	9.4	9.5	0.90	0.70	0.80
2	2	084458	1	Schedule (i)	1.11	1.05	2.31	3	-S9	27.6	26.6	27.1	1.10	0.90	1.00
2	2	084458	1	Schedule (i)	1.67	1.58	3.47	3	-S9	51.0	45.3	48.2	1.40	1.20	1.30
2	2	084458	1	Schedule (i)	2.22	2.11	4.63	3	-S9	58.6	61.9	60.2	1.80	1.60	1.70
2	4	084458	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.60	0.70	0.65
2	4	084458	2	Schedule (i)	0.834	0.791	1.96	3	-S9	17.0	22.4	19.7	0.80	0.80	0.80
2	4	084458	2	Schedule (i)	1.11	1.05	2.62	3	-S9	36.8	35.5	36.2	1.00	1.10	1.05
2	4	084458	2	Schedule (i)	1.67	1.58	3.92	3	-S9	49.1	51.4	50.2	1.10	1.30	1.20
2	4	084458	2	Schedule (i)	2.22	2.11	5.23	3	-S9	62.3	70.1	66.2	1.50	1.50	1.50
2	8	084458	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.50	0.40	0.45
2	8	084458	3	Schedule (i)	0.834	0.791	1.85	3	-S9	12.4	7.5	10.0	0.70	0.70	0.70
2	8	084458	3	Schedule (i)	1.11	1.05	2.47	3	-S9	15.5	13.2	14.4	1.00	0.90	0.95
2	8	084458	3	Schedule (i)	1.67	1.58	3.71	3	-S9	24.2	23.3	23.7	1.20	1.10	1.15
2	8	084458	3	Schedule (i)	2.22	2.11	4.94	3	-S9	33.5	33.3	33.4	1.40	1.30	1.35

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))**

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	4	084394	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.70	0.65
3	4	084394	1	Schedule (ii)	0.834	0.569	10.4	3	+S9	6.8	5.5	6.1	0.70	0.90	0.80
3	4	084394	1	Schedule (ii)	1.11	0.759	13.9	3	+S9	10.5	7.8	9.2	0.90	1.00	0.95
3	4	084394	1	Schedule (ii)	1.67	1.14	20.9	3	+S9	22.6	21.9	22.2	1.00	1.00	1.00
3	4	084394	1	Schedule (ii)	2.22	1.52	27.8	3	+S9	36.8	31.3	34.0	1.10	1.00	1.05
3	6	084394	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.50	0.60	0.55
3	6	084394	2	Schedule (ii)	0.833	0.569	10.8	3	+S9	8.1	11.6	9.9	0.60	0.70	0.65
3	6	084394	2	Schedule (ii)	1.11	0.759	14.4	3	+S9	18.7	20.2	19.4	0.80	0.80	0.80
3	6	084394	2	Schedule (ii)	1.67	1.14	21.5	3	+S9	29.3	28.7	29.0	0.90	0.90	0.90
3	6	084394	2	Schedule (ii)	2.22	1.52	28.7	3	+S9	40.7	43.4	42.0	1.10	1.00	1.05
3	13	084394	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.60	0.60
3	13	084394	3	Schedule (ii)	0.834	0.569	11.1	3	+S9	15.7	8.9	12.3	0.70	0.70	0.70
3	13	084394	3	Schedule (ii)	1.11	0.759	14.7	3	+S9	29.9	22.8	26.3	0.90	0.90	0.90
3	13	084394	3	Schedule (ii)	1.67	1.14	22.1	3	+S9	35.4	33.3	34.4	1.00	0.90	0.95
3	13	084394	3	Schedule (ii)	2.22	1.52	29.5	3	+S9	47.2	46.3	46.8	1.10	1.20	1.15
3	9	084395	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.40	0.70	0.55
3	9	084395	1	Schedule (ii)	0.834	0.383	11.3	3	+S9	11.4	13.3	12.3	0.60	0.80	0.70
3	9	084395	1	Schedule (ii)	1.11	0.511	15.0	3	+S9	16.3	21.9	19.1	0.80	0.80	0.80
3	9	084395	1	Schedule (ii)	1.67	0.767	22.5	3	+S9	30.1	31.3	30.7	0.90	1.00	0.95
3	9	084395	1	Schedule (ii)	2.22	1.02	30.0	3	+S9	37.4	37.5	37.4	1.00	1.00	1.00
3	11	084395	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.70	0.65
3	11	084395	2	Schedule (ii)	0.834	0.383	11.0	3	+S9	8.1	3.6	5.9	0.70	0.80	0.75
3	11	084395	2	Schedule (ii)	1.11	0.511	14.7	3	+S9	12.5	11.7	12.1	0.90	0.90	0.90
3	11	084395	2	Schedule (ii)	1.67	0.767	22.0	3	+S9	26.5	21.9	24.2	0.90	1.00	0.95
3	11	084395	2	Schedule (ii)	2.22	1.02	29.4	3	+S9	29.4	30.7	30.0	1.00	1.00	1.00
3	15	084395	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.50	0.70	0.60
3	15	084395	3	Schedule (ii)	0.834	0.383	11.8	3	+S9	15.4	4.0	9.7	0.60	0.80	0.70
3	15	084395	3	Schedule (ii)	1.11	0.511	15.7	3	+S9	20.0	21.6	20.8	0.80	0.90	0.85
3	15	084395	3	Schedule (ii)	1.67	0.767	23.6	3	+S9	35.4	28.0	31.7	0.90	1.00	0.95
3	15	084395	3	Schedule (ii)	2.22	1.02	31.4	3	+S9	43.1	42.4	42.7	1.00	1.10	1.05
3	2	084454	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.50	0.70	0.60
3	2	084454	1	Schedule (ii)	0.834	0.741	3.08	3	+S9	9.4	10.3	9.8	0.70	0.80	0.75
3	2	084454	1	Schedule (ii)	1.11	0.988	4.11	3	+S9	26.6	27.8	27.2	0.90	0.90	0.90
3	2	084454	1	Schedule (ii)	1.67	1.48	6.16	3	+S9	39.8	35.7	37.8	1.00	1.10	1.05
3	2	084454	1	Schedule (ii)	2.22	1.98	8.22	3	+S9	47.7	50.0	48.8	1.20	1.20	1.20

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))**

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	10	084454	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.50	0.55
3	10	084454	2	Schedule (ii)	0.834	0.741	3.00	3	+S9	2.9	3.6	3.3	0.60	0.60	0.60
3	10	084454	2	Schedule (ii)	1.11	0.988	4.00	3	+S9	10.1	7.3	8.7	0.70	0.80	0.75
3	10	084454	2	Schedule (ii)	1.67	1.48	6.00	3	+S9	23.0	21.2	22.1	0.90	1.00	0.95
3	10	084454	2	Schedule (ii)	2.22	1.98	8.00	3	+S9	26.6	27.7	27.2	1.10	1.20	1.15
3	12	084454	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.70	0.50	0.60
3	12	084454	3	Schedule (ii)	0.834	0.741	2.87	3	+S9	6.6	5.6	6.1	0.80	0.70	0.75
3	12	084454	3	Schedule (ii)	1.11	0.988	3.83	3	+S9	9.9	11.3	10.6	1.00	0.90	0.95
3	12	084454	3	Schedule (ii)	1.67	1.48	5.75	3	+S9	28.9	29.0	29.0	1.10	1.00	1.05
3	12	084454	3	Schedule (ii)	2.22	1.98	7.66	3	+S9	37.2	41.1	39.2	1.20	1.30	1.25
3	1	084455	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.70	0.65
3	1	084455	1	Schedule (ii)	0.834	0.783	3.31	3	+S9	17.5	16.4	16.9	0.80	0.80	0.80
3	1	084455	1	Schedule (ii)	1.11	1.04	4.42	3	+S9	33.3	27.9	30.6	0.90	0.90	0.90
3	1	084455	1	Schedule (ii)	1.67	1.57	6.62	3	+S9	42.1	36.9	39.5	1.00	1.00	1.00
3	1	084455	1	Schedule (ii)	2.22	2.09	8.83	3	+S9	54.0	50.8	52.4	1.10	1.10	1.10
3	3	084455	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.50	0.55
3	3	084455	2	Schedule (ii)	0.834	0.783	4.02	3	+S9	9.4	16.5	13.0	0.80	0.70	0.75
3	3	084455	2	Schedule (ii)	1.11	1.04	5.37	3	+S9	23.4	27.8	25.6	0.80	0.80	0.80
3	3	084455	2	Schedule (ii)	1.67	1.57	8.05	3	+S9	32.0	33.1	32.6	0.90	0.90	0.90
3	3	084455	2	Schedule (ii)	2.22	2.09	10.7	3	+S9	40.6	42.9	41.7	1.20	1.10	1.15
3	7	084455	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.50	0.50	0.50
3	7	084455	3	Schedule (ii)	0.833	0.783	3.03	3	+S9	17.1	17.7	17.4	0.70	0.70	0.70
3	7	084455	3	Schedule (ii)	1.11	1.04	4.03	3	+S9	24.8	29.8	27.3	0.90	0.90	0.90
3	7	084455	3	Schedule (ii)	1.67	1.57	6.05	3	+S9	36.8	41.9	39.3	1.00	1.00	1.00
3	7	084455	3	Schedule (ii)	2.22	2.09	8.07	3	+S9	48.7	47.6	48.1	1.10	1.10	1.10
2	7	084456	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.70	0.60	0.65
2	7	084456	1	Schedule (ii)	0.834	0.372	10.6	3	+S9	14.7	13.1	13.9	0.80	0.70	0.75
2	7	084456	1	Schedule (ii)	1.11	0.496	14.2	3	+S9	25.7	23.8	24.8	0.90	0.80	0.85
2	7	084456	1	Schedule (ii)	1.67	0.744	21.2	3	+S9	27.2	28.5	27.8	1.00	1.00	1.00
2	7	084456	1	Schedule (ii)	2.22	0.992	28.3	3	+S9	34.6	30.8	32.7	1.10	1.10	1.10
2	9	084456	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.70	0.65
2	9	084456	2	Schedule (ii)	0.833	0.372	10.3	3	+S9	10.0	5.5	7.8	0.70	0.70	0.70
2	9	084456	2	Schedule (ii)	1.11	0.496	13.7	3	+S9	14.7	15.9	15.3	0.90	0.80	0.85
2	9	084456	2	Schedule (ii)	1.67	0.744	20.6	3	+S9	27.3	22.8	25.0	1.00	0.80	0.90
2	9	084456	2	Schedule (ii)	2.22	0.992	27.4	3	+S9	34.0	31.0	32.5	1.10	1.00	1.05

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))**

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (µg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
2	10	084456	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.50	0.60	0.55
2	10	084456	3	Schedule (ii)	0.834	0.372	10.2	3	+S9	13.3	19.7	16.5	0.70	0.70	0.70
2	10	084456	3	Schedule (ii)	1.11	0.496	13.6	3	+S9	22.1	29.9	26.0	0.80	0.90	0.85
2	10	084456	3	Schedule (ii)	1.67	0.744	20.4	3	+S9	34.5	33.3	33.9	0.90	1.00	0.95
2	10	084456	3	Schedule (ii)	2.22	0.992	27.2	3	+S9	46.0	51.3	48.6	1.00	1.10	1.05
2	3	084457	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.70	0.70	0.70
2	3	084457	1	Schedule (ii)	0.833	0.803	4.69	3	+S9	6.2	5.6	5.9	0.80	0.80	0.80
2	3	084457	1	Schedule (ii)	1.11	1.07	6.25	3	+S9	16.3	16.7	16.5	0.90	0.90	0.90
2	3	084457	1	Schedule (ii)	1.67	1.61	9.38	3	+S9	20.2	21.4	20.8	1.10	1.00	1.05
2	3	084457	1	Schedule (ii)	2.22	2.14	12.5	3	+S9	27.9	25.4	26.7	1.20	1.20	1.20
2	5	084457	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.70	0.60	0.65
2	5	084457	2	Schedule (ii)	0.833	0.803	4.68	3	+S9	2.1	8.3	5.2	0.80	0.80	0.80
2	5	084457	2	Schedule (ii)	1.11	1.07	6.24	3	+S9	14.3	20.1	17.2	1.00	0.90	0.95
2	5	084457	2	Schedule (ii)	1.67	1.61	9.35	3	+S9	20.7	24.3	22.5	1.10	1.10	1.10
2	5	084457	2	Schedule (ii)	2.22	2.14	12.5	3	+S9	24.3	29.9	27.1	1.20	1.30	1.25
2	6	084457	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.60	0.60
2	6	084457	3	Schedule (ii)	0.833	0.803	4.68	3	+S9	5.6	15.9	10.8	0.80	0.70	0.75
2	6	084457	3	Schedule (ii)	1.11	1.07	6.25	3	+S9	23.4	21.2	22.3	0.90	0.90	0.90
2	6	084457	3	Schedule (ii)	1.67	1.61	9.37	3	+S9	33.1	34.1	33.6	1.10	1.00	1.05
2	6	084457	3	Schedule (ii)	2.22	2.14	12.5	3	+S9	41.9	48.5	45.2	1.30	1.20	1.25
2	2	084458	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.70	0.60	0.65
2	2	084458	1	Schedule (ii)	0.833	0.790	1.74	3	+S9	6.1	5.4	5.7	0.90	0.80	0.85
2	2	084458	1	Schedule (ii)	1.11	1.05	2.31	3	+S9	10.7	8.5	9.6	1.20	1.10	1.15
2	2	084458	1	Schedule (ii)	1.67	1.58	3.47	3	+S9	14.5	15.4	14.9	1.40	1.30	1.35
2	2	084458	1	Schedule (ii)	2.22	2.11	4.63	3	+S9	23.7	19.2	21.4	1.60	1.50	1.55
2	4	084458	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.60	0.60
2	4	084458	2	Schedule (ii)	0.834	0.791	1.96	3	+S9	6.9	8.2	7.5	0.80	0.80	0.80
2	4	084458	2	Schedule (ii)	1.11	1.05	2.62	3	+S9	12.2	12.7	12.5	1.00	0.90	0.95
2	4	084458	2	Schedule (ii)	1.67	1.58	3.92	3	+S9	13.0	17.2	15.1	1.10	1.10	1.10
2	4	084458	2	Schedule (ii)	2.22	2.11	5.23	3	+S9	29.8	34.3	32.0	1.30	1.40	1.35
2	8	084458	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.60	0.60
2	8	084458	3	Schedule (ii)	0.834	0.791	1.85	3	+S9	13.5	15.3	14.4	0.80	0.80	0.80
2	8	084458	3	Schedule (ii)	1.11	1.05	2.47	3	+S9	27.0	32.4	29.7	0.90	0.90	0.90
2	8	084458	3	Schedule (ii)	1.67	1.58	3.71	3	+S9	45.9	40.5	43.2	1.10	1.10	1.10
2	8	084458	3	Schedule (ii)	2.22	2.11	4.94	3	+S9	52.3	46.8	49.5	1.30	1.40	1.35

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262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

Period: November 28 - December 17, 2008

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(Assay Information)**

Sample ID	Replicate Number	Assay Date	Treatment Schedule	Metabolic Activation	Treatment (hours)	Recovery (hours)	Before Treatment (Cells (x10 ⁵) per mL)		Negative Control (Cells (x10 ⁵) per mL)		Increase > 90%	
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1	Flask 2
084394	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	2.00	7.44	7.68	≥ 90%	≥ 90%
084394	2	04-Nov-08	Schedule (i)	-S9	3	27	1.92	2.08	7.44	7.20	≥ 90%	≥ 90%
084394	3	05-Nov-08	Schedule (i)	-S9	3	27	2.12	2.04	9.84	10.28	≥ 90%	≥ 90%
084395	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.72	7.56	≥ 90%	≥ 90%
084395	2	04-Nov-08	Schedule (i)	-S9	3	27	1.96	1.96	8.20	8.32	≥ 90%	≥ 90%
084395	3	05-Nov-08	Schedule (i)	-S9	3	27	2.04	2.04	9.40	9.04	≥ 90%	≥ 90%
084454	1	28-Nov-08	Schedule (i)	-S9	3	27	1.96	1.96	7.76	7.84	≥ 90%	≥ 90%
084454	2	04-Nov-08	Schedule (i)	-S9	3	27	2.08	2.04	7.84	8.00	≥ 90%	≥ 90%
084454	3	05-Nov-08	Schedule (i)	-S9	3	27	2.08	2.04	9.88	9.84	≥ 90%	≥ 90%
084455	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.52	7.64	≥ 90%	≥ 90%
084455	2	04-Nov-08	Schedule (i)	-S9	3	27	2.04	1.96	7.64	7.40	≥ 90%	≥ 90%
084455	3	05-Nov-08	Schedule (i)	-S9	3	27	2.08	2.12	10.48	10.60	≥ 90%	≥ 90%
084456	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.72	7.80	≥ 90%	≥ 90%
084456	2	04-Nov-08	Schedule (i)	-S9	3	27	1.96	2.08	6.88	6.72	≥ 90%	≥ 90%
084456	3	05-Nov-08	Schedule (i)	-S9	3	27	2.12	2.04	8.64	8.48	≥ 90%	≥ 90%
084457	1	28-Nov-08	Schedule (i)	-S9	3	27	1.96	2.00	7.56	7.32	≥ 90%	≥ 90%
084457	2	04-Nov-08	Schedule (i)	-S9	3	27	2.04	1.96	6.56	6.80	≥ 90%	≥ 90%
084457	3	05-Nov-08	Schedule (i)	-S9	3	27	2.00	2.12	8.24	8.24	≥ 90%	≥ 90%
084458	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.72	7.52	≥ 90%	≥ 90%
084458	2	04-Nov-08	Schedule (i)	-S9	3	27	1.96	2.08	6.20	6.36	≥ 90%	≥ 90%
084458	3	05-Nov-08	Schedule (i)	-S9	3	27	2.08	2.00	8.52	8.36	≥ 90%	≥ 90%

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***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(Assay Information)**

Sample ID	Replicate Number	Assay Date	Treatment Schedule	Metabolic Activation	Treatment (hours)	Recovery (hours)	Before Treatment (Cells (x10 ⁵) per mL)		Negative Control (Cells (x10 ⁵) per mL)		Increase > 90%	
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1	Flask 2
084394	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.04	7.36	7.16	≥ 90%	≥ 90%
084394	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.00	7.00	7.16	≥ 90%	≥ 90%
084394	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.00	7.12	6.92	≥ 90%	≥ 90%
084395	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.12	2.12	7.04	7.24	≥ 90%	≥ 90%
084395	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.04	1.92	7.48	7.40	≥ 90%	≥ 90%
084395	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	1.96	7.20	6.96	≥ 90%	≥ 90%
084454	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.00	7.20	7.04	≥ 90%	≥ 90%
084454	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.00	2.04	7.56	7.52	≥ 90%	≥ 90%
084454	3	17-Dec-08	Schedule (ii)	+S9	3	27	1.96	1.96	6.80	6.92	≥ 90%	≥ 90%
084455	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.04	7.08	6.92	≥ 90%	≥ 90%
084455	2	12-Dec-08	Schedule (ii)	+S9	3	27	1.96	2.00	7.08	7.32	≥ 90%	≥ 90%
084455	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.04	1.96	6.72	6.92	≥ 90%	≥ 90%
084456	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.12	7.52	7.32	≥ 90%	≥ 90%
084456	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.12	8.08	7.92	≥ 90%	≥ 90%
084456	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	2.04	6.52	6.72	≥ 90%	≥ 90%
084457	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.08	7.20	7.12	≥ 90%	≥ 90%
084457	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.08	7.64	7.84	≥ 90%	≥ 90%
084457	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	1.96	6.96	7.24	≥ 90%	≥ 90%
084458	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.00	7.32	7.20	≥ 90%	≥ 90%
084458	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.12	2.16	7.36	7.52	≥ 90%	≥ 90%
084458	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	2.00	6.44	6.44	≥ 90%	≥ 90%

Sample ID	Sample Description
084394	Camel SNUS Frost
084395	2S3 Research Moist smokeless tobacco
084396	Kentucky Reference 2R4F
084454	Fresh Strips
084455	Mellow Sticks
084456	Copenhagen Long Cut
084457	Ariva Wintergreen
084458	Fresh Orbs
control	Kentucky Reference 3R4F

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**Positive and Negative Controls for *In Vitro* Micronucleus Assay with (+) and without (-) S9 Metabolic Activation
(Observations per flask)**

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration (µg/mL)	Flask Number 1				Flask Number 2			
						Normal Cells	MN Cells	No. of MN	cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	cells (x10 ⁵ /mL)
Negative Control (-)	28-Nov-08	Schedule (i)	3	-S9		995	5	5	7.72	995	5	5	7.52
	28-Nov-08	Schedule (i)	3	-S9		994	6	6	7.72	995	5	5	7.80
	28-Nov-08	Schedule (i)	3	-S9		995	5	5	7.76	994	6	7	7.84
	28-Nov-08	Schedule (i)	3	-S9		995	5	5	7.72	994	6	6	7.56
	04-Dec-08	Schedule (i)	3	-S9		994	6	6	6.20	993	7	7	6.36
	04-Dec-08	Schedule (i)	3	-S9		995	5	5	6.88	995	5	5	6.72
	04-Dec-08	Schedule (i)	3	-S9		994	6	6	7.44	995	5	6	7.20
	04-Dec-08	Schedule (i)	3	-S9		994	6	6	8.20	996	4	4	8.32
	05-Dec-08	Schedule (i)	3	-S9		996	4	4	8.24	996	4	4	8.24
	05-Dec-08	Schedule (i)	3	-S9		994	6	6	8.64	993	7	7	8.48
	05-Dec-08	Schedule (i)	3	-S9		996	4	5	9.88	994	6	6	9.84
	05-Dec-08	Schedule (i)	3	-S9		994	6	6	9.40	995	5	5	9.04
	11-Dec-08	Schedule (ii)	3	+S9		993	7	7	7.32	994	6	6	7.20
	11-Dec-08	Schedule (ii)	3	+S9		993	7	7	7.52	994	6	6	7.32
	11-Dec-08	Schedule (ii)	3	+S9		995	5	5	7.20	993	7	7	7.04
	11-Dec-08	Schedule (ii)	3	+S9		996	4	4	7.04	993	7	7	7.24
	12-Dec-08	Schedule (ii)	3	+S9		994	6	6	7.36	994	6	6	7.52
	12-Dec-08	Schedule (ii)	3	+S9		994	6	6	8.08	993	7	7	7.92
	12-Dec-08	Schedule (ii)	3	+S9		995	5	5	7.00	994	6	6	7.16
	12-Dec-08	Schedule (ii)	3	+S9		994	6	6	7.48	993	7	7	7.40
	17-Dec-08	Schedule (ii)	3	+S9		994	6	6	6.96	994	6	6	7.24
	17-Dec-08	Schedule (ii)	3	+S9		995	5	5	6.52	994	6	6	6.72
	17-Dec-08	Schedule (ii)	3	+S9		993	7	7	6.80	995	5	5	6.92
	17-Dec-08	Schedule (ii)	3	+S9		995	5	5	7.20	993	7	7	6.96

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**Positive and Negative Controls for *In Vitro* Micronucleus Assay with (+) and without (-) S9 Metabolic Activation
(Observations per flask)**

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration (µg/mL)	Flask Number 1				Flask Number 2			
						Normal Cells	MN Cells	No. of MN	cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	cells (x10 ⁵ /mL)
Positive Control (+)													
Mitomycin C	28-Nov-08	Schedule (i)	3	-S9	2	841	159	175	3.96	830	170	183	4.24
	28-Nov-08	Schedule (i)	3	-S9	2	837	163	187	4.40	833	167	179	4.08
	28-Nov-08	Schedule (i)	3	-S9	2	840	160	175	4.52	842	158	173	4.68
	28-Nov-08	Schedule (i)	3	-S9	2	839	161	185	4.20	841	159	177	4.28
	04-Dec-08	Schedule (i)	3	-S9	2	837	163	187	3.84	840	160	178	3.60
	04-Dec-08	Schedule (i)	3	-S9	2	835	165	184	4.08	838	162	182	4.04
	04-Dec-08	Schedule (i)	3	-S9	2	835	165	173	4.12	837	163	178	4.12
	04-Dec-08	Schedule (i)	3	-S9	2	843	157	173	4.16	838	162	178	4.44
	05-Dec-08	Schedule (i)	3	-S9	2	836	164	184	4.68	836	164	181	4.76
	05-Dec-08	Schedule (i)	3	-S9	2	832	168	182	4.92	835	165	177	4.60
	05-Dec-08	Schedule (i)	3	-S9	2	841	159	181	5.08	838	162	178	4.84
	05-Dec-08	Schedule (i)	3	-S9	2	840	160	184	4.56	842	158	181	4.44
Colchicine	28-Nov-08	Schedule (i)	3	-S9	2	909	91	95	2.56	904	96	103	2.64
	28-Nov-08	Schedule (i)	3	-S9	2	907	93	108	2.76	909	91	104	2.60
	28-Nov-08	Schedule (i)	3	-S9	2	909	91	101	2.28	908	92	100	2.52
	28-Nov-08	Schedule (i)	3	-S9	2	909	91	104	2.12	907	93	103	2.32
	04-Dec-08	Schedule (i)	3	-S9	2	908	92	103	1.96	911	89	107	1.88
	04-Dec-08	Schedule (i)	3	-S9	2	910	90	102	1.88	908	92	102	1.64
	04-Dec-08	Schedule (i)	3	-S9	2	912	88	94	2.16	909	91	98	2.16
	04-Dec-08	Schedule (i)	3	-S9	2	910	90	100	2.36	905	95	103	2.60
	05-Dec-08	Schedule (i)	3	-S9	2	912	88	96	2.28	908	92	102	2.12
	05-Dec-08	Schedule (i)	3	-S9	2	904	96	101	2.44	916	84	98	2.64
	05-Dec-08	Schedule (i)	3	-S9	2	910	90	99	2.44	910	90	100	2.56
	05-Dec-08	Schedule (i)	3	-S9	2	910	90	100	2.36	907	93	102	2.32

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**Positive and Negative Controls for *In Vitro* Micronucleus Assay with (+) and without (-) S9 Metabolic Activation
(Observations per flask)**

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration (µg/mL)	Flask Number 1				Flask Number 2			
						Normal Cells	MN Cells	No. of MN	cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	cells (x10 ⁵ /mL)
Cyclophosphamide	11-Dec-08	Schedule (ii)	3	+S9	7.5	968	32	35	4.28	968	32	35	4.08
	11-Dec-08	Schedule (ii)	3	+S9	7.5	968	32	32	3.96	969	31	36	4.08
	11-Dec-08	Schedule (ii)	3	+S9	7.5	969	31	34	4.20	964	36	36	4.32
	11-Dec-08	Schedule (ii)	3	+S9	7.5	970	30	32	4.04	971	29	31	4.08
	12-Dec-08	Schedule (ii)	3	+S9	7.5	968	32	34	4.04	968	32	33	4.00
	12-Dec-08	Schedule (ii)	3	+S9	7.5	968	32	32	4.20	968	32	34	4.36
	12-Dec-08	Schedule (ii)	3	+S9	7.5	969	31	32	4.12	967	33	35	4.24
	12-Dec-08	Schedule (ii)	3	+S9	7.5	970	30	32	4.08	970	30	34	3.96
	17-Dec-08	Schedule (ii)	3	+S9	7.5	969	31	32	4.56	971	29	32	4.32
	17-Dec-08	Schedule (ii)	3	+S9	7.5	970	30	33	4.36	967	33	35	4.52
	17-Dec-08	Schedule (ii)	3	+S9	7.5	969	31	35	4.48	969	31	33	4.40
	17-Dec-08	Schedule (ii)	3	+S9	7.5	969	31	34	4.36	969	31	32	4.20

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262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

Period: November 28 - December 17, 2008

**Positive and Negative Controls for *In Vitro* Micronucleus Assay with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity)**

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration (µg/mL)	% Cytotoxicity			% Micronuclei				
						Flask 1	Flask 2	Average	Flask 1	QC	Flask 2	QC	Average
Negative Control (-)	28-Nov-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.500	< 2.5% MN	0.500
	28-Nov-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.500	< 2.5% MN	0.550
	28-Nov-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.700	< 2.5% MN	0.600
	28-Nov-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.600	< 2.5% MN	0.550
	04-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.700	< 2.5% MN	0.650
	04-Dec-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.500	< 2.5% MN	0.500
	04-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.600	< 2.5% MN	0.600
	04-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.400	< 2.5% MN	0.500
	05-Dec-08	Schedule (i)	3	-S9					0.400	< 2.5% MN	0.400	< 2.5% MN	0.400
	05-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.700	< 2.5% MN	0.650
	05-Dec-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.600	< 2.5% MN	0.550
	05-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.500	< 2.5% MN	0.550
	11-Dec-08	Schedule (ii)	3	+S9					0.700	< 2.5% MN	0.600	< 2.5% MN	0.650
	11-Dec-08	Schedule (ii)	3	+S9					0.700	< 2.5% MN	0.600	< 2.5% MN	0.650
	11-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.700	< 2.5% MN	0.600
	11-Dec-08	Schedule (ii)	3	+S9					0.400	< 2.5% MN	0.700	< 2.5% MN	0.550
	12-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.600	< 2.5% MN	0.600
	12-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.700	< 2.5% MN	0.650
	12-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.600	< 2.5% MN	0.550
	12-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.700	< 2.5% MN	0.650
	17-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.600	< 2.5% MN	0.600
	17-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.600	< 2.5% MN	0.550
	17-Dec-08	Schedule (ii)	3	+S9					0.700	< 2.5% MN	0.500	< 2.5% MN	0.600
	17-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.700	< 2.5% MN	0.600

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**Positive and Negative Controls for *In Vitro* Micronucleus Assay with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity)**

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration (µg/mL)	% Cytotoxicity			% Micronuclei				
						Flask 1	Flask 2	Average	Flask 1	QC	Flask 2	QC	Average
Positive Control (+)													
Mitomycin C	28-Nov-08	Schedule (i)	3	-S9	2	48.7	43.6	46.2	17.5	0.868	18.3	0.243	17.9
	28-Nov-08	Schedule (i)	3	-S9	2	43.0	47.7	45.3	18.7	0.067	17.9	0.617	18.3
	28-Nov-08	Schedule (i)	3	-S9	2	41.8	40.3	41.0	17.5	0.868	17.3	0.617	17.4
	28-Nov-08	Schedule (i)	3	-S9	2	45.6	43.4	44.5	18.5	0.134	17.7	0.868	18.1
	04-Dec-08	Schedule (i)	3	-S9	2	38.1	43.4	40.7	18.7	0.067	17.8	0.739	18.3
	04-Dec-08	Schedule (i)	3	-S9	2	40.7	39.9	40.3	18.4	0.182	18.2	0.317	18.3
	04-Dec-08	Schedule (i)	3	-S9	2	44.6	42.8	43.7	17.3	0.617	17.8	0.739	17.6
	04-Dec-08	Schedule (i)	3	-S9	2	49.3	46.6	48.0	17.3	0.617	17.8	0.739	17.6
	05-Dec-08	Schedule (i)	3	-S9	2	43.2	42.2	42.7	18.4	0.182	18.1	0.405	18.3
	05-Dec-08	Schedule (i)	3	-S9	2	43.1	45.8	44.4	18.2	0.317	17.7	0.868	18.0
	05-Dec-08	Schedule (i)	3	-S9	2	48.6	50.8	49.7	18.1	0.405	17.8	0.739	18.0
	05-Dec-08	Schedule (i)	3	-S9	2	51.5	50.9	51.2	18.4	0.182	18.1	0.405	18.3
Colchicine	28-Nov-08	Schedule (i)	3	-S9	2	66.8	64.9	65.9	9.5	0.046	10.3	1.000	9.9
	28-Nov-08	Schedule (i)	3	-S9	2	64.2	66.7	65.5	10.8	0.211	10.4	0.803	10.6
	28-Nov-08	Schedule (i)	3	-S9	2	70.6	67.9	69.2	10.1	0.617	10.0	0.453	10.1
	28-Nov-08	Schedule (i)	3	-S9	2	72.5	69.3	70.9	10.4	0.803	10.3	1.000	10.4
	04-Dec-08	Schedule (i)	3	-S9	2	68.4	70.4	69.4	10.3	1.000	10.7	0.317	10.5
	04-Dec-08	Schedule (i)	3	-S9	2	72.7	75.6	74.1	10.2	0.803	10.2	0.803	10.2
	04-Dec-08	Schedule (i)	3	-S9	2	71.0	70.0	70.5	9.4	0.024	9.8	0.211	9.6
	04-Dec-08	Schedule (i)	3	-S9	2	71.2	68.8	70.0	10.0	0.453	10.3	1.000	10.2
	05-Dec-08	Schedule (i)	3	-S9	2	72.3	74.3	73.3	9.6	0.080	10.2	0.803	9.9
	05-Dec-08	Schedule (i)	3	-S9	2	71.8	68.9	70.3	10.1	0.617	9.8	0.211	10.0
	05-Dec-08	Schedule (i)	3	-S9	2	75.3	74.0	74.6	9.9	0.317	10.0	0.453	10.0
	05-Dec-08	Schedule (i)	3	-S9	2	74.9	74.3	74.6	10.0	0.453	10.2	0.803	10.1

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262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

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**Positive and Negative Controls for *In Vitro* Micronucleus Assay with (+) and without (-) S9 Metabolic Activation
(% Micronuclei and % Cytotoxicity)**

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration (µg/mL)	% Cytotoxicity			% Micronuclei				
						Flask 1	Flask 2	Average	Flask 1	QC	Flask 2	QC	Average
Cyclophosphamide	11-Dec-08	Schedule (ii)	3	+S9	7.5	41.5	43.3	42.4	3.5	0.617	3.5	0.617	3.5
	11-Dec-08	Schedule (ii)	3	+S9	7.5	47.3	44.3	45.8	3.2	0.317	3.6	0.317	3.4
	11-Dec-08	Schedule (ii)	3	+S9	7.5	41.7	38.6	40.2	3.4	1.000	3.6	0.317	3.5
	11-Dec-08	Schedule (ii)	3	+S9	7.5	42.6	43.6	43.1	3.2	0.317	3.1	0.134	3.2
	12-Dec-08	Schedule (ii)	3	+S9	7.5	45.1	46.8	46.0	3.4	1.000	3.3	0.617	3.4
	12-Dec-08	Schedule (ii)	3	+S9	7.5	48.0	44.9	46.5	3.2	0.317	3.4	1.000	3.3
	12-Dec-08	Schedule (ii)	3	+S9	7.5	41.1	40.8	41.0	3.2	0.317	3.5	0.617	3.4
	12-Dec-08	Schedule (ii)	3	+S9	7.5	45.5	46.5	46.0	3.2	0.317	3.4	1.000	3.3
	17-Dec-08	Schedule (ii)	3	+S9	7.5	34.5	40.3	37.4	3.2	0.317	3.2	0.317	3.2
	17-Dec-08	Schedule (ii)	3	+S9	7.5	33.1	32.7	32.9	3.3	0.617	3.5	0.617	3.4
	17-Dec-08	Schedule (ii)	3	+S9	7.5	34.1	36.4	35.3	3.5	0.617	3.3	0.617	3.4
	17-Dec-08	Schedule (ii)	3	+S9	7.5	39.4	39.7	39.5	3.4	1.000	3.2	0.317	3.3

Control Substance	[Conc] (µg/mL)	Expected Values	
		Mean	Std. Dev.
Mitomycin C	2	17.6	0.6
Mitomycin C	0.5	13.7	0.4
Colchicine	2	10.3	0.4
Colchicine	0.5	9.30	0.40
Cyclophosphamide	7.5	3.40	0.20

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation**
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))

Sample ID	Replicate Number	Treatment Schedule	TPM (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)	% Micronuclei
						Flask 1	Flask 1
control	1	Schedule (i)	0	3	-S9	0	0.60
control	1	Schedule (i)	0.075	3	-S9	20.5	0.80
control	1	Schedule (i)	0.100	3	-S9	30.8	1.10
control	1	Schedule (i)	0.150	3	-S9	40.4	1.30
control	1	Schedule (i)	0.200	3	-S9	55.5	1.60
control	2	Schedule (i)	0	3	-S9	0	0.50
control	2	Schedule (i)	0.075	3	-S9	16.9	0.90
control	2	Schedule (i)	0.100	3	-S9	35.1	1.10
control	2	Schedule (i)	0.150	3	-S9	39.9	1.30
control	2	Schedule (i)	0.200	3	-S9	52.0	1.70
control	3	Schedule (i)	0	3	-S9	0	0.70
control	3	Schedule (i)	0.075	3	-S9	16.2	0.80
control	3	Schedule (i)	0.100	3	-S9	36.0	1.20
control	3	Schedule (i)	0.150	3	-S9	51.4	1.40
control	3	Schedule (i)	0.200	3	-S9	79.3	1.60
control	4	Schedule (i)	0	3	-S9	0	0.50
control	4	Schedule (i)	0.075	3	-S9	9.8	0.80
control	4	Schedule (i)	0.100	3	-S9	26.3	1.10
control	4	Schedule (i)	0.150	3	-S9	44.4	1.40
control	4	Schedule (i)	0.200	3	-S9	66.9	1.70
control	5	Schedule (i)	0	3	-S9	0	0.50
control	5	Schedule (i)	0.075	3	-S9	11.3	0.70
control	5	Schedule (i)	0.100	3	-S9	24.8	0.90
control	5	Schedule (i)	0.150	3	-S9	38.3	1.30
control	5	Schedule (i)	0.200	3	-S9	60.3	1.50
control	6	Schedule (i)	0	3	-S9	0	0.50
control	6	Schedule (i)	0.075	3	-S9	8.5	0.70
control	6	Schedule (i)	0.100	3	-S9	16.5	1.00
control	6	Schedule (i)	0.150	3	-S9	37.2	1.30
control	6	Schedule (i)	0.200	3	-S9	55.3	1.50

***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation**
(% Micronuclei and % Cytotoxicity as determined by Relative Increase in Cell Counts (RICC))

Sample ID	Replicate Number	Treatment Schedule	TPM (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity (by RICC)	% Micronuclei
						Flask 1	Flask 1
control	1	Schedule (ii)	0	3	+S9	0	0.50
control	1	Schedule (ii)	0.075	3	+S9	10.9	0.70
control	1	Schedule (ii)	0.100	3	+S9	15.2	0.90
control	1	Schedule (ii)	0.150	3	+S9	23.9	1.00
control	1	Schedule (ii)	0.200	3	+S9	38.4	1.30
control	2	Schedule (ii)	0	3	+S9	0	0.70
control	2	Schedule (ii)	0.075	3	+S9	9.9	0.70
control	2	Schedule (ii)	0.100	3	+S9	22.1	0.90
control	2	Schedule (ii)	0.150	3	+S9	29.0	1.00
control	2	Schedule (ii)	0.200	3	+S9	42.7	1.40
control	3	Schedule (ii)	0	3	+S9	0	0.70
control	3	Schedule (ii)	0.075	3	+S9	7.7	0.80
control	3	Schedule (ii)	0.100	3	+S9	18.6	0.80
control	3	Schedule (ii)	0.150	3	+S9	30.1	1.20
control	3	Schedule (ii)	0.200	3	+S9	37.8	1.30
control	4	Schedule (ii)	0	3	+S9	0	0.70
control	4	Schedule (ii)	0.075	3	+S9	9.8	0.80
control	4	Schedule (ii)	0.100	3	+S9	19.0	0.90
control	4	Schedule (ii)	0.150	3	+S9	32.7	1.10
control	4	Schedule (ii)	0.200	3	+S9	40.5	1.30
control	5	Schedule (ii)	0	3	+S9	0	0.60
control	5	Schedule (ii)	0.075	3	+S9	12.2	0.70
control	5	Schedule (ii)	0.100	3	+S9	23.7	0.90
control	5	Schedule (ii)	0.150	3	+S9	36.0	1.10
control	5	Schedule (ii)	0.200	3	+S9	47.5	1.30
control	6	Schedule (ii)	0	3	+S9	0	0.60
control	6	Schedule (ii)	0.075	3	+S9	10.5	0.70
control	6	Schedule (ii)	0.100	3	+S9	20.3	0.90
control	6	Schedule (ii)	0.150	3	+S9	28.6	1.10
control	6	Schedule (ii)	0.200	3	+S9	41.4	1.50

LABSTAT INTERNATIONAL ULC

262 Manitou Drive, Kitchener, Ontario, Canada N2C 1L3

Phone (519) 748-5409 FAX (519) 748-1654

Project: M100

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***In Vitro* Micronucleus Assay of CHO cells with (+) and without (-) S9 Metabolic Activation
(Assay Information)**

Sample ID	Replicate Number	Assay Date	Treatment Schedule	Metabolic Activation	Treatment (hours)	Recovery (hours)	Before Treatment (Cells (x10 ⁵) per mL)		Negative Control (Cells (x10 ⁵) per mL)		Increase > 90%	
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1	Flask 2
control	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92		7.76		≥ 90%	
control	2	28-Nov-08	Schedule (i)	-S9	3	27	1.96		7.88		≥ 90%	
control	3	04-Dec-08	Schedule (i)	-S9	3	27	1.96		6.40		≥ 90%	
control	4	04-Dec-08	Schedule (i)	-S9	3	27	1.96		7.28		≥ 90%	
control	5	05-Dec-08	Schedule (i)	-S9	3	27	2.08		7.72		≥ 90%	
control	6	05-Dec-08	Schedule (i)	-S9	3	27	2.08		9.60		≥ 90%	
control	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04		7.56		≥ 90%	
control	2	11-Dec-08	Schedule (ii)	+S9	3	27	2.00		7.24		≥ 90%	
control	3	12-Dec-08	Schedule (ii)	+S9	3	27	2.12		8.36		≥ 90%	
control	4	12-Dec-08	Schedule (ii)	+S9	3	27	1.92		8.04		≥ 90%	
control	5	17-Dec-08	Schedule (ii)	+S9	3	27	1.96		7.52		≥ 90%	
control	6	17-Dec-08	Schedule (ii)	+S9	3	27	2.04		7.36		≥ 90%	

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Phone (519) 748-5409 FAX (519) 748-1654

Project: M100**Period: November 28 - December 17, 2008****Control: Kentucky Reference 3R4F****Comparison of Internal KR 3R4F Control Slopes with Expected (Historical) Slopes
(Mainstream Tobacco Smoke 'Intense' Conditions *)**

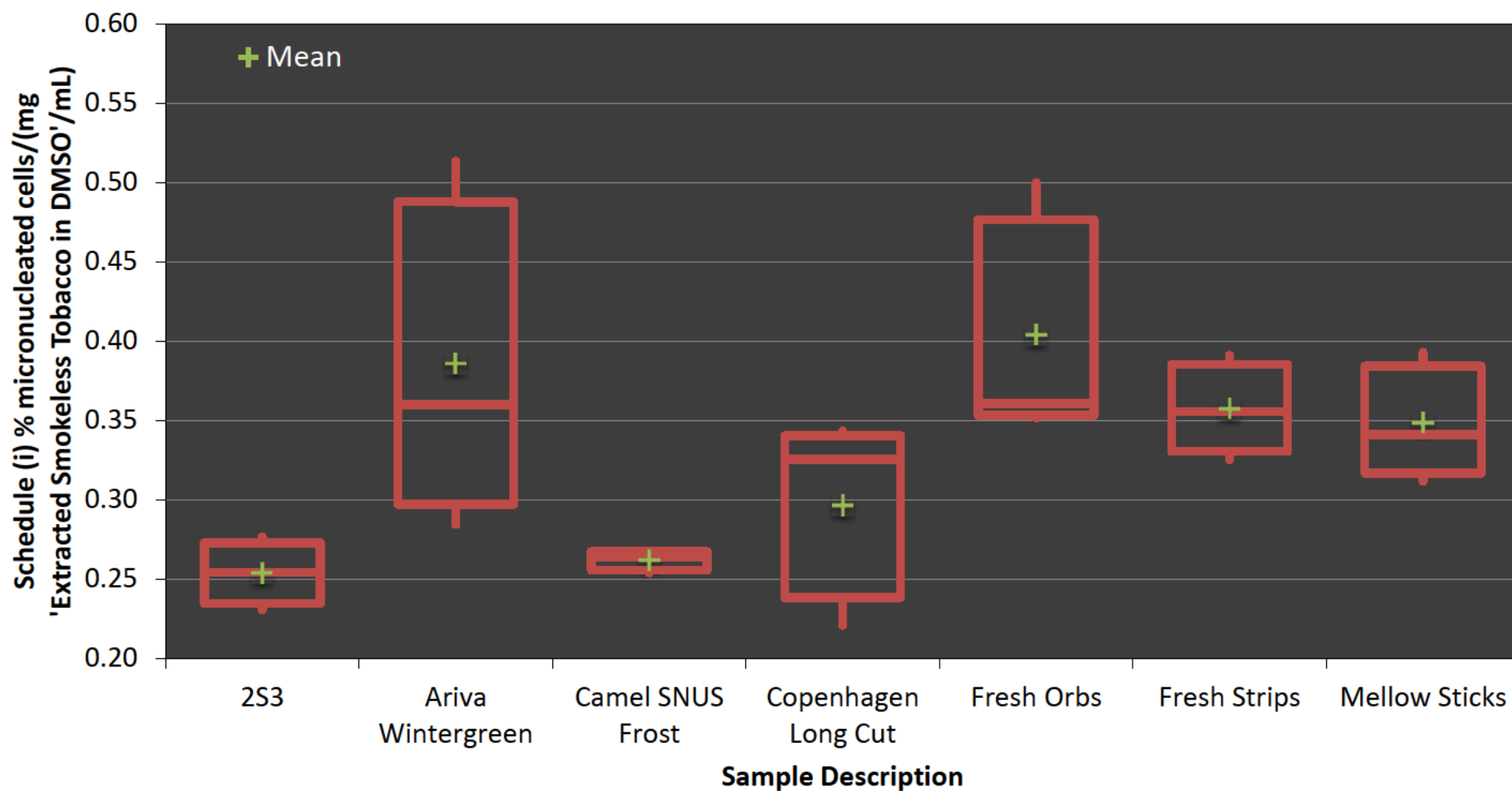
Treatment Schedule	Assay Date	Target Slope		Unit	This Study Slope	Z Score	P Value
		Average	Std Dev				
Schedule (i)	28-Nov-08	5.10	0.50	(%MN per mg TPM/mL)	5.13	-0.051	0.959
Schedule (i)	28-Nov-08	5.10	0.50	(%MN per mg TPM/mL)	5.87	-1.531	0.126
Schedule (i)	04-Dec-08	5.10	0.50	(%MN per mg TPM/mL)	4.85	0.515	0.607
Schedule (i)	04-Dec-08	5.10	0.50	(%MN per mg TPM/mL)	6.20	-2.184	0.029
Schedule (i)	05-Dec-08	5.10	0.50	(%MN per mg TPM/mL)	5.35	-0.487	0.627
Schedule (i)	05-Dec-08	5.10	0.50	(%MN per mg TPM/mL)	5.33	-0.443	0.658
Schedule (ii)	11-Dec-08	4.15	0.49	(%MN per mg TPM/mL)	3.93	0.436	0.663
Schedule (ii)	11-Dec-08	4.15	0.49	(%MN per mg TPM/mL)	3.43	1.452	0.146
Schedule (ii)	12-Dec-08	4.15	0.49	(%MN per mg TPM/mL)	3.30	1.718	0.086
Schedule (ii)	12-Dec-08	4.15	0.49	(%MN per mg TPM/mL)	3.09	2.160	0.031
Schedule (ii)	17-Dec-08	4.15	0.49	(%MN per mg TPM/mL)	3.67	0.966	0.334
Schedule (ii)	17-Dec-08	4.15	0.49	(%MN per mg TPM/mL)	4.50	-0.713	0.476

* internal control samples generated under 'Intense' smoking conditions:
55mL puff volume; 30 second interval; 2 second duration; 100% vent blocking.

Test Describe - Comparative

Performed by Schedule (i) % micronucleated cells/(mg 'Extracted Smokeless Tobacco in DMSO'/mL) by Sample Description
Wendy Wagstaff

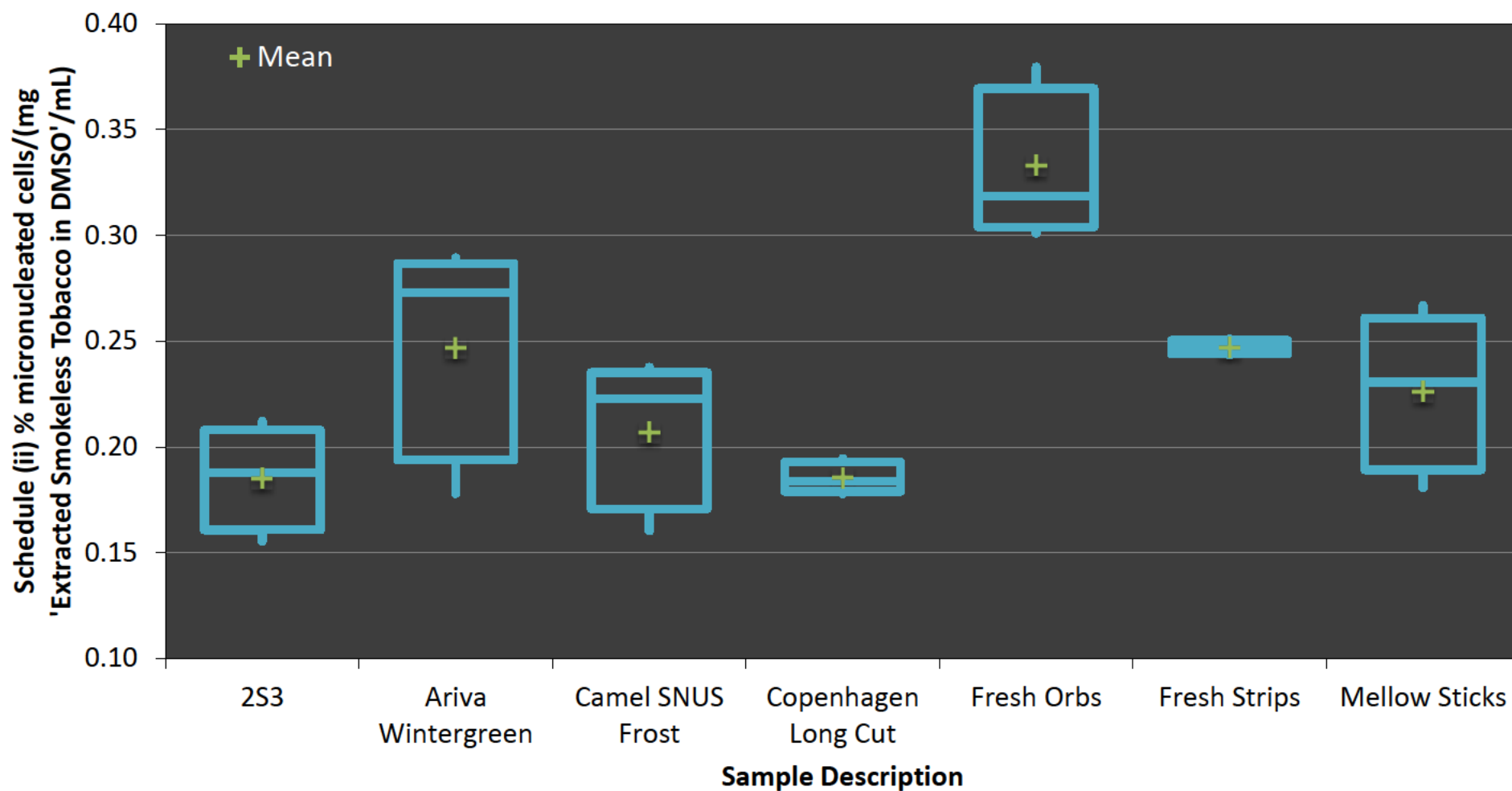
Date 2 November 2009



Test Describe - Comparative

Performed by Schedule (ii) % micronucleated cells/(mg 'Extracted Smokeless Tobacco in DMSO'/mL) by Sample Description
Wendy Wagstaff

Date 2 November 2009



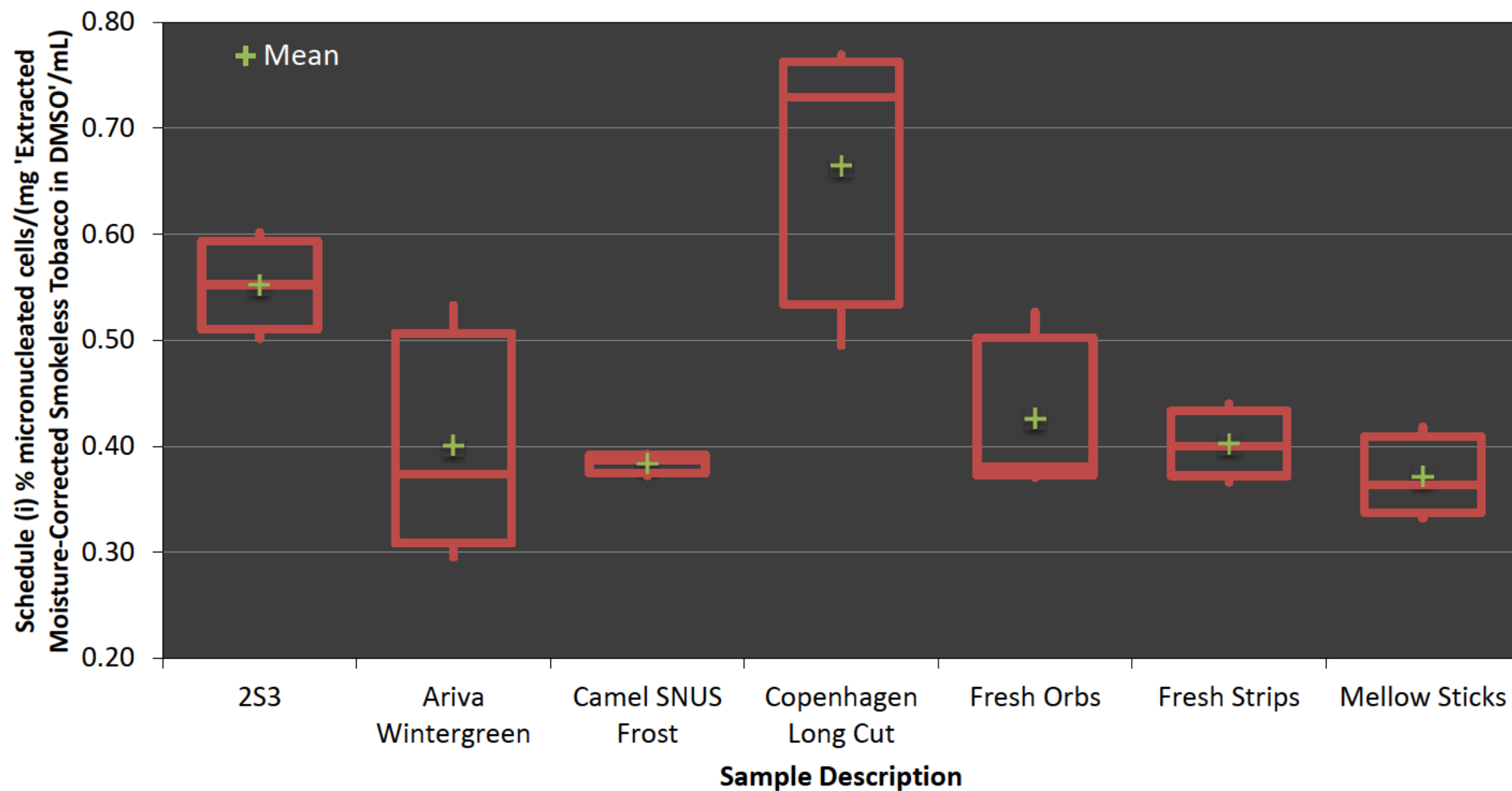
Test Describe - Comparative

Performed by

Schedule (i) % micronucleated cells/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL) by Sample Description
Wendy Wagstaff

Date

2 November 2009



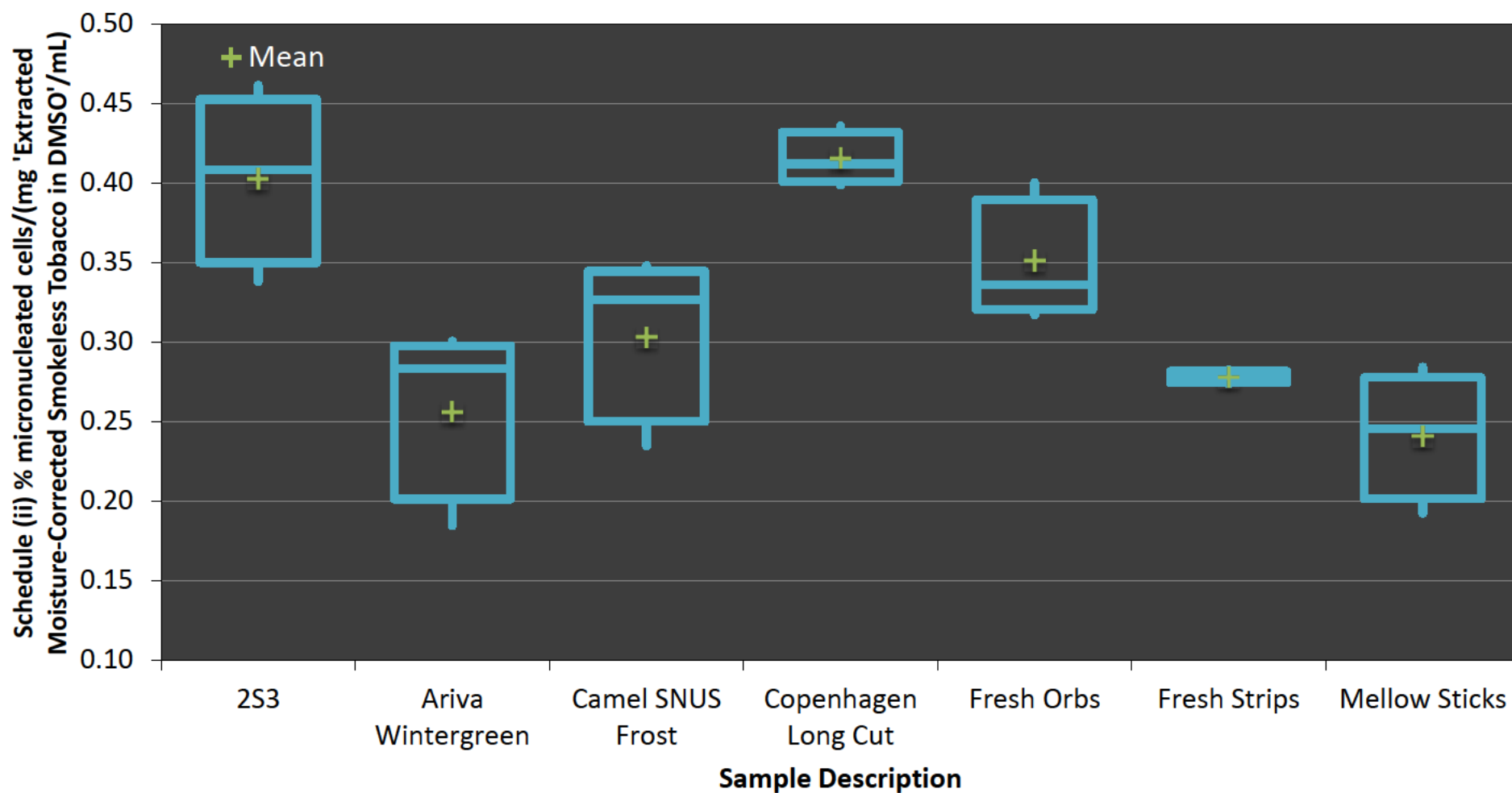
Test Describe - Comparative

Performed by

Schedule (ii) % micronucleated cells/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL) by Sample Description
Wendy Wagstaff

Date

2 November 2009



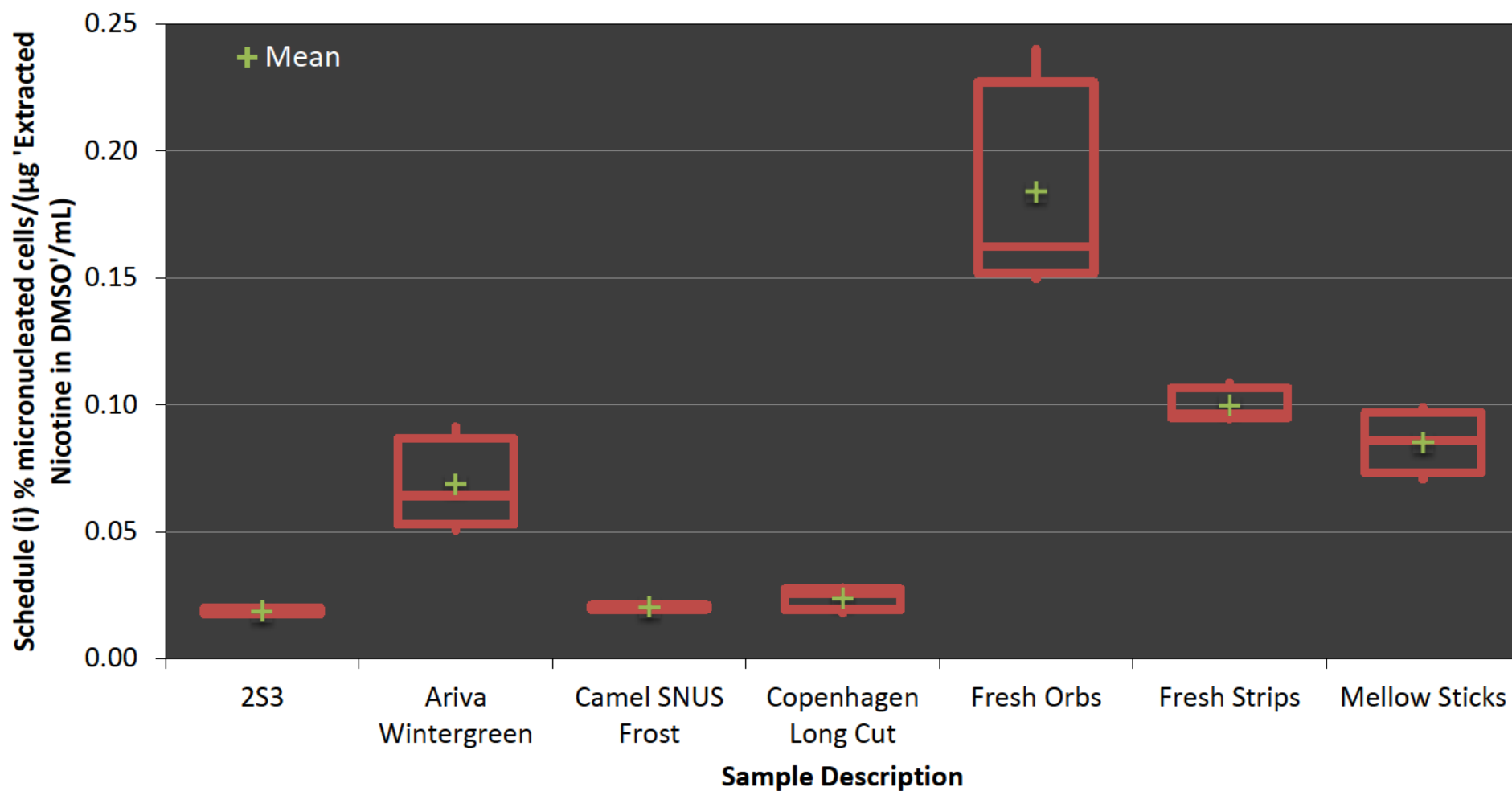
Test Describe - Comparative

Performed by

Schedule (i) % micronucleated cells/(μ g 'Extracted Nicotine in DMSO'/mL) by Sample Description
Wendy Wagstaff

Date

4 February 2011



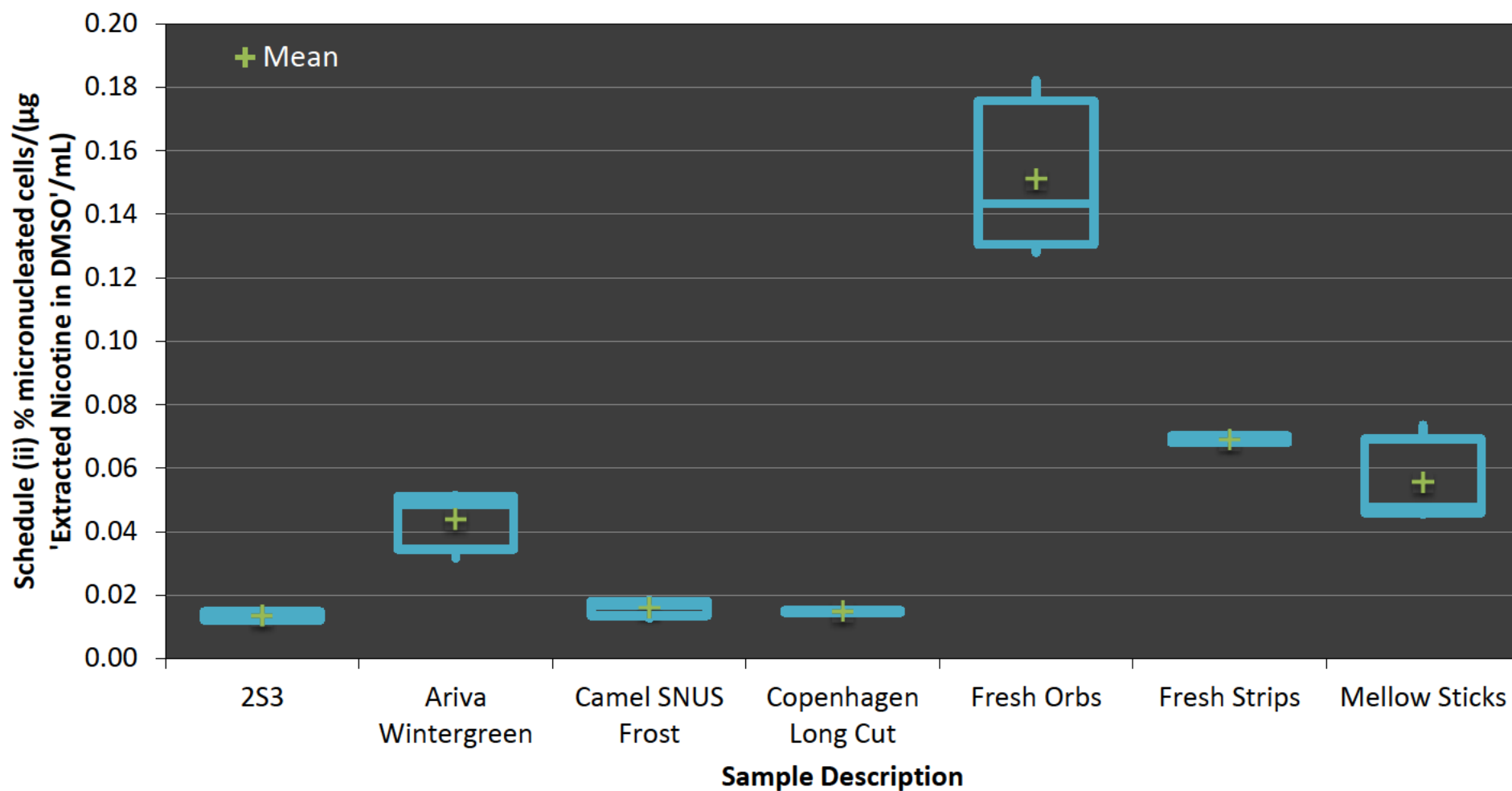
Test Describe - Comparative

Performed by

Schedule (ii) % micronucleated cells/(μ g 'Extracted Nicotine in DMSO'/mL) by Sample Description
Wendy Wagstaff

Date

4 February 2011



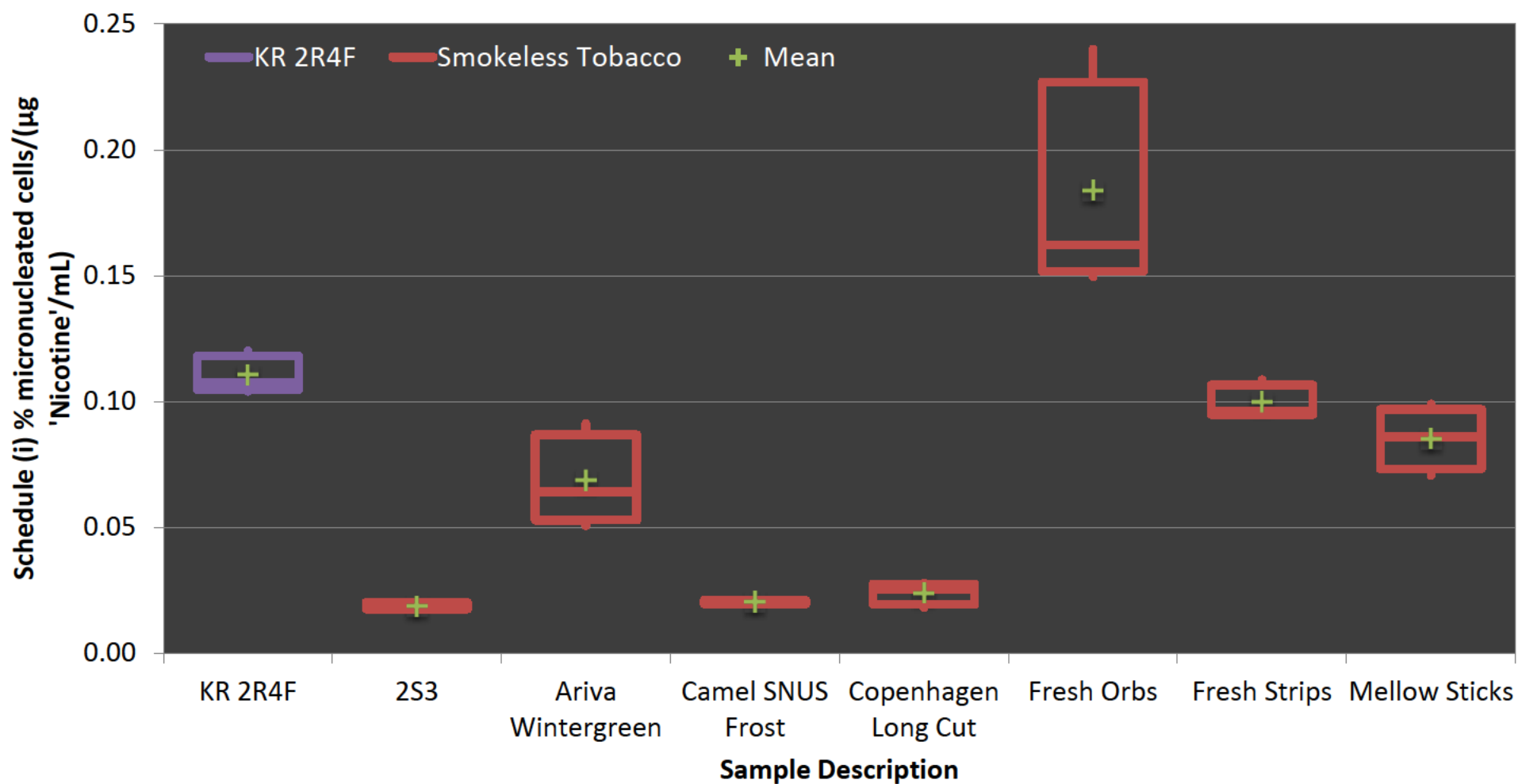
Test Describe - Comparative

Performed by

Schedule (i) % micronucleated cells/(μ g 'Nicotine in CSC'/mL) (KR 2R4F) and % micronucleated cells/(μ g 'Extracted Nicotine in DMSO'/mL) by Sample De
Wendy Wagstaff

Date

4 February 2011



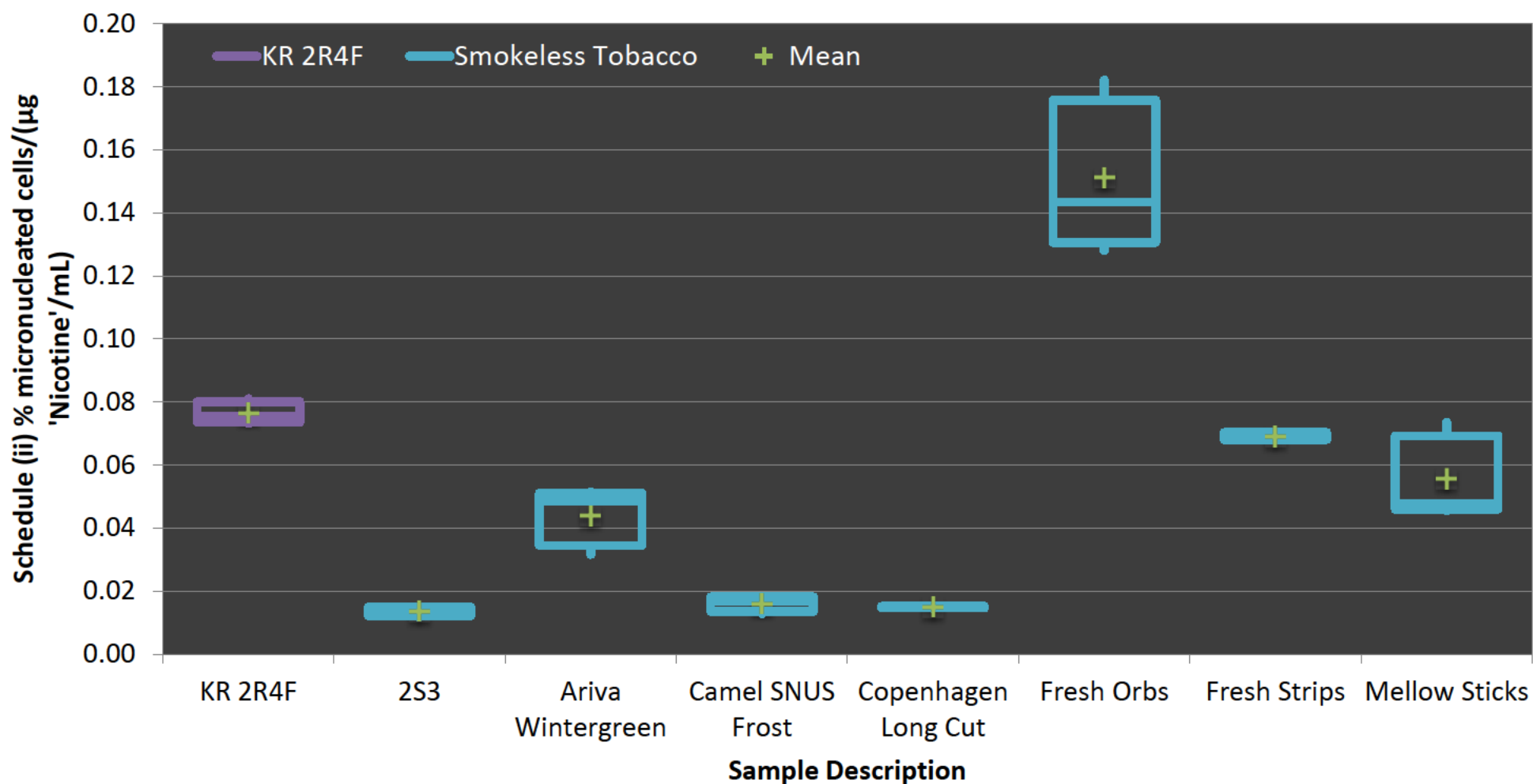
Test Describe - Comparative

Performed by

Schedule (ii) % micronucleated cells/(μ g 'Nicotine in CSC'/mL) (KR 2R4F) and % micronucleated cells/(μ g 'Extracted Nicotine in DMSO'/mL) by Sample Description
Wendy Wagstaff

Date

4 February 2011



Slope Analysis of the Linear Portion of the Dose-Response Curve for Smokeless Tobacco [%MNC*/(µg 'Extracted Nicotine in DMSO'/mL)] and Smoked Tobacco [%MNC*/(µg 'Nicotine in CSC'/mL)] Samples

Treatment Schedule	Sample ID	Sample Description	% MNC / (µg 'Nicotine in CSC'/mL) (KR 2R4F) or % MNC / (µg 'Extracted Nicotine in DMSO'/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'Nic.' Slope Estimates				
			Dose Range (µg 'Nic.'/mL)		Dose Range (µg 'Nic.'/mL)		Dose Range (µg 'Nic.'/mL)		Standard		t-test p-value (H ₀ : mean = 0)		
				slope		slope		slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 27.8	0.021	0 - 28.7	0.021	0 - 29.5	0.019	0.020	0.001	0.018 - 0.023	0.001	significant
Schedule (i)	084395	2S3	0 - 30	0.021	0 - 29.4	0.017	0 - 31.4	0.018	0.019	0.001	0.015 - 0.023	0.003	significant
Schedule (i)	084396	KR 2R4F	0 - 13.4	0.120	0 - 14.2	0.108	0 - 14	0.104	0.111	0.005	0.09 - 0.132	0.002	significant
Schedule (i)	084454	Fresh Strips	0 - 8.22	0.096	0 - 8	0.109	0 - 7.66	0.094	0.100	0.004	0.081 - 0.119	0.002	significant
Schedule (i)	084455	Mellow S icks	0 - 8.83	0.099	0 - 10.7	0.071	0 - 8.07	0.086	0.085	0.008	0.05 - 0.12	0.009	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 28.3	0.026	0 - 27.4	0.028	0 - 27.2	0.018	0.024	0.003	0.011 - 0.037	0.015	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 12.5	0.091	0 - 12.5	0.064	0 - 12.5	0.051	0.069	0.012	0.017 - 0.12	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 4.63	0.240	0 - 5.23	0.150	0 - 4.94	0.162	0.184	0.028	0.062 - 0.305	0.023	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 27.8	0.013	0 - 28.7	0.018	0 - 29.5	0.017	0.016	0.002	0.009 - 0.023	0.011	significant
Schedule (ii)	084395	2S3	0 - 30	0.014	0 - 29.4	0.012	0 - 31.4	0.015	0.014	0.001	0.009 - 0.018	0.005	significant
Schedule (ii)	084396	KR 2R4F	0 - 13.4	0.081	0 - 14.2	0.075	0 - 14	0.073	0.077	0.002	0.066 - 0.087	0.001	significant
Schedule (ii)	084454	Fresh Strips	0 - 8.22	0.068	0 - 8	0.068	0 - 7.66	0.071	0.069	0.001	0.066 - 0.073	0.000	significant
Schedule (ii)	084455	Mellow S icks	0 - 8.83	0.046	0 - 10.7	0.048	0 - 8.07	0.074	0.056	0.009	0.017 - 0.094	0.025	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 28.3	0.015	0 - 27.4	0.015	0 - 27.2	0.015	0.015	0.000	0.014 - 0.016	0.000	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 12.5	0.032	0 - 12.5	0.049	0 - 12.5	0.052	0.044	0.006	0.017 - 0.071	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 4.63	0.182	0 - 5.23	0.128	0 - 4.94	0.143	0.151	0.016	0.082 - 0.221	0.011	significant

* MNC = micronucleated cells

Cigarette smoke condensate (CSC) test sample with µg 'Nicotine in CSC'/mL dose basis

One-Way ANOVA of Mean 'Nicotine in CSC' and 'Extracted Nicotine in DMSO' Slope Estimates

Schedule (i)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.068	7	0.010	24.42	0.000
Within Samples	0.006	16	0.000		
Total (Corr.)	0.074	23			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.045	7	0.006	43.69	0.000
Within Samples	0.002	16	0.000		
Total (Corr.)	0.047	23			

One-way ANOVA analysis indicates significant differences (at $\alpha = 0.05$) among mean 'Nicotine' specific activity slope estimates for test samples under both Treatment Schedules (i) and (ii).

Evaluation of Ratio (Max ÷ Min) of Standard Deviations of 'Nicotine in CSC' and 'Extracted Nicotine in DMSO' Slope Estimates and Corresponding Method of Comparison

Treatment Schedule	Std. Dev. Ratio (Max ÷ Min)	Method of Comparison
Schedule (i)	47.5	Pairwise T-test (unequal variance)
Schedule (ii)	76.3	Pairwise T-test (unequal variance)

ANOVA-Based Comparisons of Smokeless Tobacco Mean 'Extracted Nicotine in DMSO' Slope to Control Brand KR 2R4F (084396) Mean 'Nicotine in CSC' Slope using Bonferroni-adjusted p-values

ANOVA-Based Comparison	Schedule (i)			Schedule (ii)		
	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	30.732	4.4E-05	significant	37.632	1.4E-05	significant
084395 vs. 084396	31.898	3.6E-05	significant	40.745	9.1E-06	significant
084454 vs. 084396	0.441	0.5163	not significant	0.577	0.4585	not significant
084455 vs. 084396	2.435	0.1382	not significant	4.483	0.0502	not significant
084456 vs. 084396	28.415	0.0001	significant	39.020	1.2E-05	significant
084457 vs. 084396	6.630	0.0204	not significant	10.918	0.0045	significant
084458 vs. 084396	20.277	0.0004	significant	57.295	1.1E-06	significant

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences were detected between the mean 'nicotine in CSC' slope of the KR 2R4F (084396) smoked tobacco samples and the mean 'extracted nicotine in DMSO' slope of the following smokeless tobacco samples under each Treatment Schedule:

Treatment Schedule (i)

{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456), Fresh Orbs (084458)}

Treatment Schedule (ii)

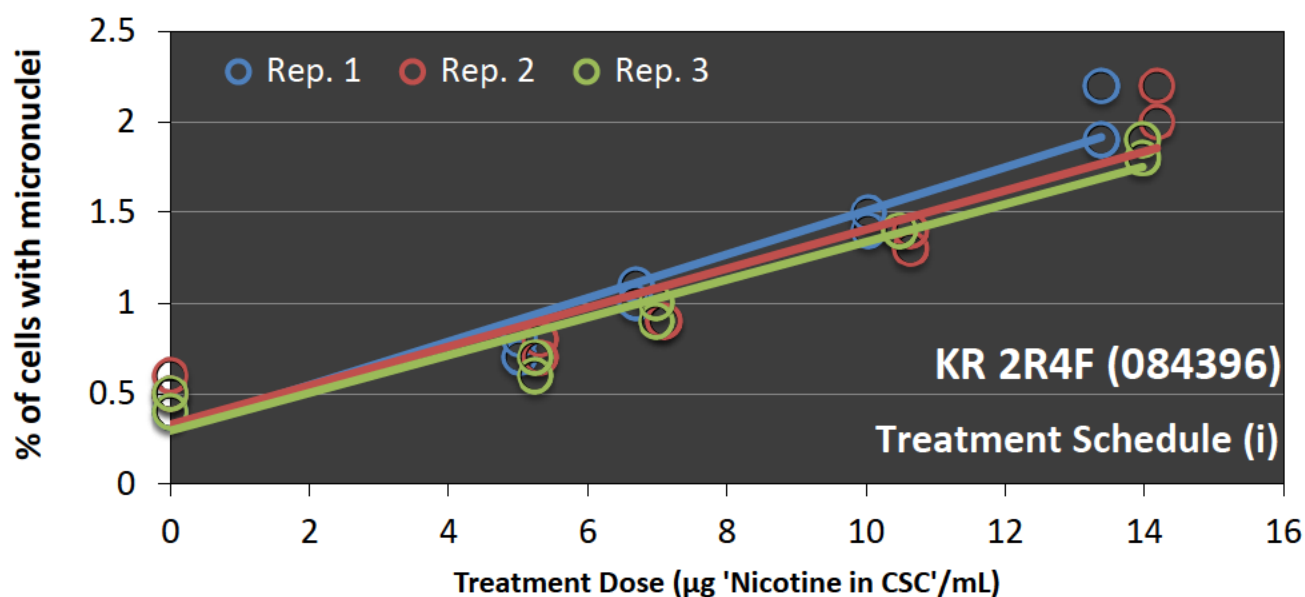
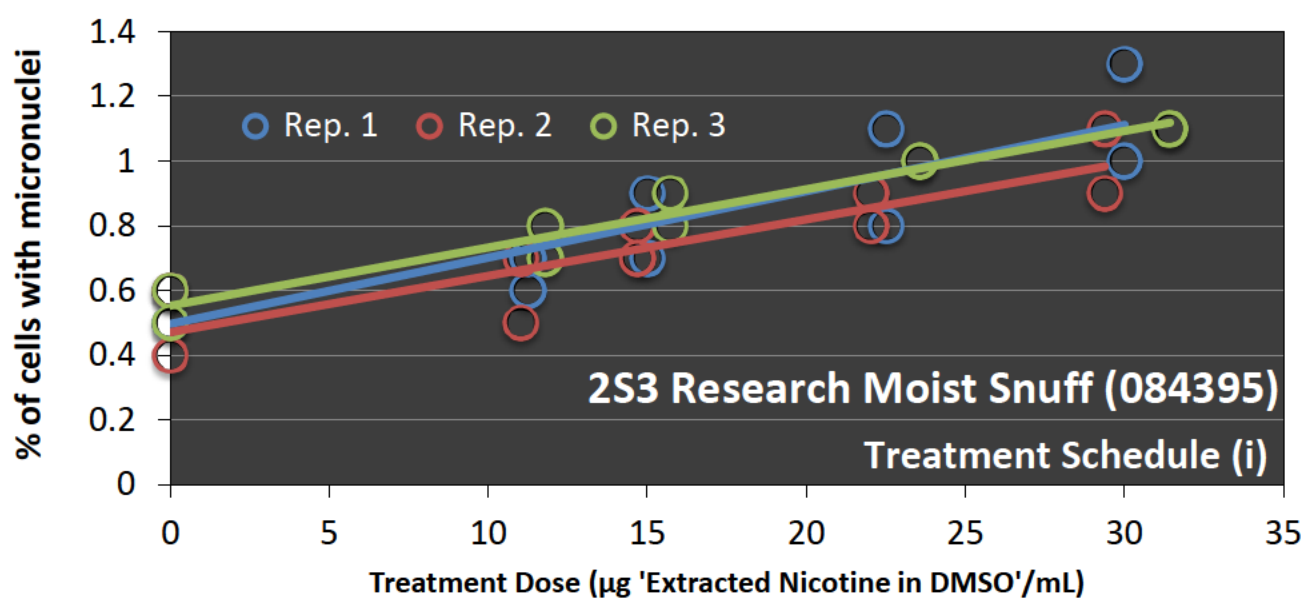
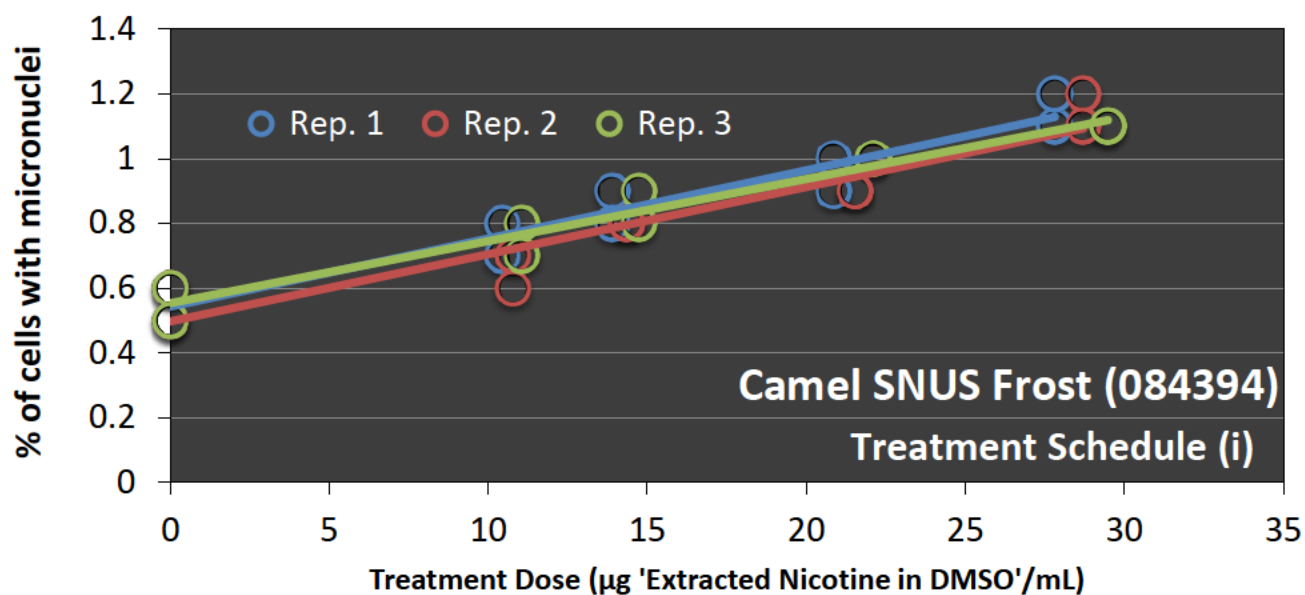
{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456), Ariva Wintergreen (084457), Fresh Orbs (084458)}

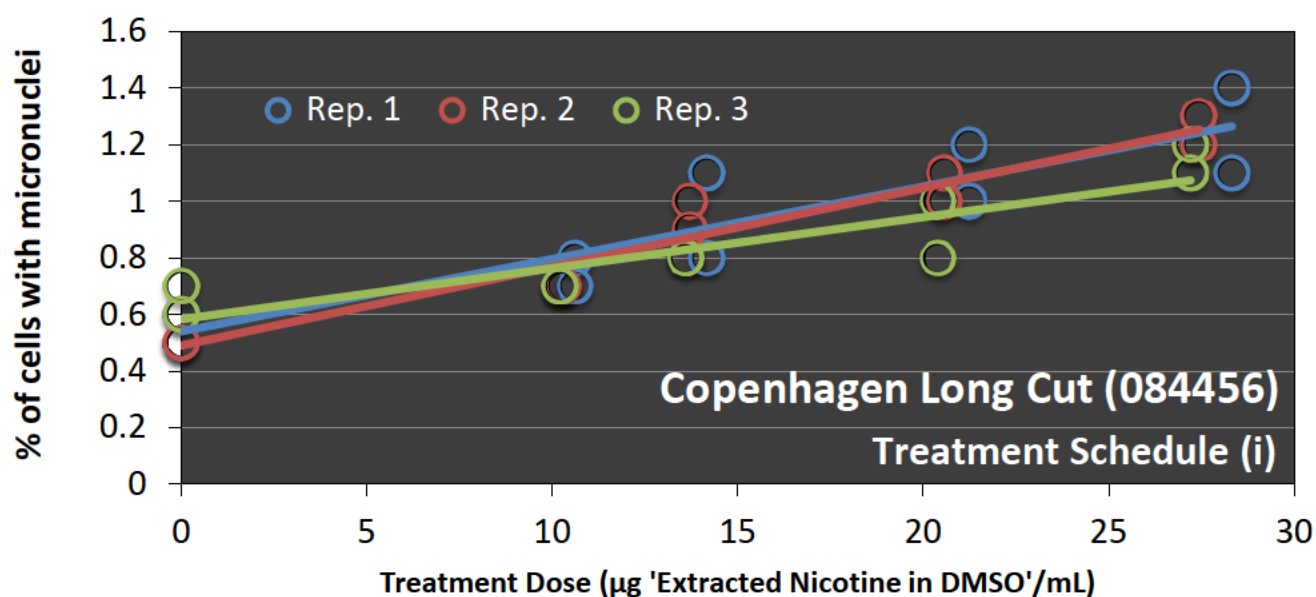
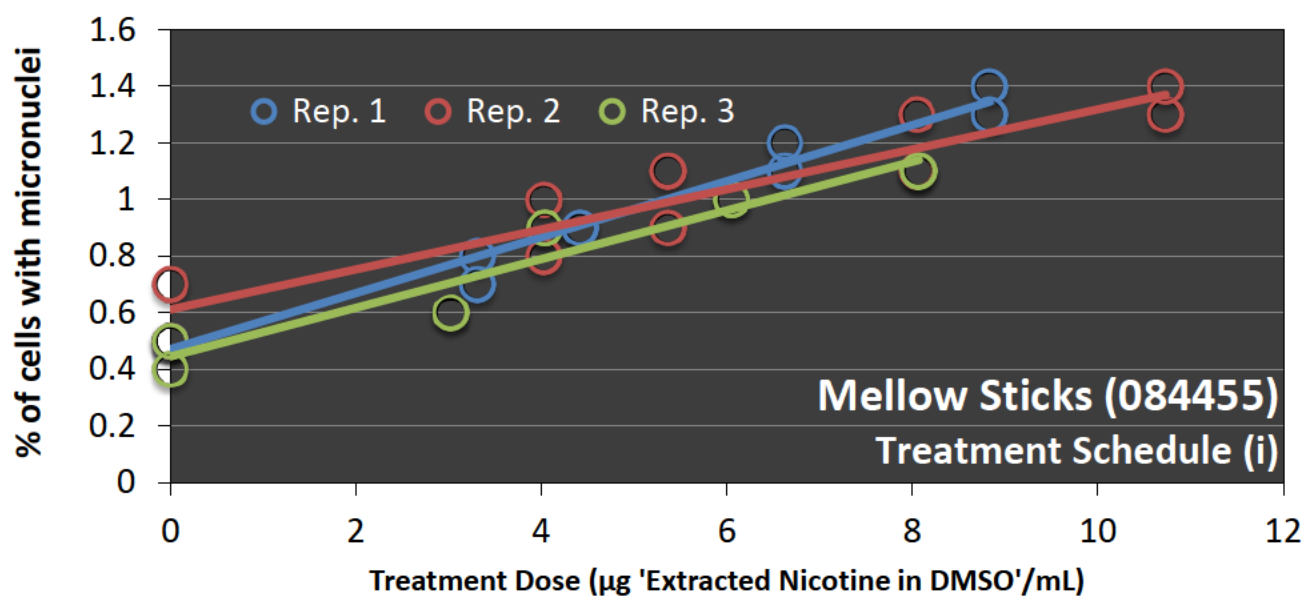
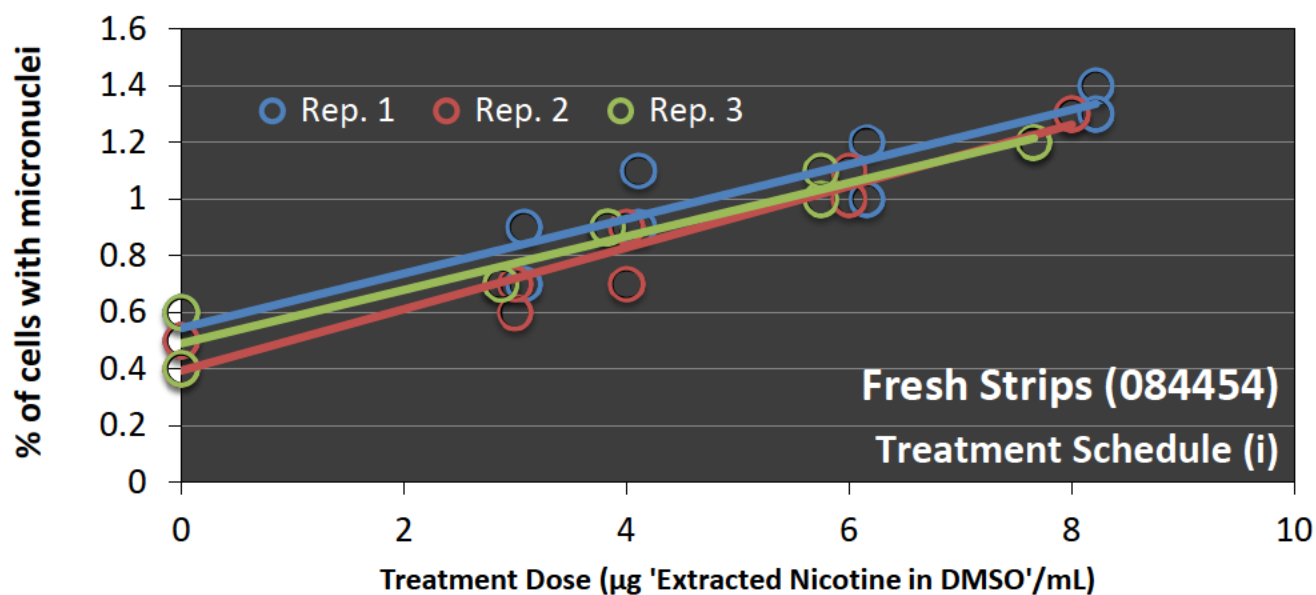
Pairwise T-test Comparisons of Smokeless Tobacco Mean 'Extracted Nicotine in DMSO' Slope to Control Brand KR 2R4F (084396) Mean 'Nicotine in CSC' Slope using Bonferroni-adjusted p-values

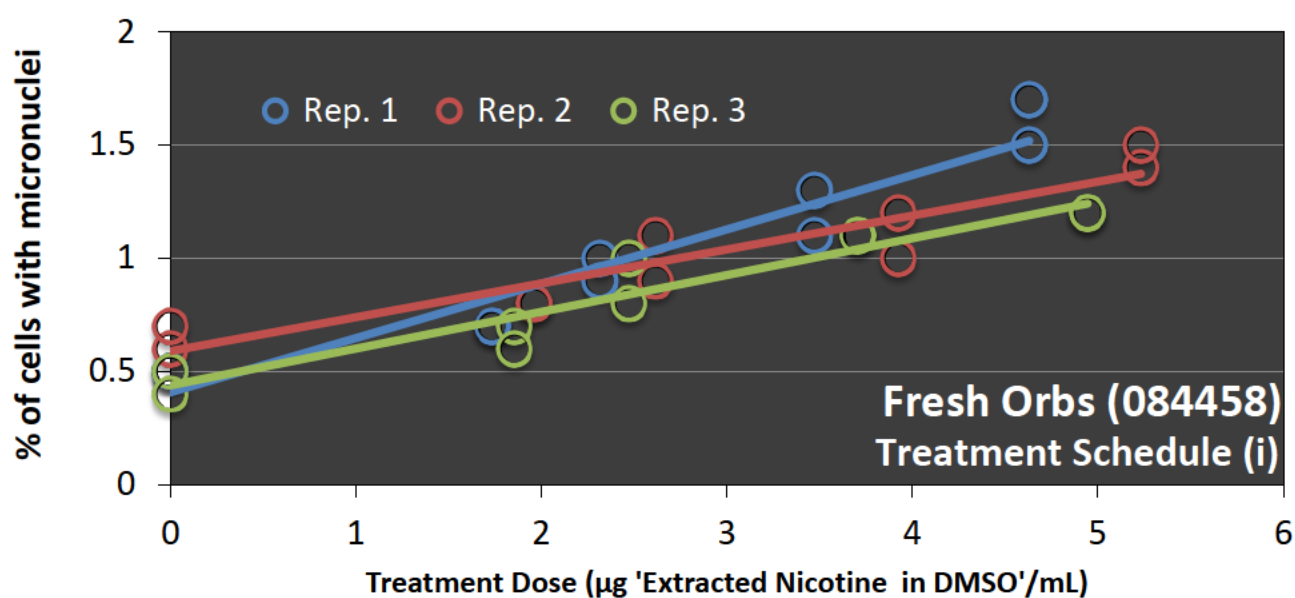
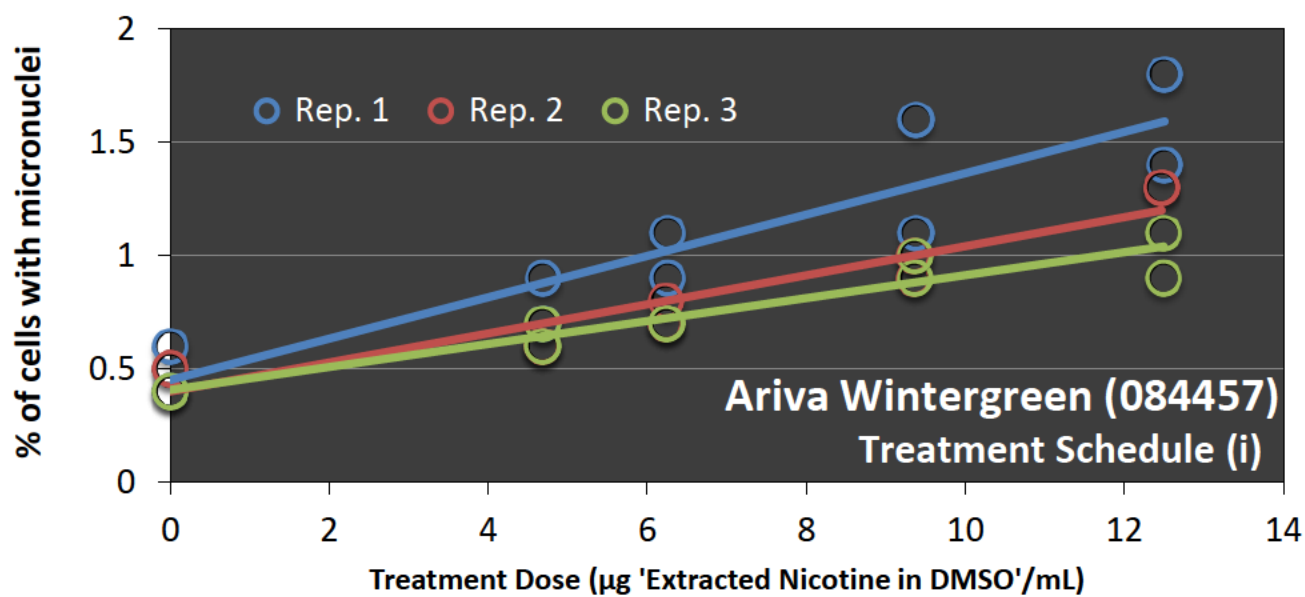
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	18.2889	5.3E-05	significant	20.9526	3.1E-05	significant
084395 vs. 084396	18.4326	5.1E-05	significant	24.7207	1.6E-05	significant
084454 vs. 084396	1.6324	0.1779	not significant	2.9980	0.0400	not significant
084455 vs. 084396	2.6682	0.0559	not significant	2.2482	0.0878	not significant
084456 vs. 084396	15.1765	1.1E-04	significant	25.9795	1.3E-05	significant
084457 vs. 084396	3.2476	0.0314	not significant	4.9121	0.0080	not significant
084458 vs. 084396	2.5583	0.0628	not significant	4.5810	0.0102	not significant

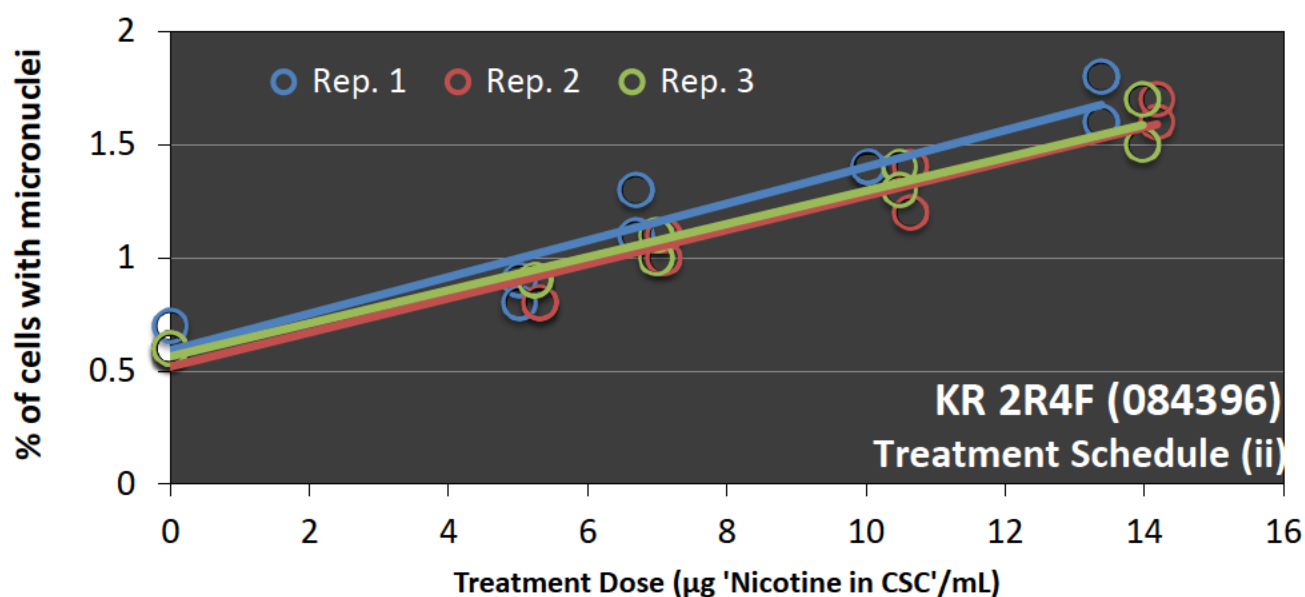
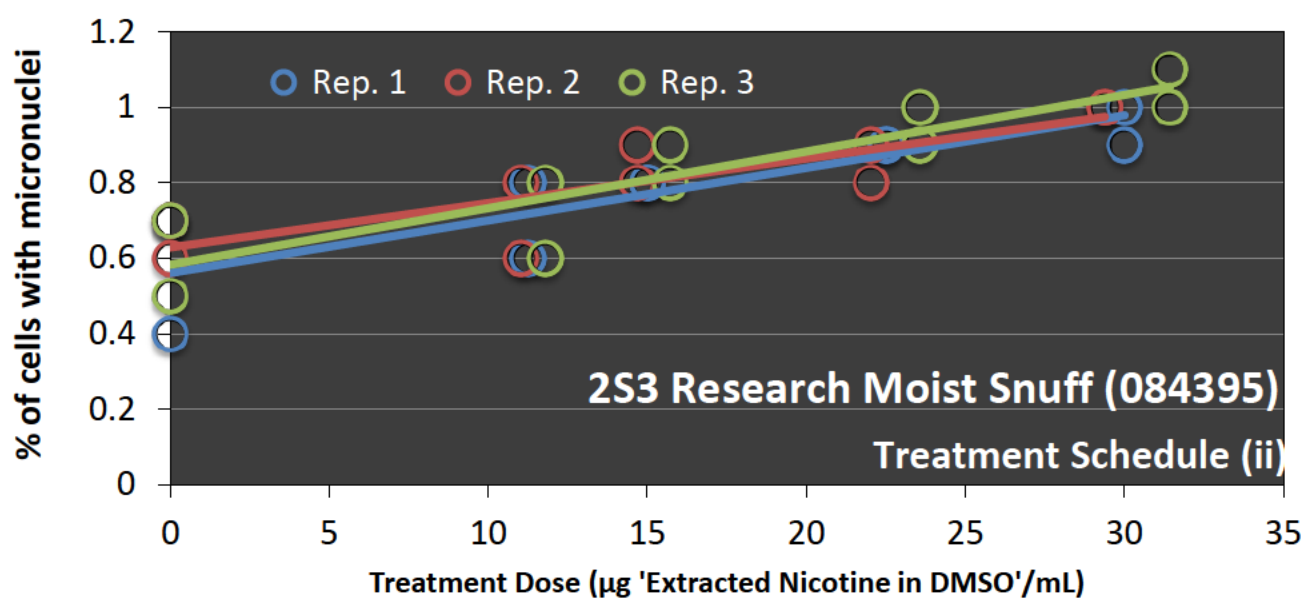
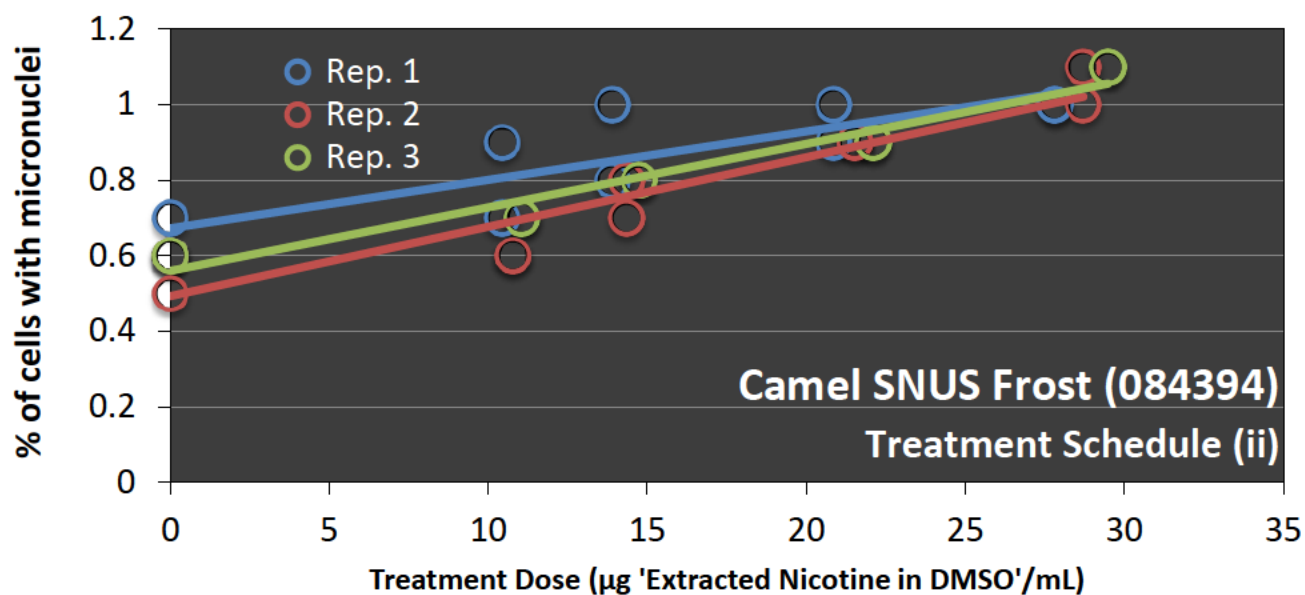
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences were detected between the mean 'nicotine in CSC' slope of the KR 2R4F (084396) smoked tobacco samples and the mean 'extracted nicotine in DMSO' slope of the following smokeless tobacco samples under both Treatment Schedules:

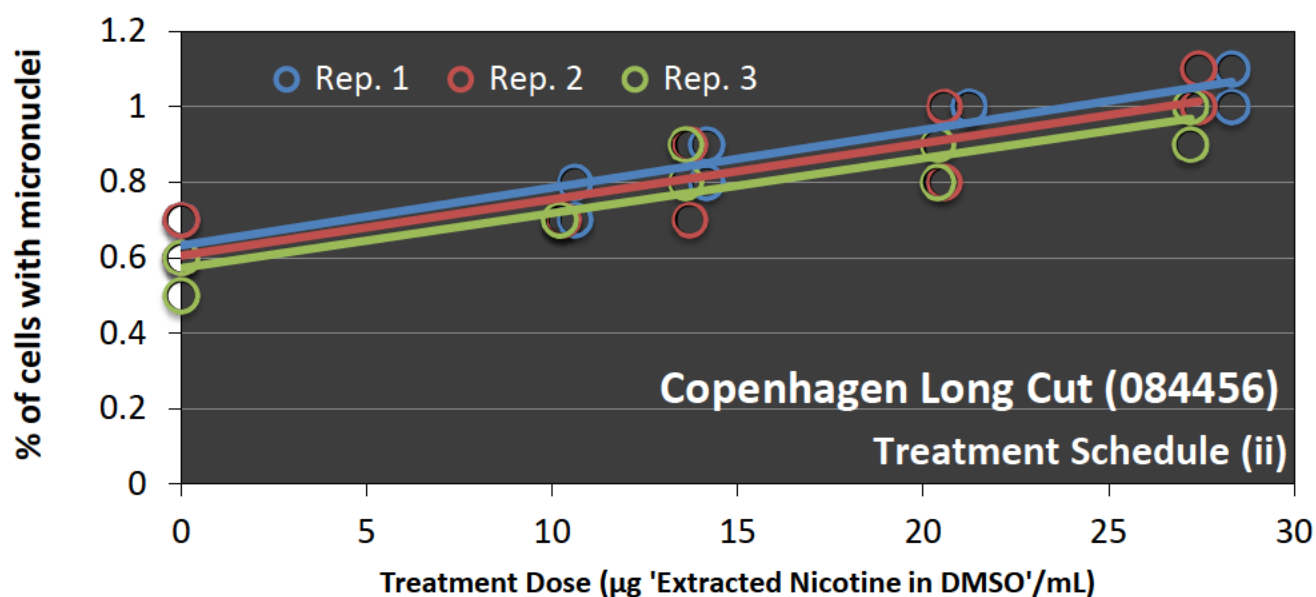
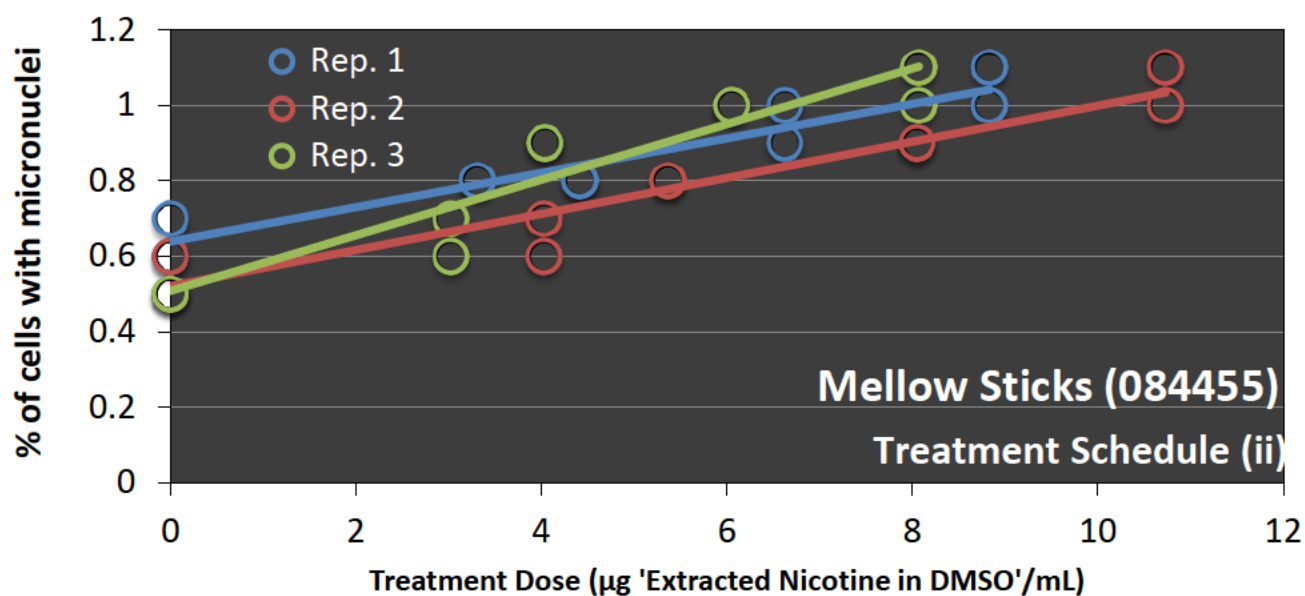
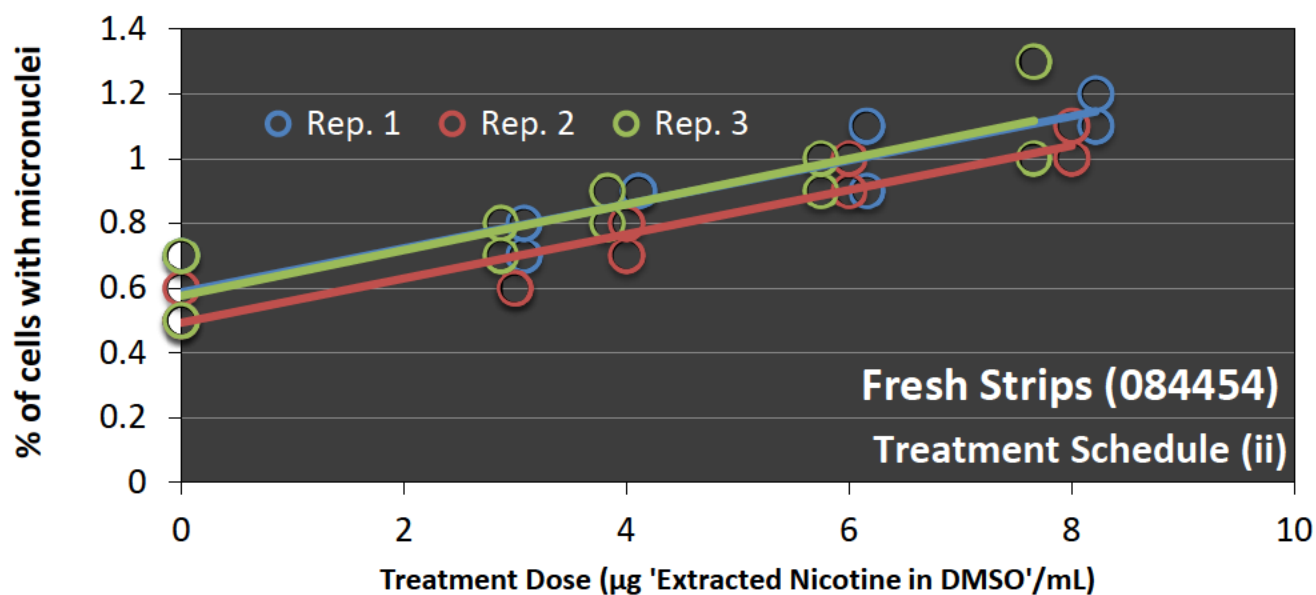
{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456)}

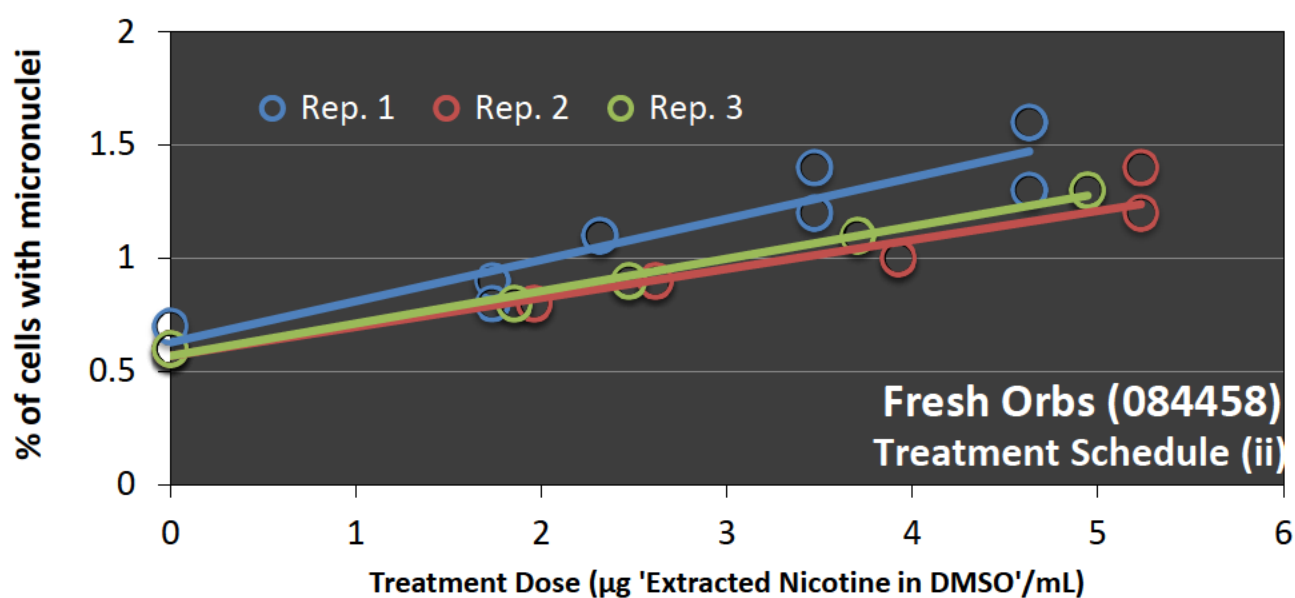
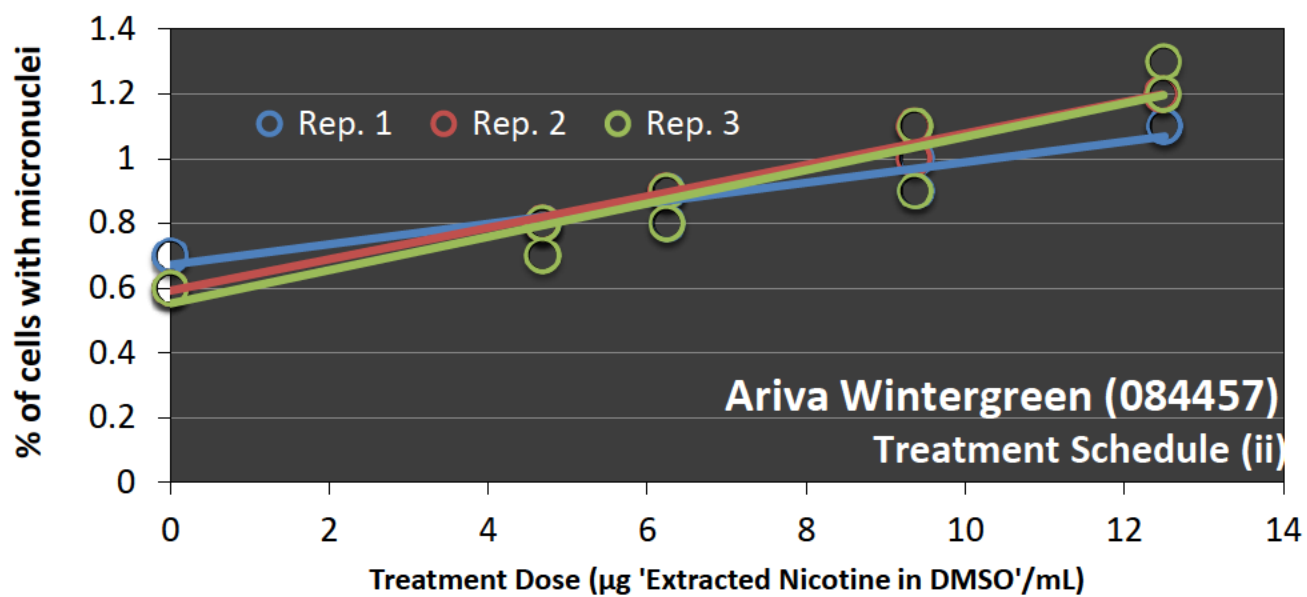


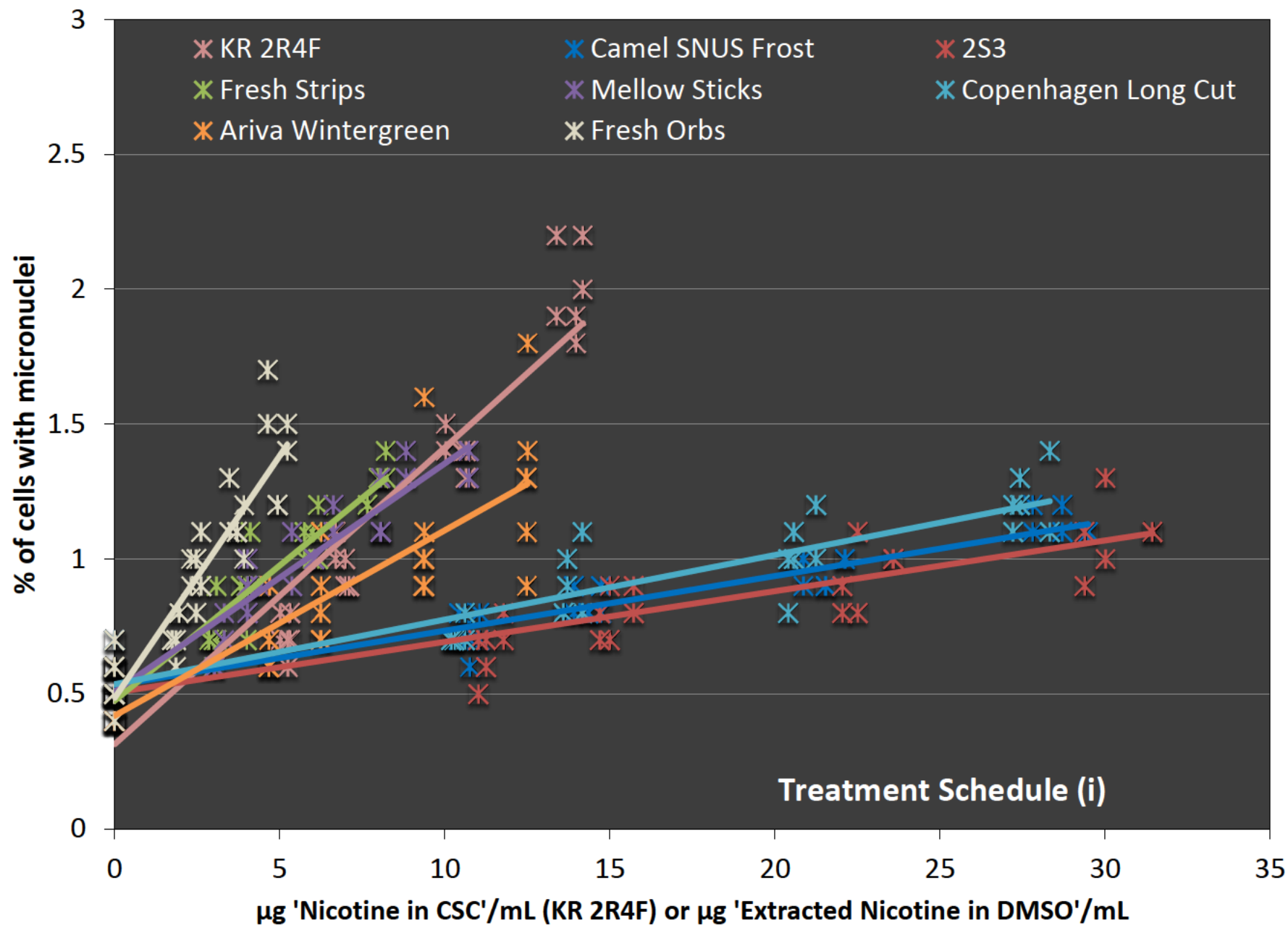


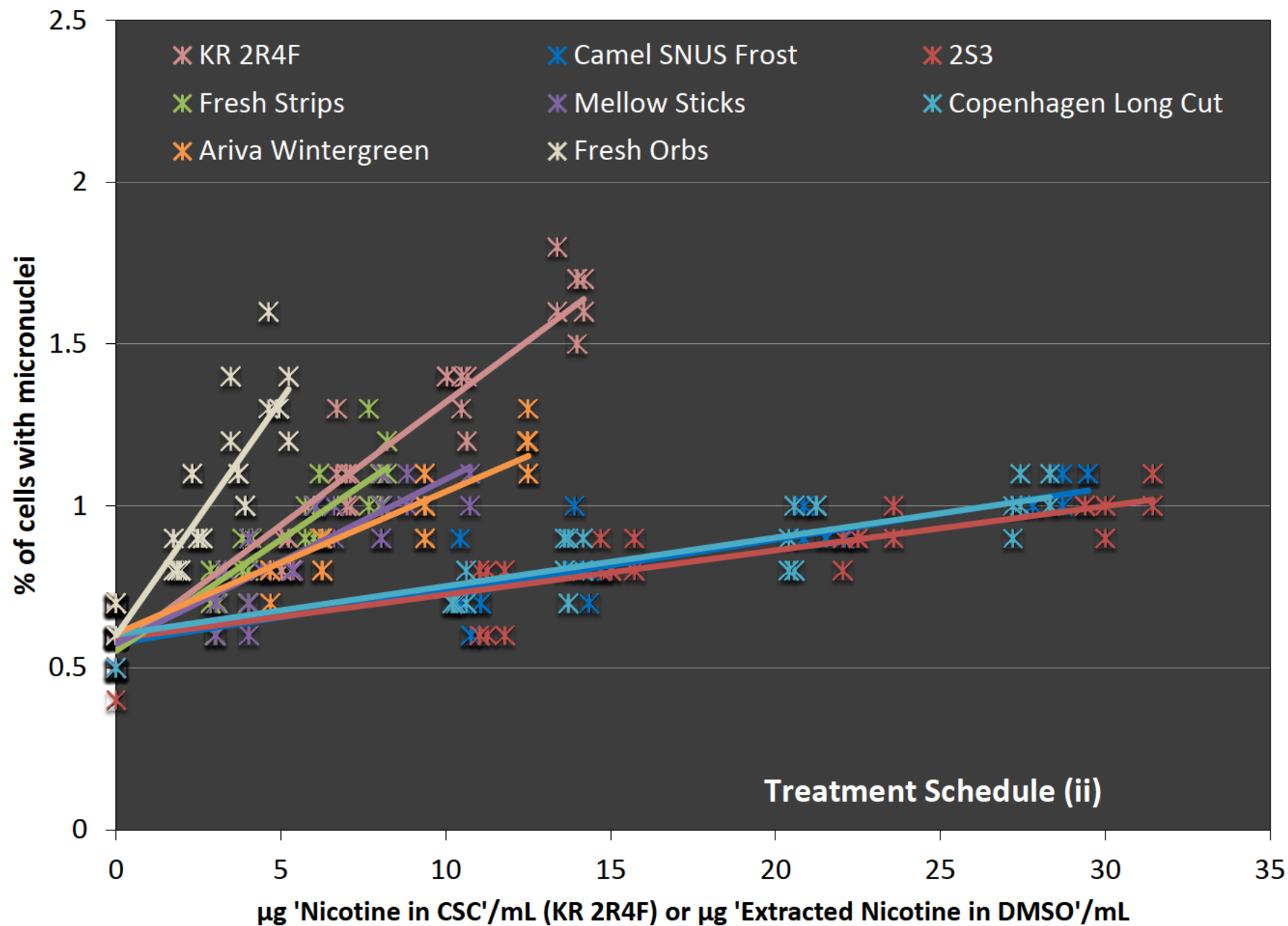






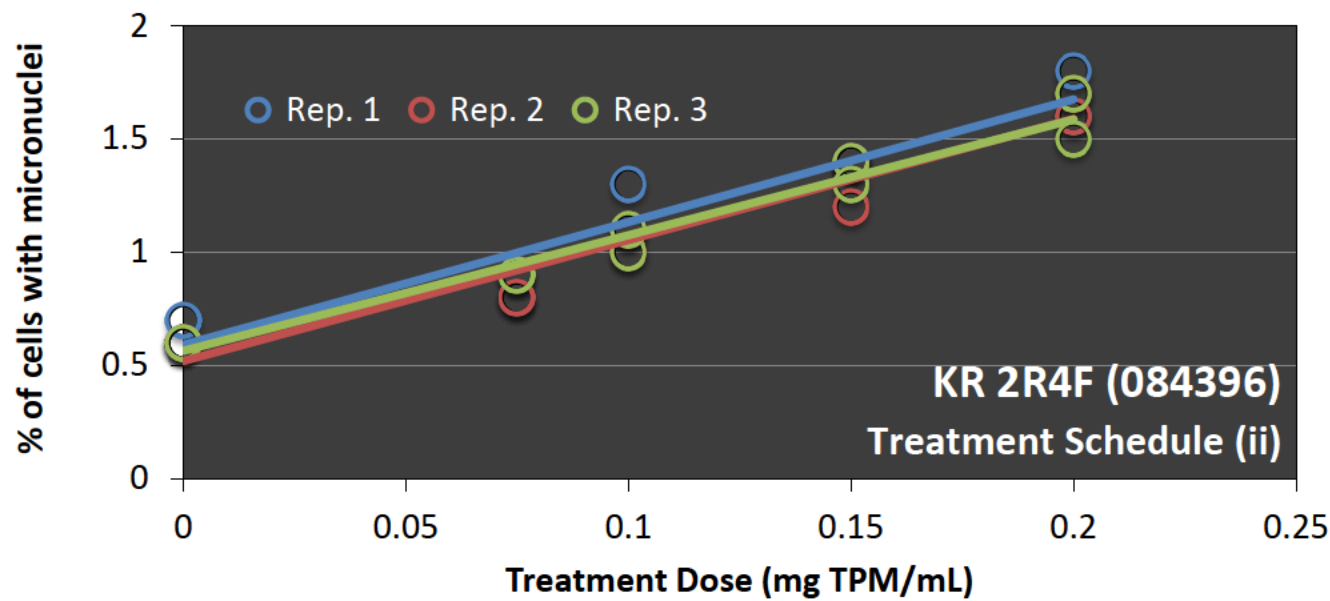
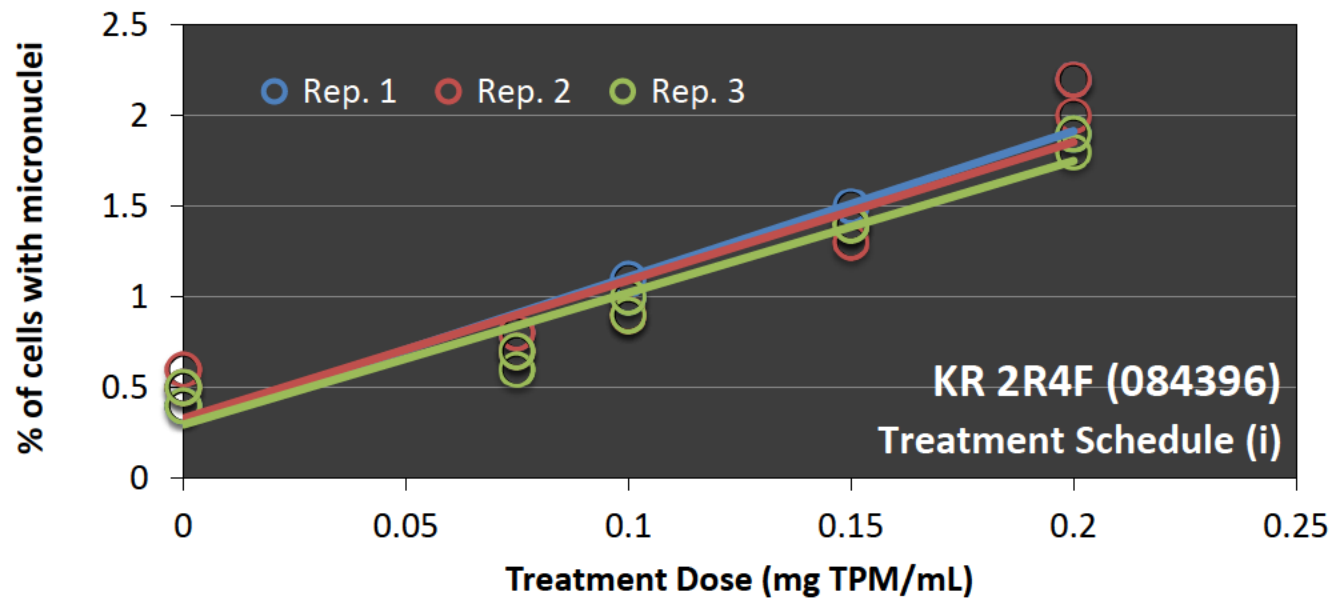


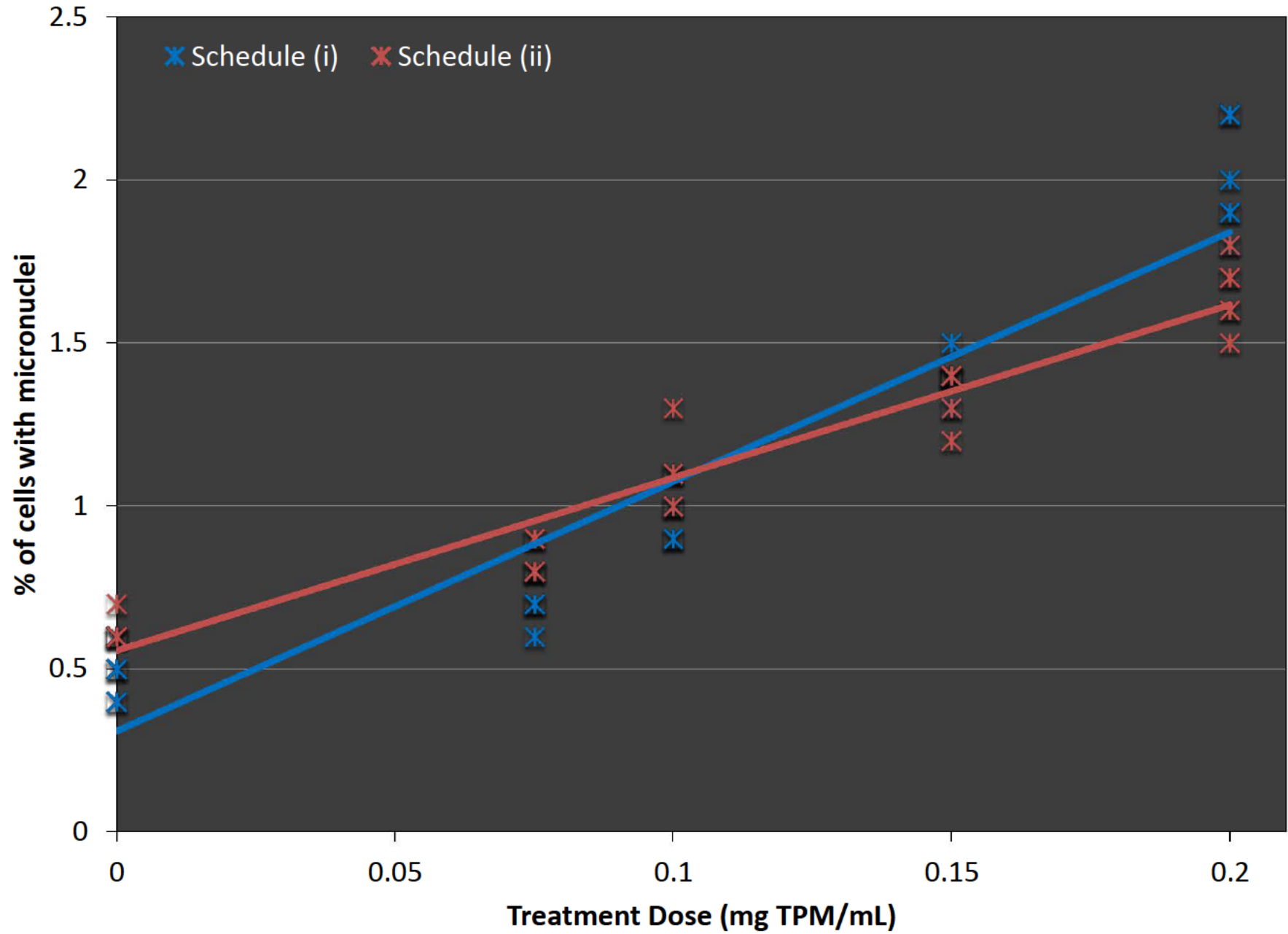




Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/(mg TPM/mL)]

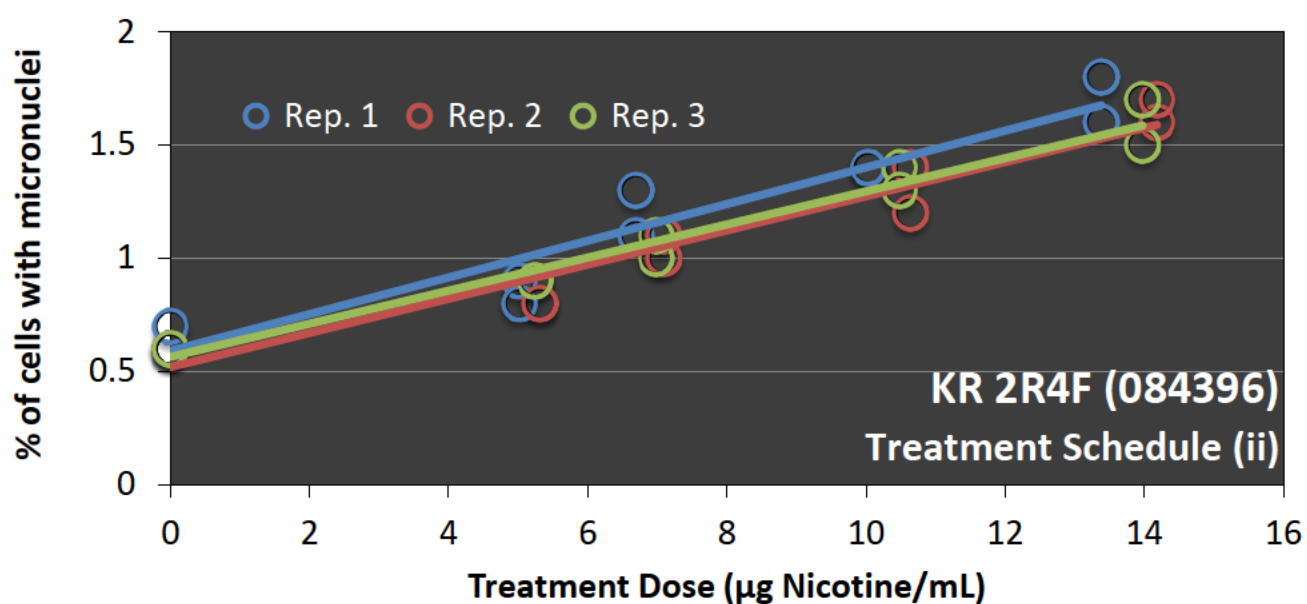
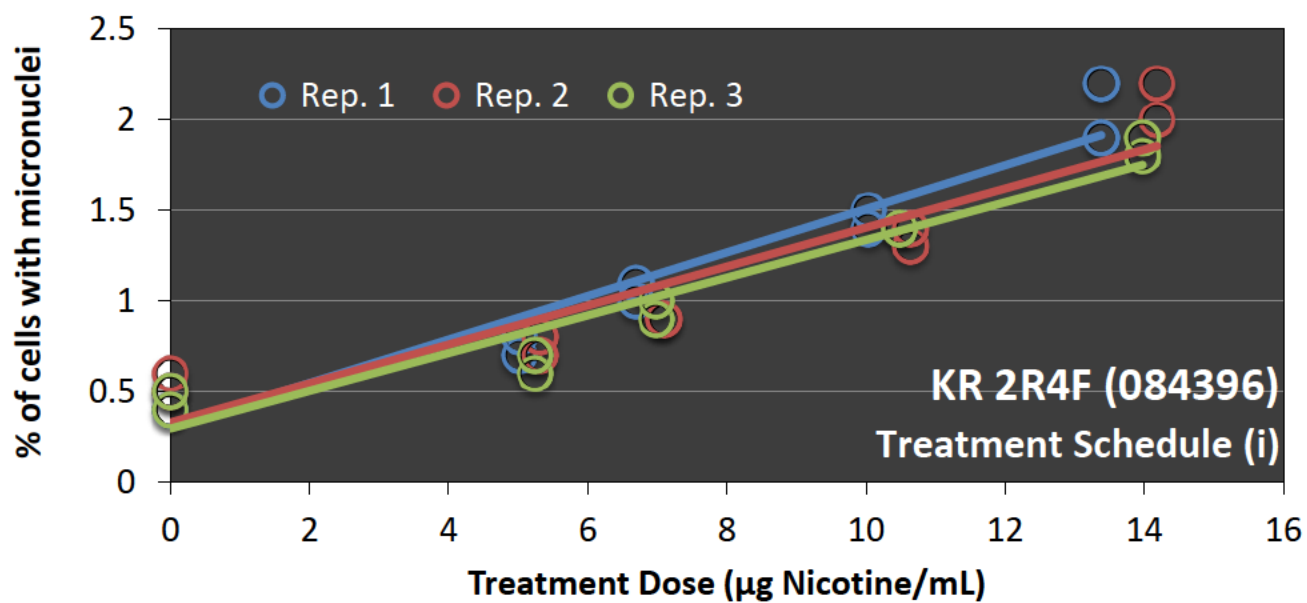
			% micronucleated cells/(mg TPM/mL)										
Treatment Schedule	Sample ID	Sample Description	Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate TPM Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			(mg TPM/mL)	slope	(mg TPM/mL)	slope	(mg TPM/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084396	Kentucky Reference 2R4F	0 - 0.2	8.04	0 - 0.2	7.63	0 - 0.2	7.27	7.65	0.22	6.69 - 8.61	0.001	significant
Schedule (ii)	084396	Kentucky Reference 2R4F	0 - 0.2	5.42	0 - 0.2	5.35	0 - 0.2	5.11	5.29	0.09	4.88 - 5.7	0.000	significant

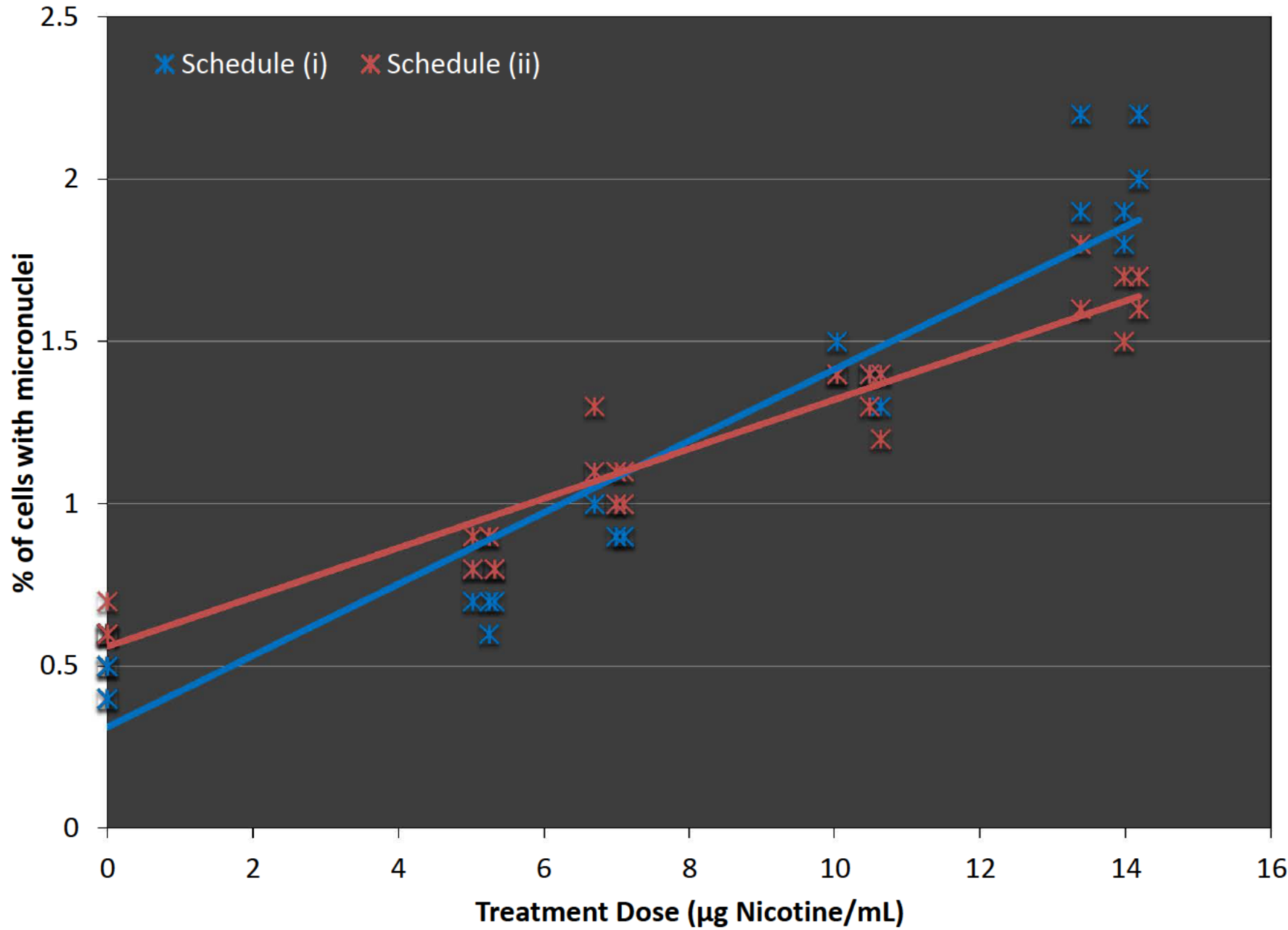




Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/(μ g Nicotine/mL)]

			% micronucleated cells/(µg Nicotine/mL)										
Treatment Schedule	Sample ID	Sample Description	Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate Nicotine Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			(µg Nic./mL)	slope	(µg Nic./mL)	slope	(µg Nic./mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084396	Kentucky Reference 2R4F	0 - 13.4	0.120	0 - 14.2	0.108	0 - 14	0.104	0.111	0.005	0.09 - 0.132	0.002	significant
Schedule (ii)	084396	Kentucky Reference 2R4F	0 - 13.4	0.081	0 - 14.2	0.075	0 - 14	0.073	0.077	0.002	0.066 - 0.087	0.001	significant





Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of cells with micronuclei/(μ g 'Extracted Nicotine in DMSO'/mL)] ('Nic.')

Treatment Schedule	Sample ID	Sample Description	% micronucleated cells /(μ g 'Extracted Nicotine in DMSO'/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'Nic.' Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard		t-test p-value (H_0 : mean = 0)		
			(μ g 'Nic.'/mL)	slope	(μ g 'Nic.'/mL)	slope	(μ g 'Nic.'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 27.8	0.021	0 - 28.7	0.021	0 - 29.5	0.019	0.020	0.001	0.018 - 0.023	0.001	significant
Schedule (i)	084395	2S3	0 - 30	0.021	0 - 29.4	0.017	0 - 31.4	0.018	0.019	0.001	0.015 - 0.023	0.003	significant
Schedule (i)	084454	Fresh Strips	0 - 8.22	0.096	0 - 8	0.109	0 - 7.66	0.094	0.100	0.004	0.081 - 0.119	0.002	significant
Schedule (i)	084455	Mellow S icks	0 - 8.83	0.099	0 - 10.7	0.071	0 - 8.07	0.086	0.085	0.008	0.05 - 0.12	0.009	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 28.3	0.026	0 - 27.4	0.028	0 - 27.2	0.018	0.024	0.003	0.011 - 0.037	0.015	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 12.5	0.091	0 - 12.5	0.064	0 - 12.5	0.051	0.069	0.012	0.017 - 0.12	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 4.63	0.240	0 - 5.23	0.150	0 - 4.94	0.162	0.184	0.028	0.062 - 0.305	0.023	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 27.8	0.013	0 - 28.7	0.018	0 - 29.5	0.017	0.016	0.002	0.009 - 0.023	0.011	significant
Schedule (ii)	084395	2S3	0 - 30	0.014	0 - 29.4	0.012	0 - 31.4	0.015	0.014	0.001	0.009 - 0.018	0.005	significant
Schedule (ii)	084454	Fresh Strips	0 - 8.22	0.068	0 - 8	0.068	0 - 7.66	0.071	0.069	0.001	0.066 - 0.073	0.000	significant
Schedule (ii)	084455	Mellow S icks	0 - 8.83	0.046	0 - 10.7	0.048	0 - 8.07	0.074	0.056	0.009	0.017 - 0.094	0.025	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 28.3	0.015	0 - 27.4	0.015	0 - 27.2	0.015	0.015	0.000	0.014 - 0.016	0.000	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 12.5	0.032	0 - 12.5	0.049	0 - 12.5	0.052	0.044	0.006	0.017 - 0.071	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 4.63	0.182	0 - 5.23	0.128	0 - 4.94	0.143	0.151	0.016	0.082 - 0.221	0.011	significant

One-Way ANOVA of Mean 'Extracted Nicotine' Slope Estimates
Among Test Samples

Schedule (i)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.0640	6	0.0107	24.00	0.000
Within Samples	0.0062	14	0.0004		
Total (Corr.)	0.0702	20			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.0431	6	0.0072	43.66	0.000
Within Samples	0.0023	14	0.0002		
Total (Corr.)	0.0454	20			

Evaluation of Ratio (Max \div Min) of Standard Deviations
of 'Extracted Nicotine' Slope Estimates and
Corresponding Method of Comparison

Treatment Schedule	Std. Dev. Ratio (Max \div Min)	Method of Comparison
Schedule (i)	47.5	Pairwise T-test (unequal variance)
Schedule (ii)	76.3	Pairwise T-test (unequal variance)

One-way ANOVA analysis indicates significant differences (at $\alpha = 0.05$) among mean 'Extracted Nicotine' specific activity slope estimates for test samples under both Treatment Schedules (i) and (ii).

**ANOVA-Based Comparisons of Mean 'Extracted Nicotine' Slope for
Contrasts of Interest using Bonferroni-adjusted p-values**

ANOVA-Based Comparison	Schedule (i)			Schedule (ii)		
	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.010	0.9229	not significant	0.055	0.8182	not significant
084394 vs. 084454	21.319	0.0004	significant	25.645	0.0002	significant
084394 vs. 084455	14.204	0.0021	significant	14.326	0.0020	significant
084394 vs. 084456	0.041	0.8431	not significant	0.011	0.9174	not significant
084394 vs. 084457	7.890	0.0139	not significant	7.111	0.0184	not significant
084394 vs. 084458	90.364	0.0000	significant	166.712	0.0000	significant
084395 vs. 084454	22.239	0.0003	significant	28.073	0.0001	significant
084395 vs. 084455	14.957	0.0017	significant	16.154	0.0013	significant
084395 vs. 084456	0.090	0.7684	not significant	0.017	0.8994	not significant
084395 vs. 084457	8.454	0.0115	not significant	8.415	0.0116	not significant
084395 vs. 084458	92.247	0.0000	significant	172.817	0.0000	significant
084454 vs. 084455	0.720	0.4104	not significant	1.636	0.2216	not significant
084454 vs. 084456	19.498	0.0006	significant	26.726	0.0001	significant
084454 vs. 084457	3.270	0.0921	not significant	5.748	0.0310	not significant
084454 vs. 084458	23.899	0.0002	significant	61.585	0.0000	significant
084455 vs. 084456	12.725	0.0031	not significant	15.136	0.0016	significant
084455 vs. 084457	0.921	0.3534	not significant	1.251	0.2823	not significant
084455 vs. 084458	32.915	0.0001	significant	83.297	0.0000	significant
084456 vs. 084457	6.798	0.0207	not significant	7.685	0.0150	not significant
084456 vs. 084458	86.570	0.0000	significant	169.450	0.0000	significant
084457 vs. 084458	44.850	0.0000	significant	104.961	0.0000	significant

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were as follows:

Schedule (i)				Schedule (ii)			
Sample Description	Sample ID	Mean Slope	Homogenous Groupings	Sample Description	Sample ID	Mean Slope	Homogenous Groupings
2S3	084395	0.019	X	2S3	084395	0.014	X
Camel SNUS Frost	084394	0.020	X	Copenhagen Long Cut	084456	0.015	X
Copenhagen Long Cut	084456	0.024	XX	Camel SNUS Frost	084394	0.016	X
Ariva Wintergreen	084457	0.069	XXX	Ariva Wintergreen	084457	0.044	XX
Mellow Sticks	084455	0.085	XX	Mellow Sticks	084455	0.056	X
Fresh Strips	084454	0.100	X	Fresh Strips	084454	0.069	X
Fresh Orbs	084458	0.184	X	Fresh Orbs	084458	0.151	X

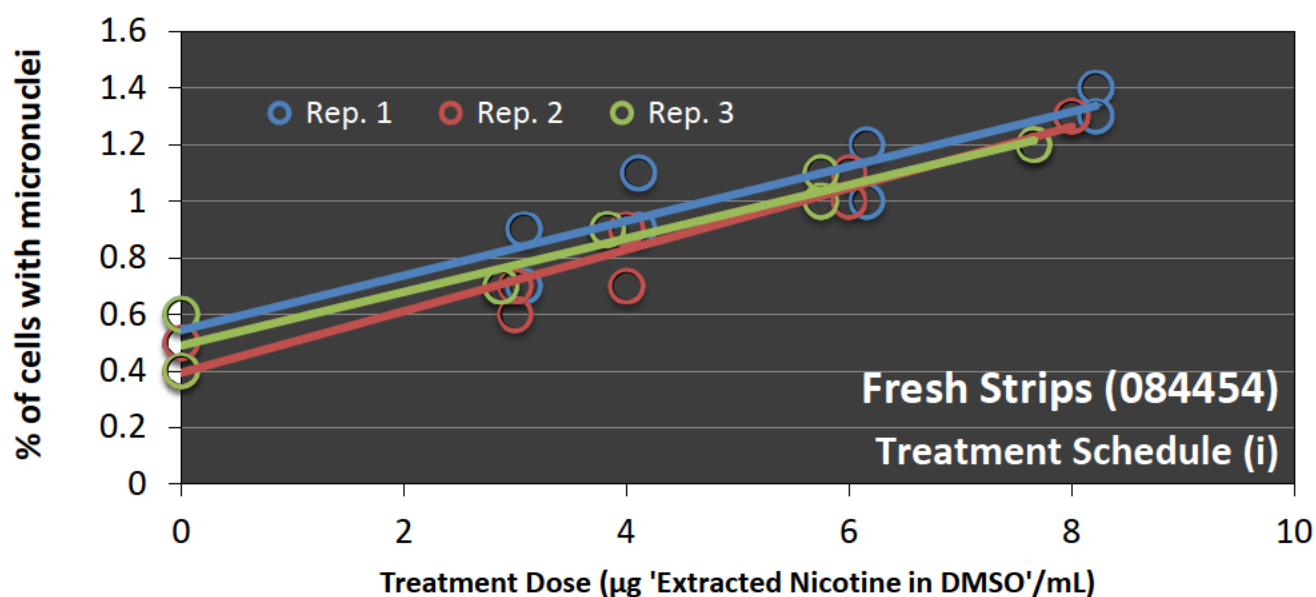
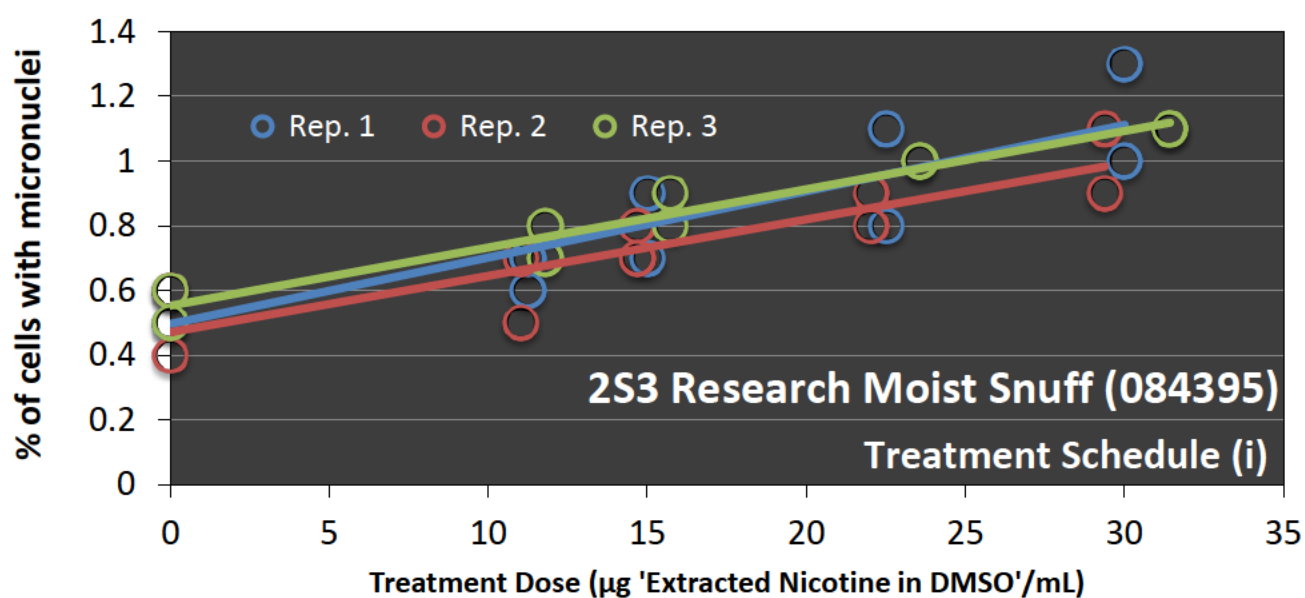
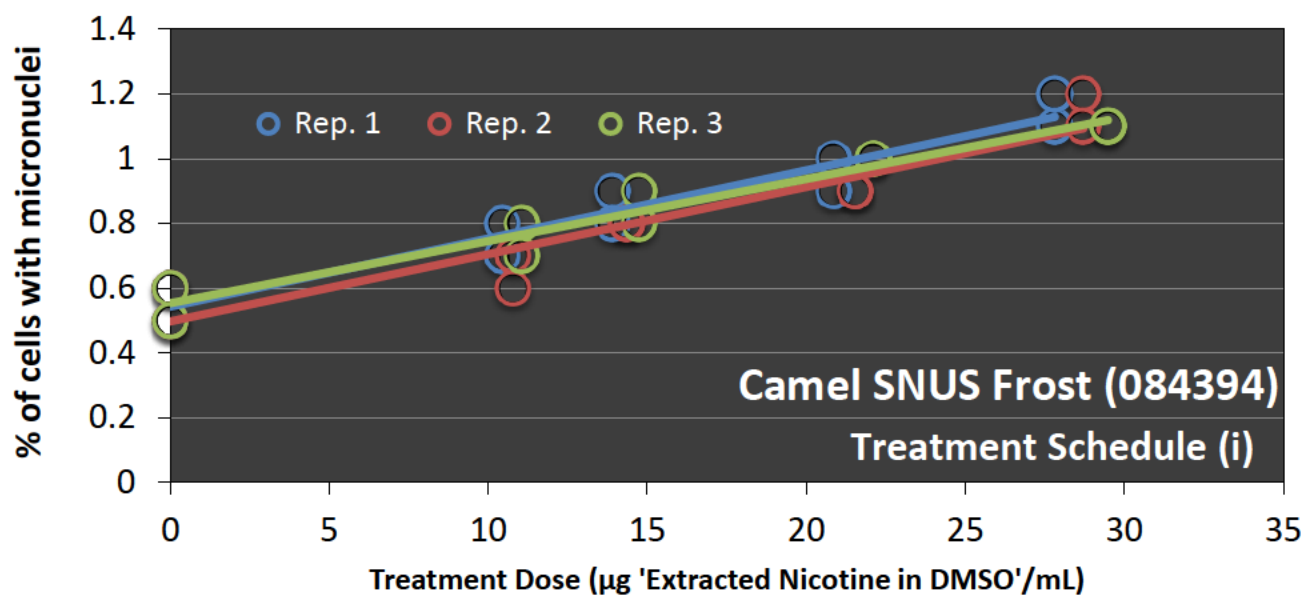
**Pairwise T-test Comparisons of Mean 'Extracted Nicotine' Slope
for Contrasts of Interest using Bonferroni-adjusted p-values**

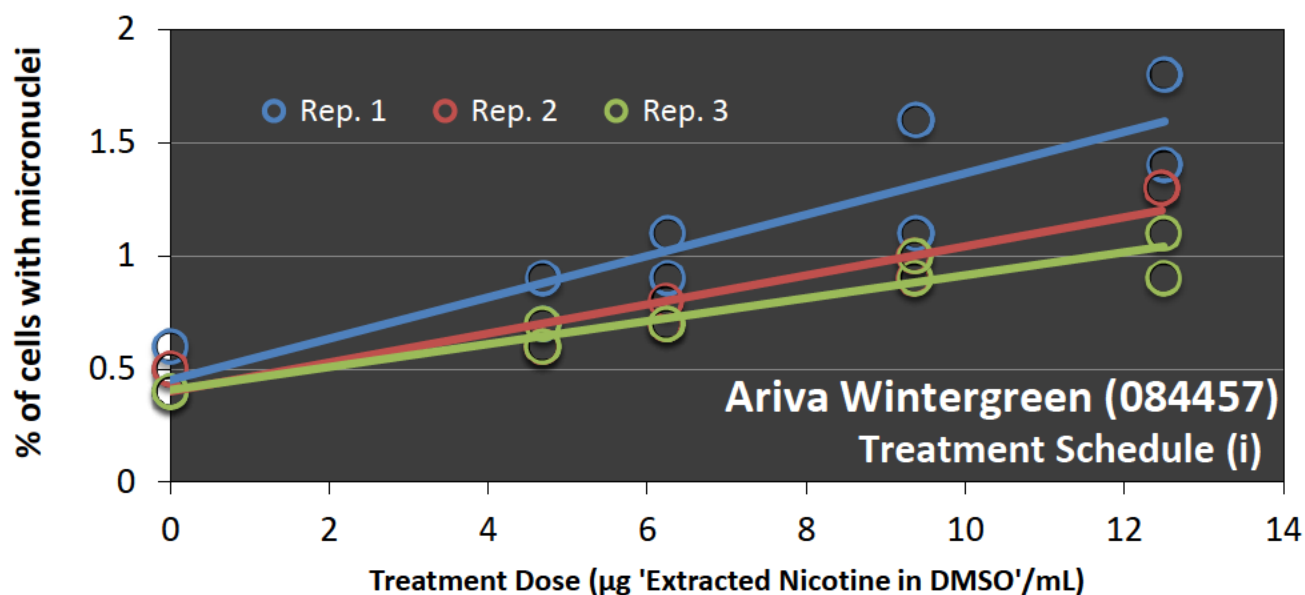
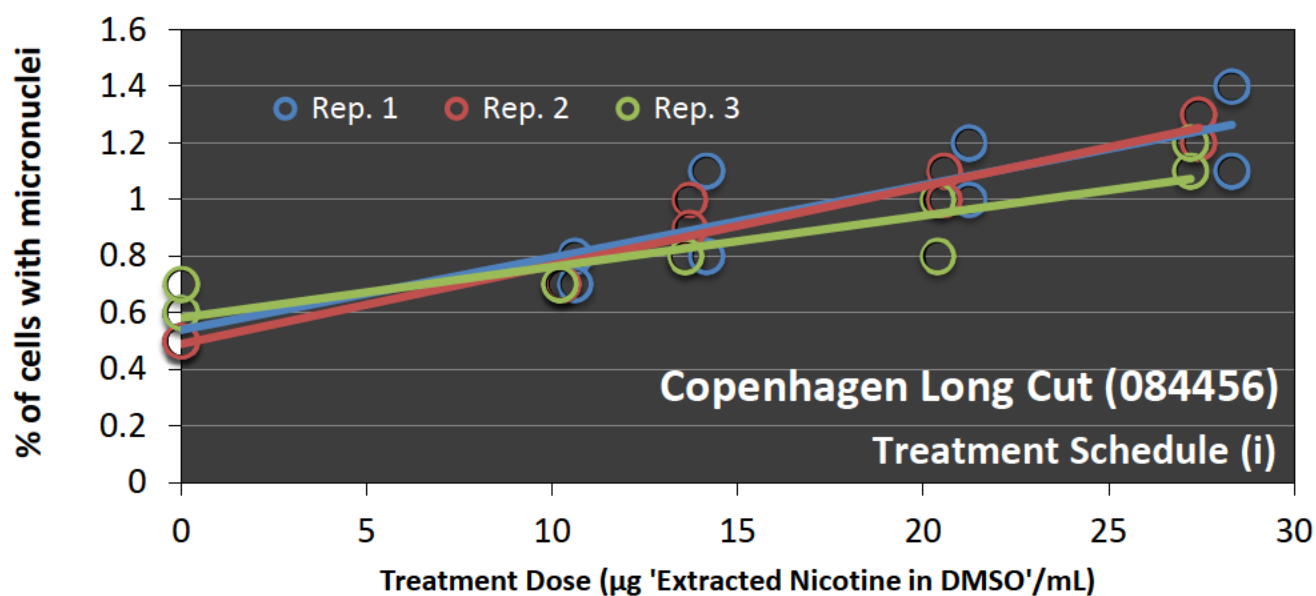
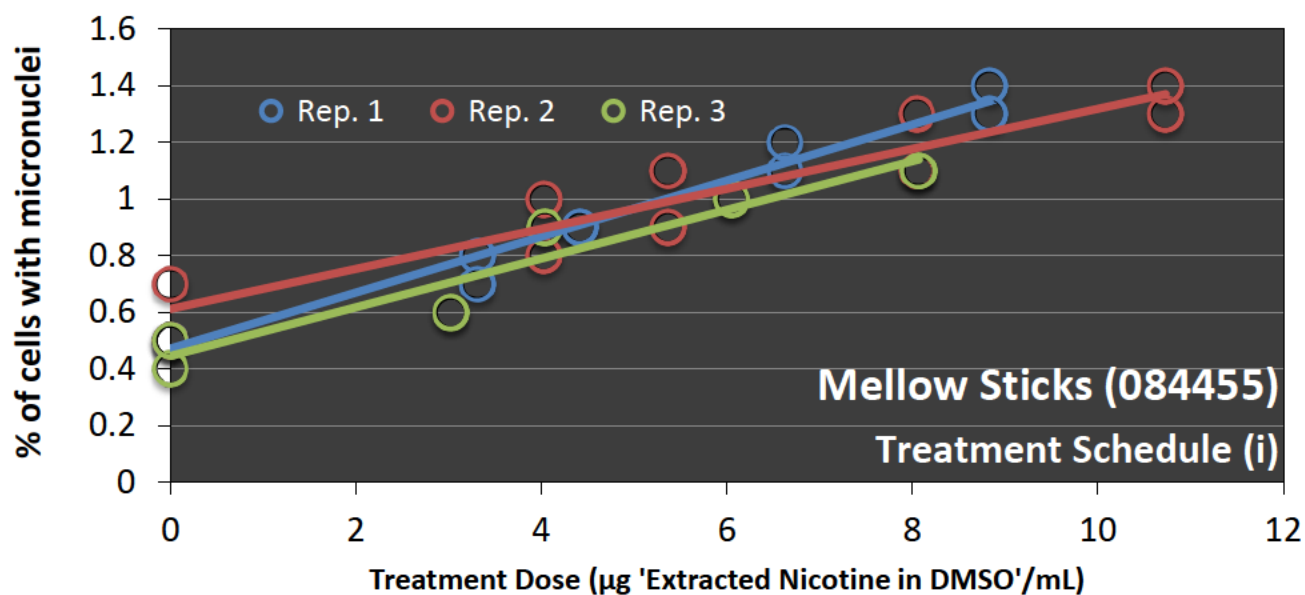
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	1.525	0.2019	not significant	1.281	0.2694	not significant
084394 vs. 084454	17.687	0.0001	significant	28.635	0.0000	significant
084394 vs. 084455	7.922	0.0014	significant	4.337	0.0123	not significant
084394 vs. 084456	1.153	0.3130	not significant	0.660	0.5453	not significant
084394 vs. 084457	4.042	0.0156	not significant	4.349	0.0122	not significant
084394 vs. 084458	5.792	0.0044	not significant	8.338	0.0011	significant
084395 vs. 084454	17.831	0.0001	significant	44.204	0.0000	significant
084395 vs. 084455	8.097	0.0013	significant	4.657	0.0096	not significant
084395 vs. 084456	1.669	0.1705	not significant	1.381	0.2393	not significant
084395 vs. 084457	4.176	0.0140	not significant	4.841	0.0084	not significant
084395 vs. 084458	5.850	0.0043	not significant	8.519	0.0010	significant
084454 vs. 084455	1.570	0.1915	not significant	1.484	0.2119	not significant
084454 vs. 084456	14.226	0.0001	significant	64.116	0.0000	significant
084454 vs. 084457	2.441	0.0711	not significant	4.013	0.0160	not significant
084454 vs. 084458	2.943	0.0423	not significant	5.088	0.0070	not significant
084455 vs. 084456	7.070	0.0021	significant	4.532	0.0106	not significant
084455 vs. 084457	1.142	0.3173	not significant	1.072	0.3439	not significant
084455 vs. 084458	3.359	0.0283	not significant	5.176	0.0066	not significant
084456 vs. 084457	3.647	0.0218	not significant	4.678	0.0095	not significant
084456 vs. 084458	5.640	0.0049	not significant	8.450	0.0011	significant
084457 vs. 084458	3.759	0.0198	not significant	6.208	0.0034	not significant

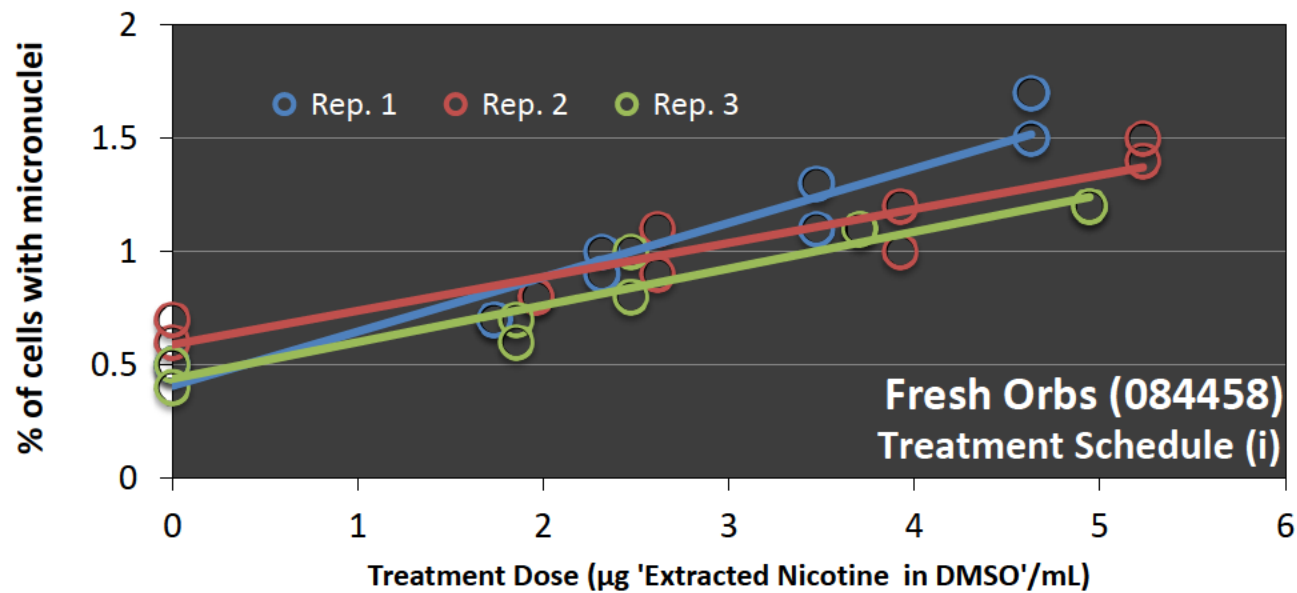
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were detected between:

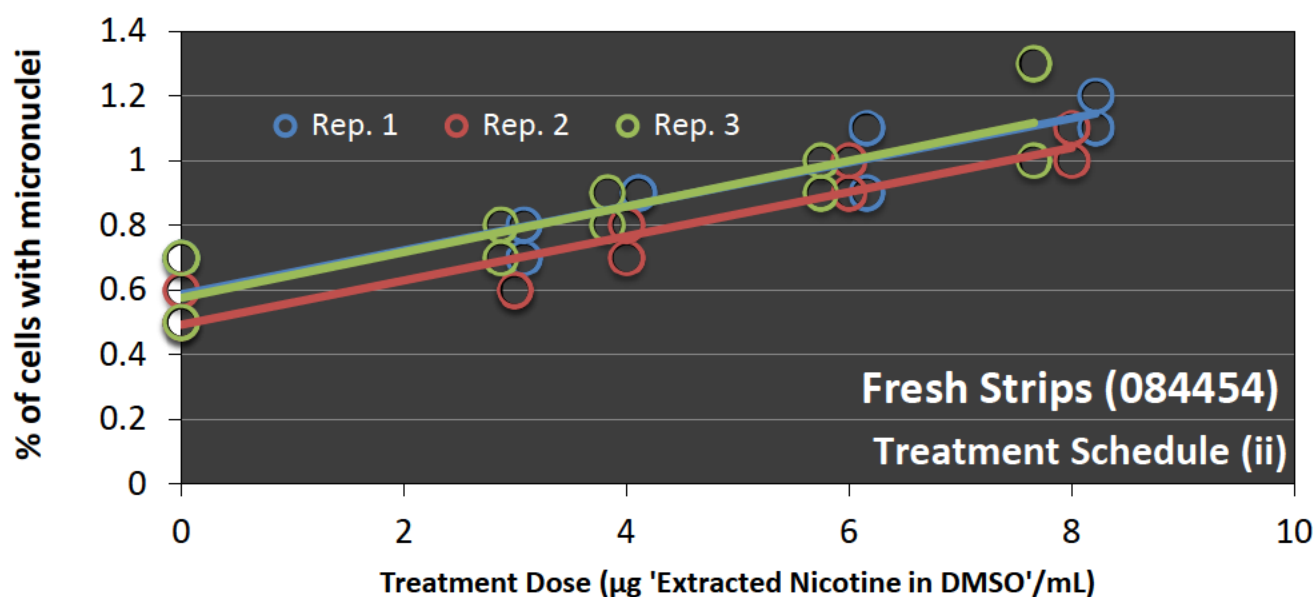
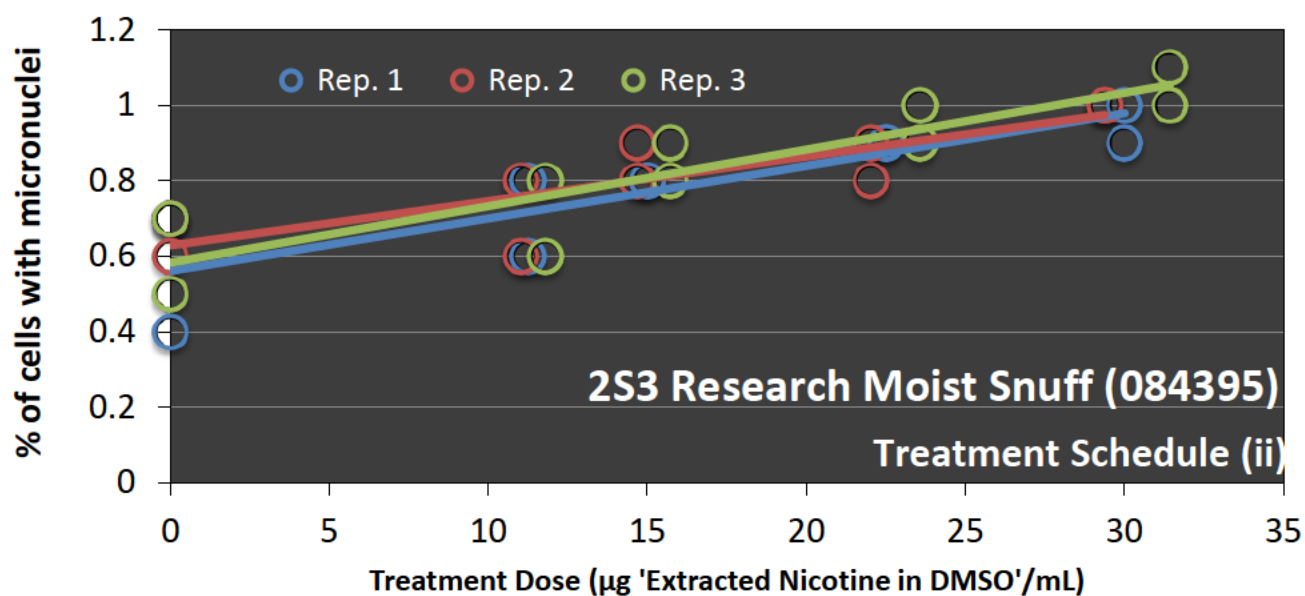
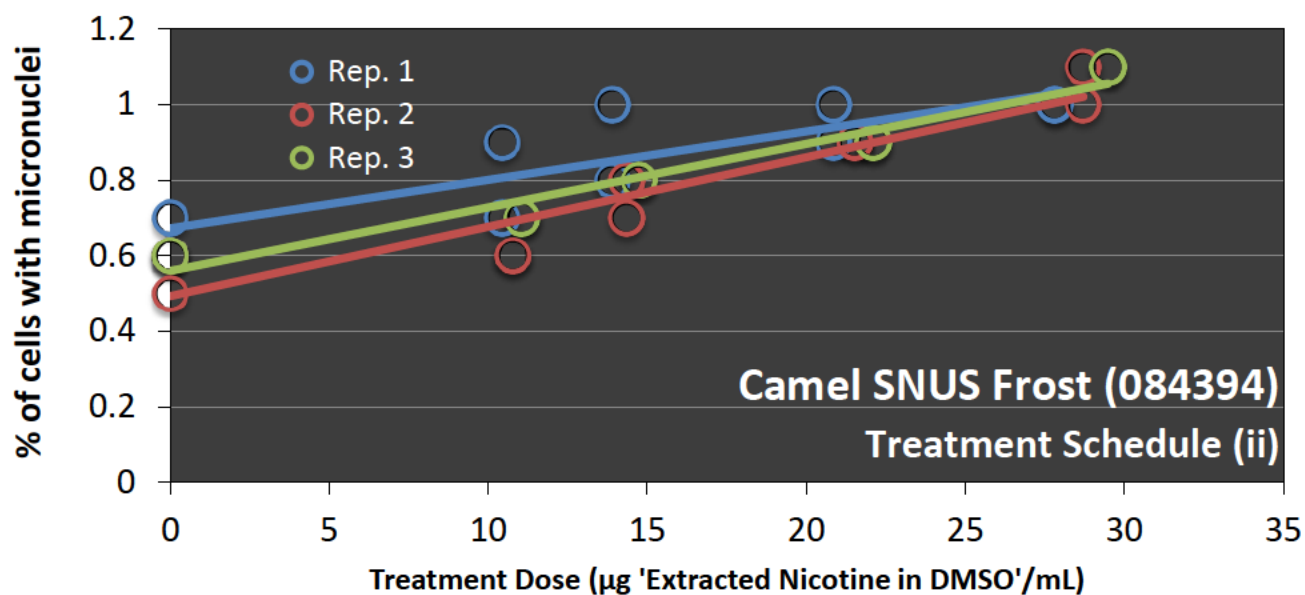
Fresh Strips (084454) as well as Mellow Sticks (084455) and each of {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)} under treatment schedule (i).

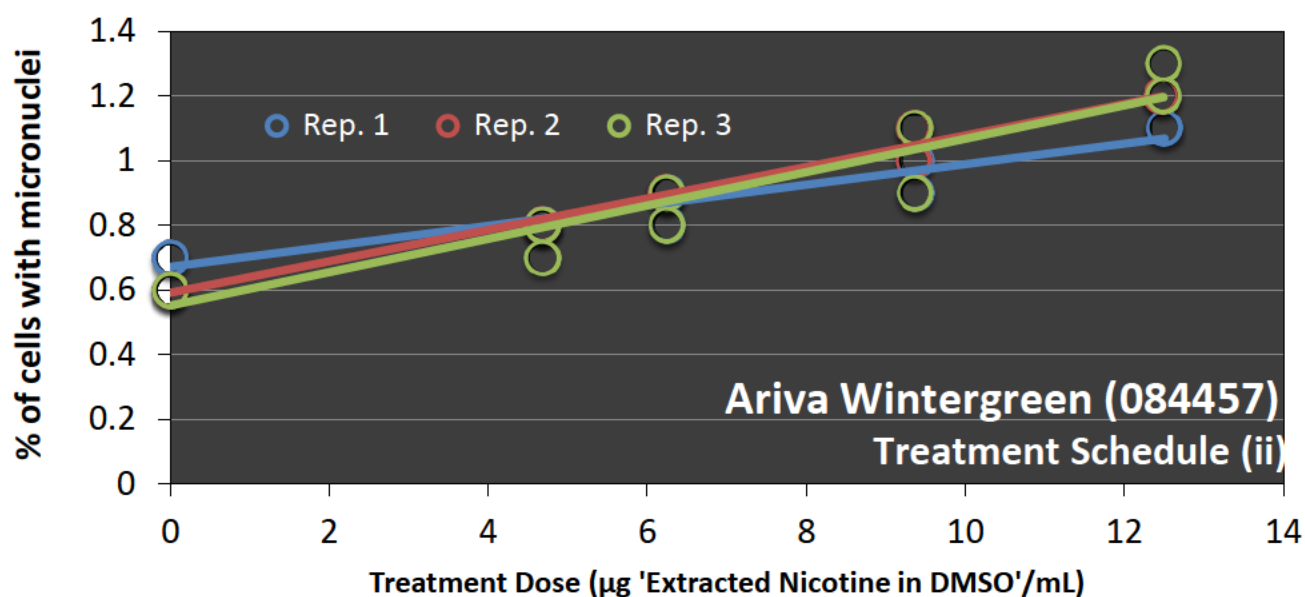
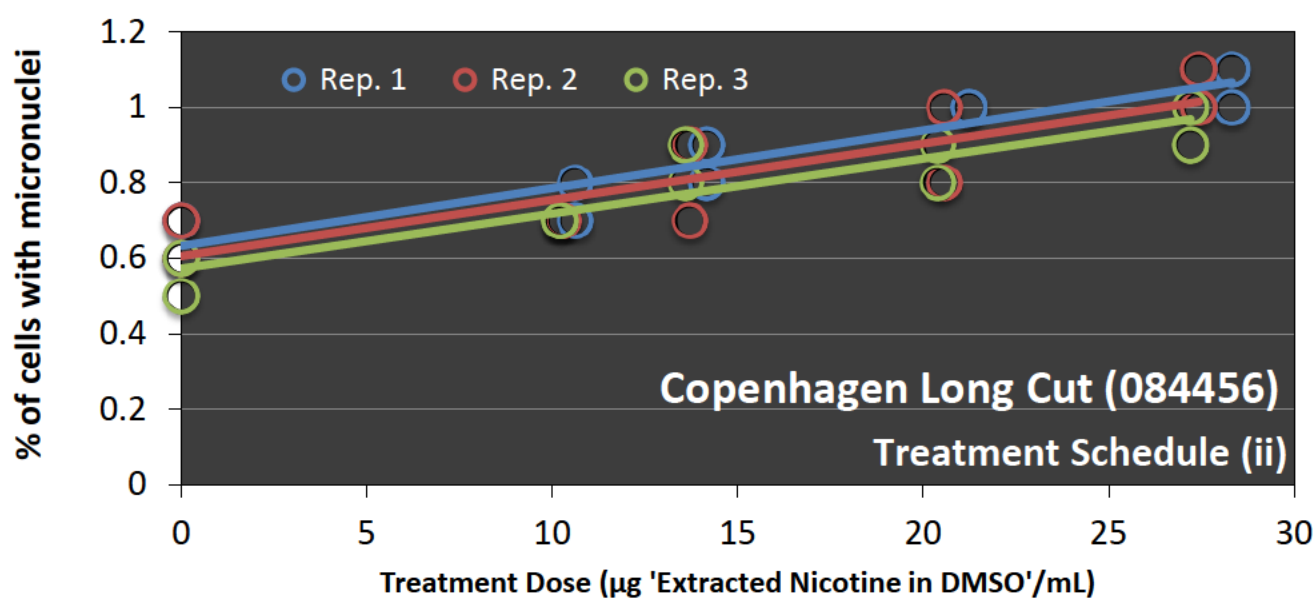
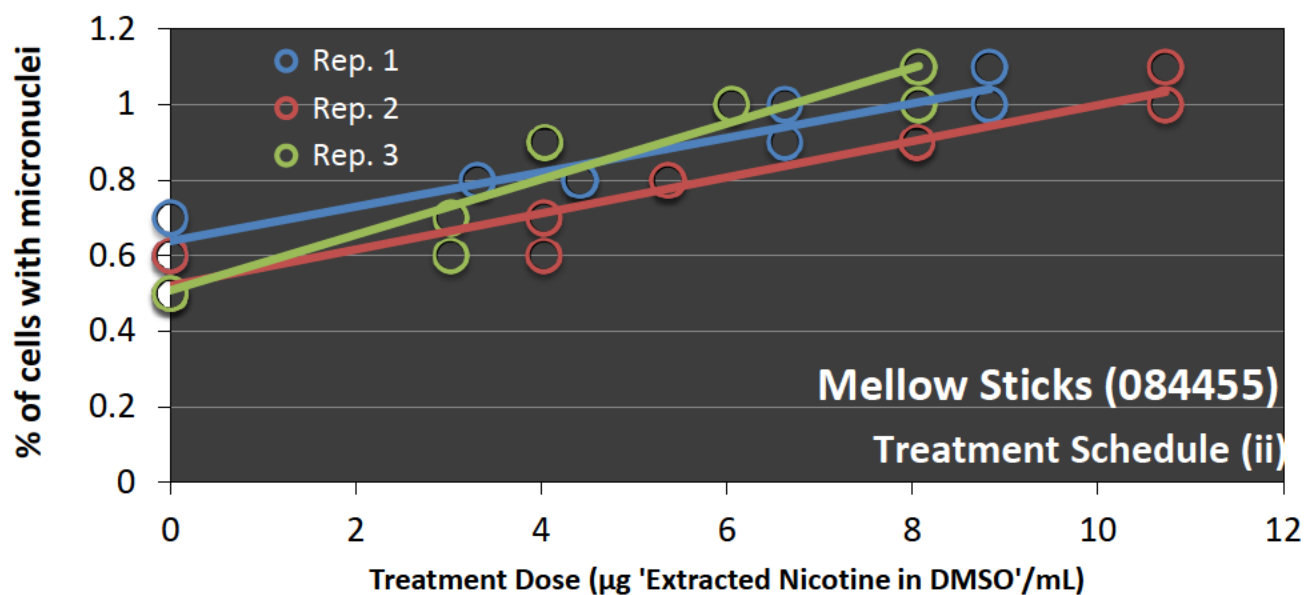
Fresh Strips (084454) as well as Fresh Orbs (084458) and each of {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)} under treatment schedule (ii).

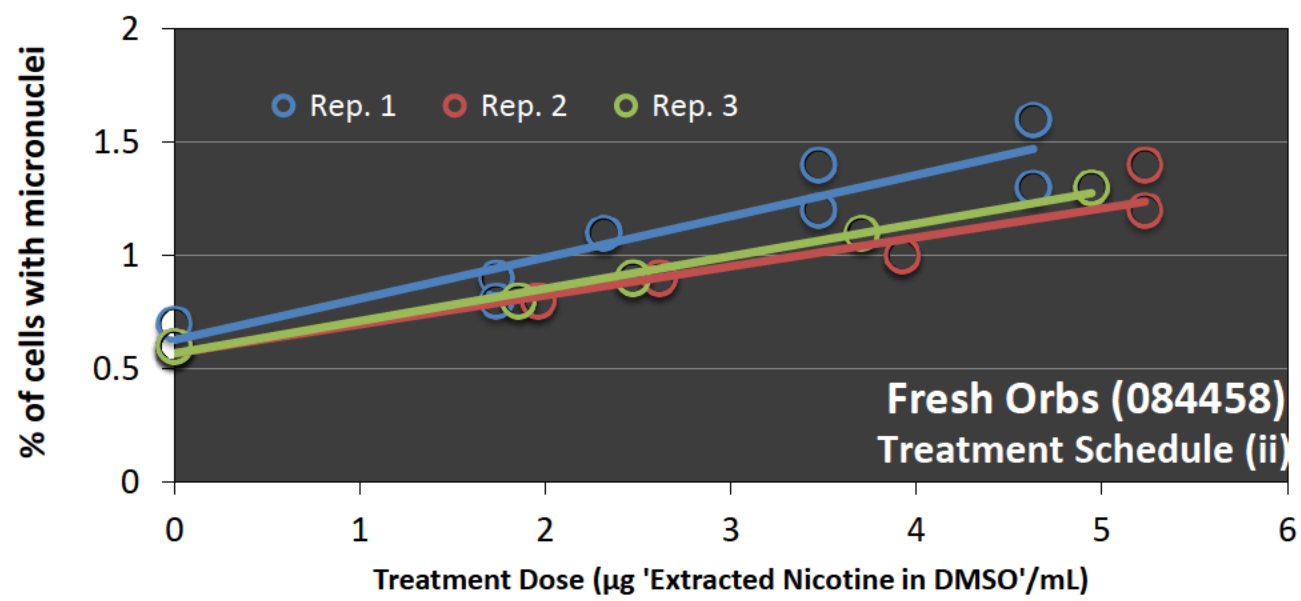


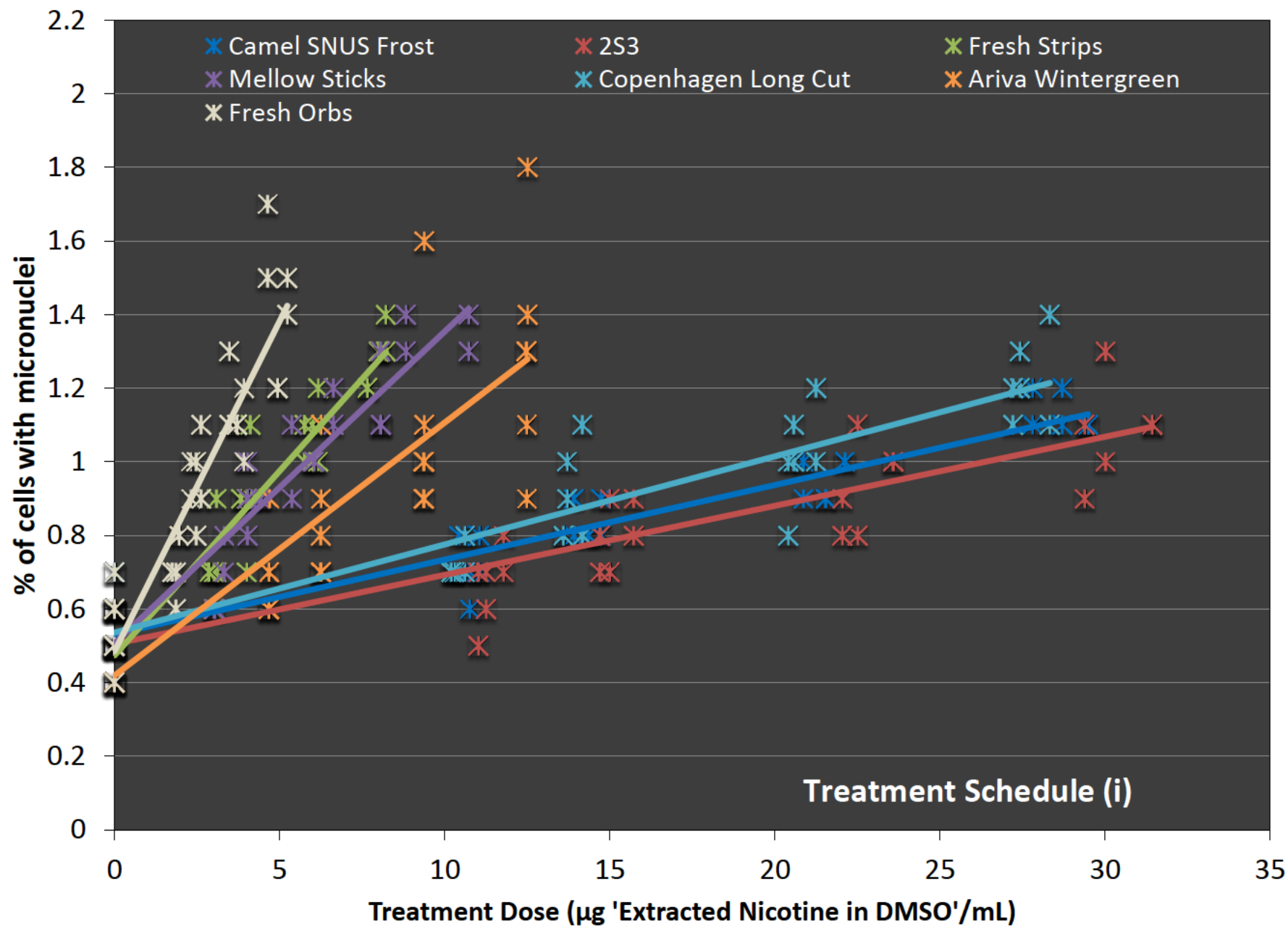


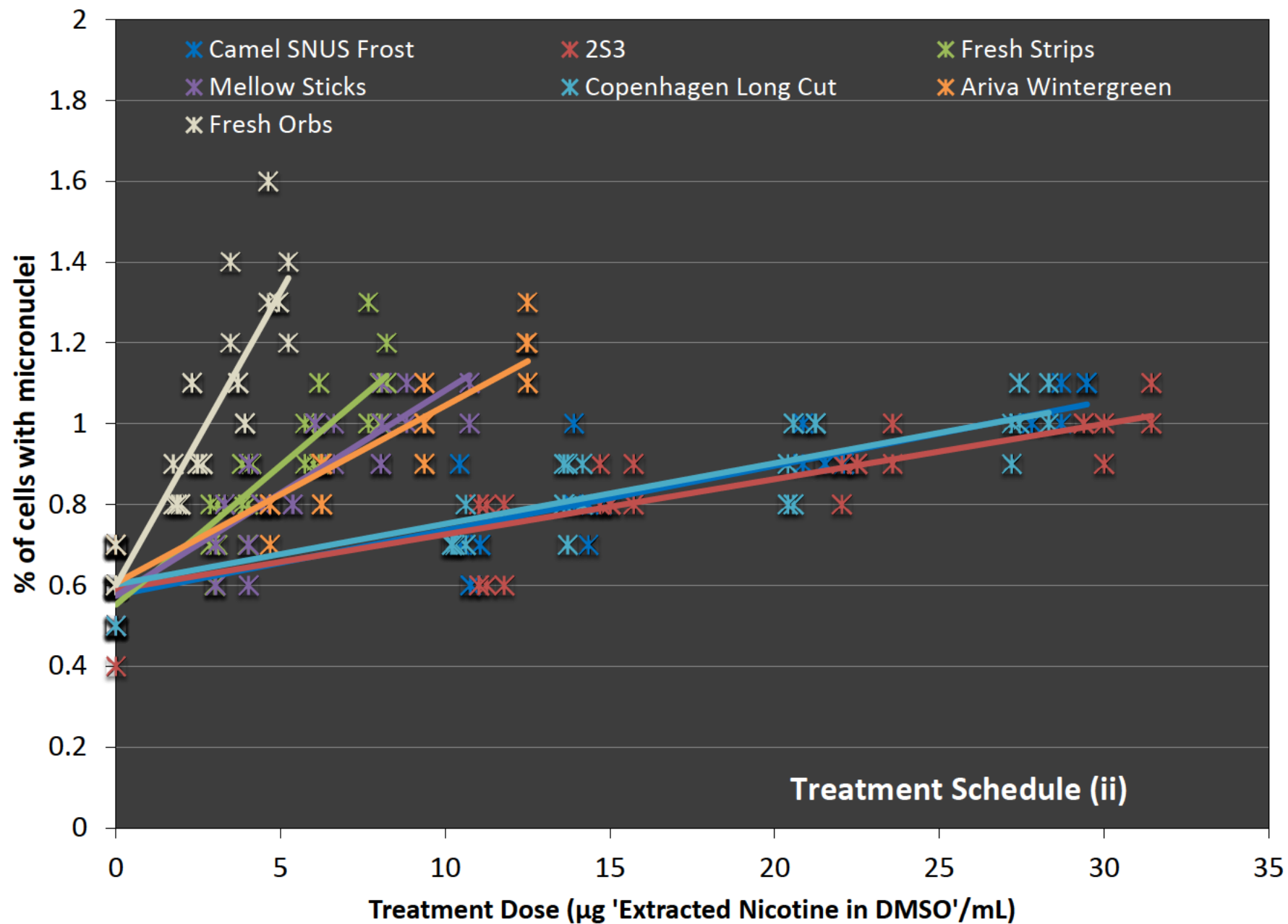












Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/(mg 'Extracted Smokeless Tobacco in DMSO'/mL)] (ST)

Treatment Schedule	Sample ID	Sample Description	% micronucleated cells/(mg 'Extracted Smokeless Tobacco in DMSO'/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'ST' Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			(mg 'ST'/mL)	slope	(mg 'ST'/mL)	slope	(mg 'ST'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 2.22	0.264	0 - 2.22	0.268	0 - 2.22	0.254	0.262	0.004	0.244 - 0.28	0.000	significant
Schedule (i)	084395	2S3	0 - 2.22	0.277	0 - 2.22	0.231	0 - 2.22	0.254	0.254	0.013	0.197 - 0.311	0.003	significant
Schedule (i)	084454	Fresh Strips	0 - 2.22	0.356	0 - 2.22	0.391	0 - 2.22	0.326	0.358	0.019	0.276 - 0.439	0.003	significant
Schedule (i)	084455	Mellow Sticks	0 - 2.22	0.393	0 - 2.22	0.341	0 - 2.22	0.312	0.349	0.024	0.247 - 0.451	0.005	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 2.22	0.326	0 - 2.22	0.343	0 - 2.22	0.221	0.297	0.038	0.132 - 0.461	0.016	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 2.22	0.514	0 - 2.22	0.360	0 - 2.22	0.285	0.386	0.067	0.096 - 0.676	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 2.22	0.500	0 - 2.22	0.352	0 - 2.22	0.361	0.404	0.048	0.198 - 0.61	0.014	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 2.22	0.160	0 - 2.22	0.238	0 - 2.22	0.223	0.207	0.024	0.105 - 0.309	0.013	significant
Schedule (ii)	084395	2S3	0 - 2.22	0.188	0 - 2.22	0.156	0 - 2.22	0.212	0.185	0.016	0.115 - 0.256	0.008	significant
Schedule (ii)	084454	Fresh Strips	0 - 2.22	0.251	0 - 2.22	0.246	0 - 2.22	0.244	0.247	0.002	0.237 - 0.257	0.000	significant
Schedule (ii)	084455	Mellow Sticks	0 - 2.22	0.181	0 - 2.22	0.231	0 - 2.22	0.267	0.226	0.025	0.119 - 0.334	0.012	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 2.22	0.195	0 - 2.22	0.184	0 - 2.22	0.178	0.185	0.005	0.165 - 0.206	0.001	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 2.22	0.178	0 - 2.22	0.273	0 - 2.22	0.290	0.247	0.035	0.097 - 0.396	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 2.22	0.380	0 - 2.22	0.301	0 - 2.22	0.319	0.333	0.024	0.231 - 0.435	0.005	significant

One-Way ANOVA of Mean 'Extracted Smokeless Tobacco' Slope Estimates Among Test Samples

Schedule (i)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.064	6	0.011	2.640	0.063
Within Samples	0.056	14	0.004		
Total (Corr.)	0.120	20			

Evaluation of Ratio (Max ÷ Min) of Standard Deviations of 'Extracted Smokeless Tobacco' Slope Estimates and Corresponding Method of Comparison

Treatment Schedule	Std. Dev. Ratio (Max ÷ Min)	Method of Comparison
Schedule (i)	16.4	Pairwise T-test (unequal variance)
Schedule (ii)	15.4	Pairwise T-test (unequal variance)

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.047	6	0.008	5.621	0.004
Within Samples	0.020	14	0.001		
Total (Corr.)	0.067	20			

One-way ANOVA analysis indicates significant differences (at $\alpha = 0.05$) among mean 'Extracted Smokeless Tobacco' specific activity slope estimates for test samples under Treatment Schedule (ii) only.

ANOVA-Based Comparisons of Mean 'Extracted Smokeless Tobacco' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

ANOVA-Based Comparison	Schedule (i)			Schedule (ii)		
	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.0246	0.8776	not significant	0.5124	0.4859	not significant
084394 vs. 084454	3.3936	0.0867	not significant	1.7258	0.2101	not significant
084394 vs. 084455	2.7981	0.1166	not significant	0.3975	0.5385	not significant
084394 vs. 084456	0.4457	0.5152	not significant	0.4966	0.4926	not significant
084394 vs. 084457	5.7233	0.0313	not significant	1.7064	0.2125	not significant
084394 vs. 084458	7.5226	0.0159	not significant	17.1092	0.0010	significant
084395 vs. 084454	3.9962	0.0654	not significant	4.1188	0.0619	not significant
084395 vs. 084455	3.3476	0.0887	not significant	1.8126	0.1996	not significant
084395 vs. 084456	0.6798	0.4235	not significant	0.0001	0.9913	not significant
084395 vs. 084457	6.4986	0.0232	not significant	4.0888	0.0627	not significant
084395 vs. 084458	8.4079	0.0117	not significant	23.5431	0.0003	significant
084454 vs. 084455	0.0287	0.8679	not significant	0.4667	0.5056	not significant
084454 vs. 084456	1.3796	0.2598	not significant	4.0738	0.0631	not significant
084454 vs. 084457	0.3027	0.5909	not significant	0.0001	0.9942	not significant
084454 vs. 084458	0.8110	0.3830	not significant	7.9673	0.0136	not significant
084455 vs. 084456	1.0103	0.3319	not significant	1.7827	0.2031	not significant
084455 vs. 084457	0.5178	0.4836	not significant	0.4567	0.5102	not significant
084455 vs. 084458	1.1449	0.3027	not significant	12.2907	0.0035	not significant
084456 vs. 084457	2.9747	0.1066	not significant	4.0440	0.0640	not significant
084456 vs. 084458	4.3062	0.0569	not significant	23.4353	0.0003	significant
084457 vs. 084458	0.1228	0.7312	not significant	8.0091	0.0134	not significant

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted smokeless tobacco' slope were as follows under treatment schedule (ii):

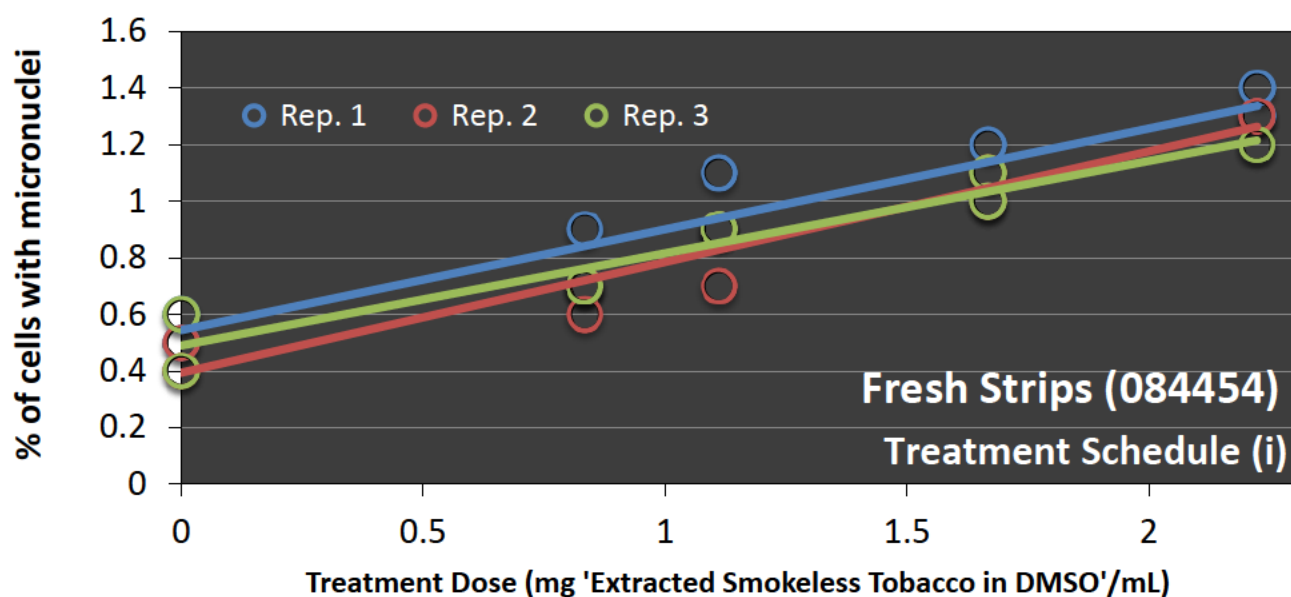
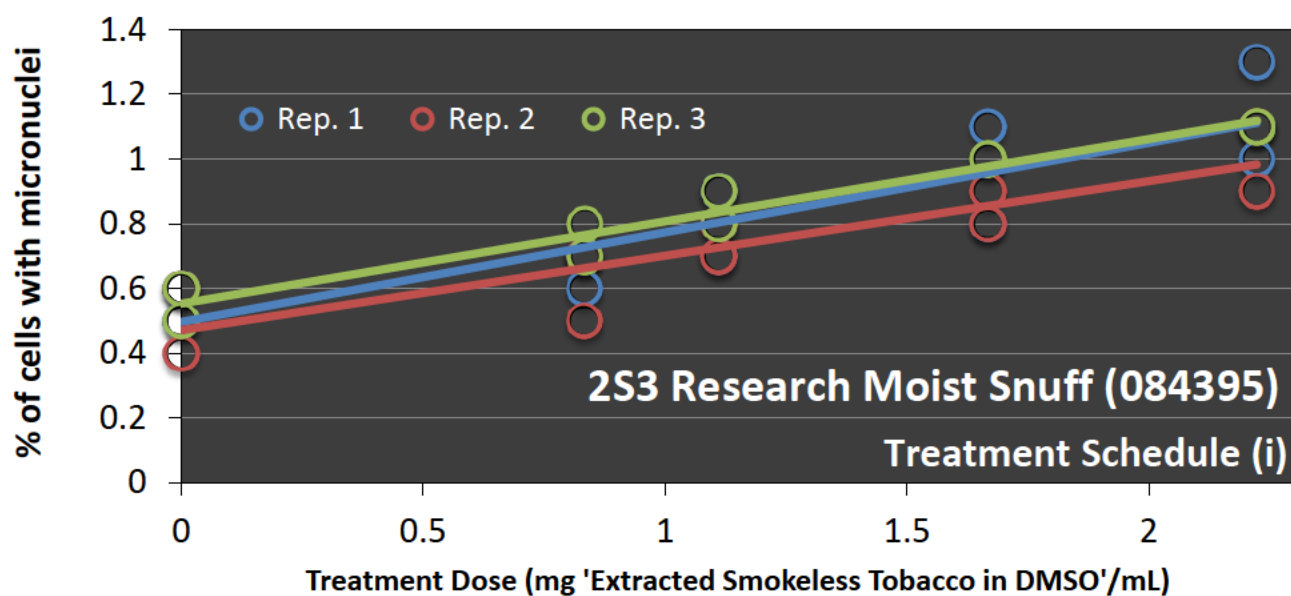
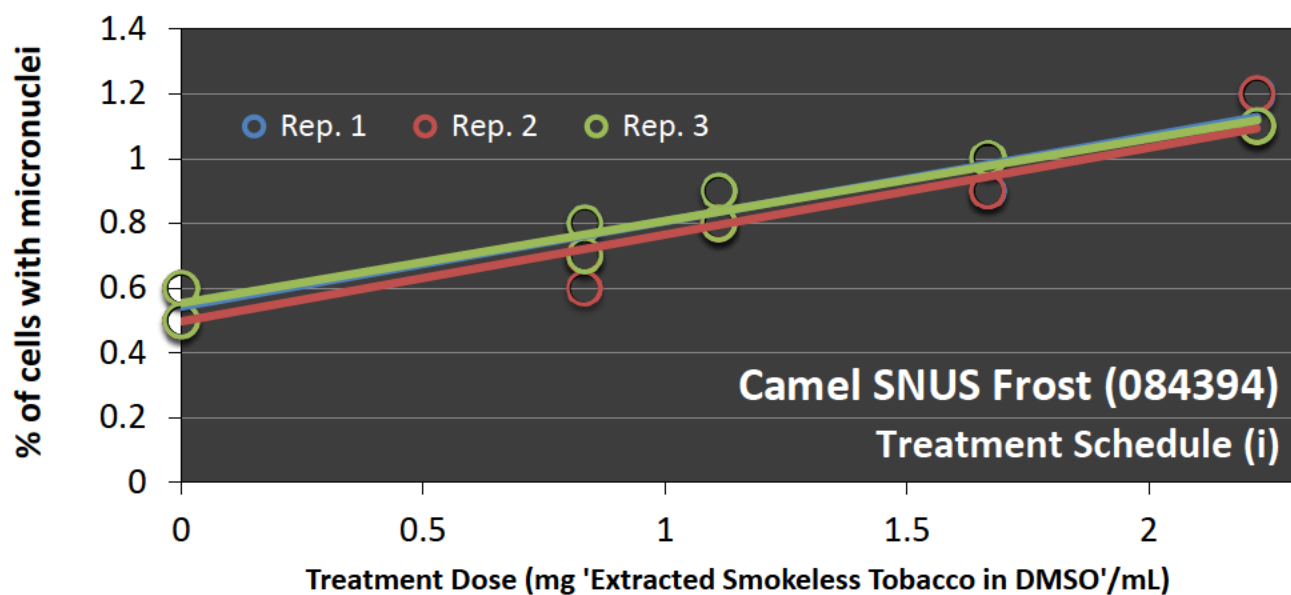
Schedule (ii)

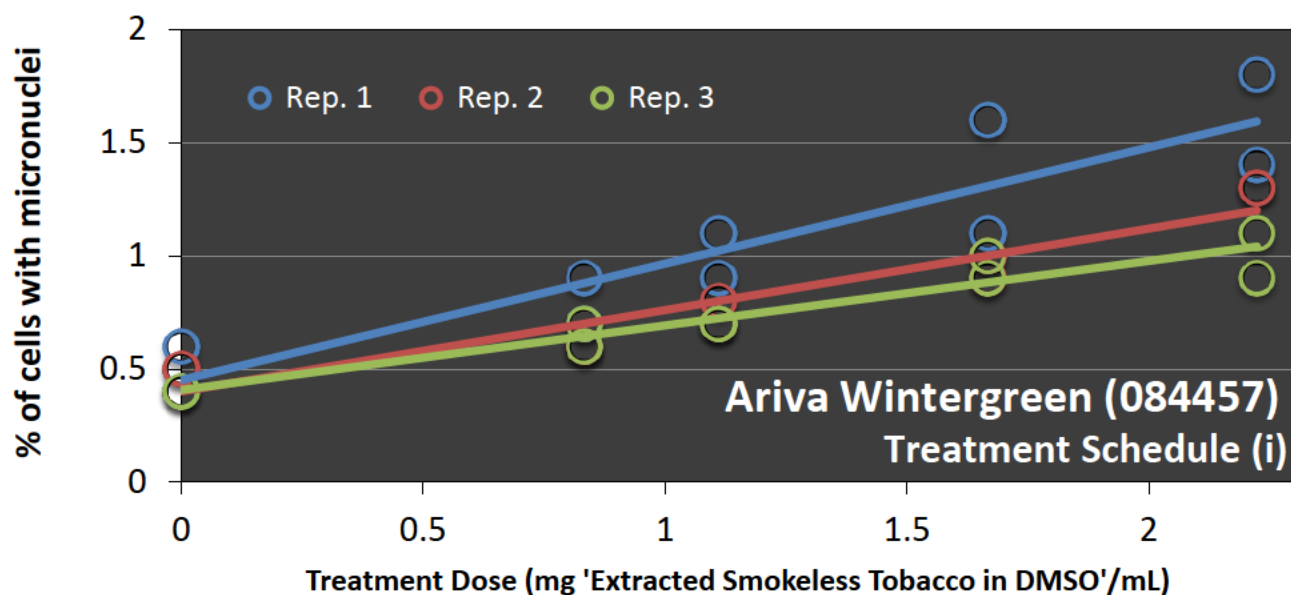
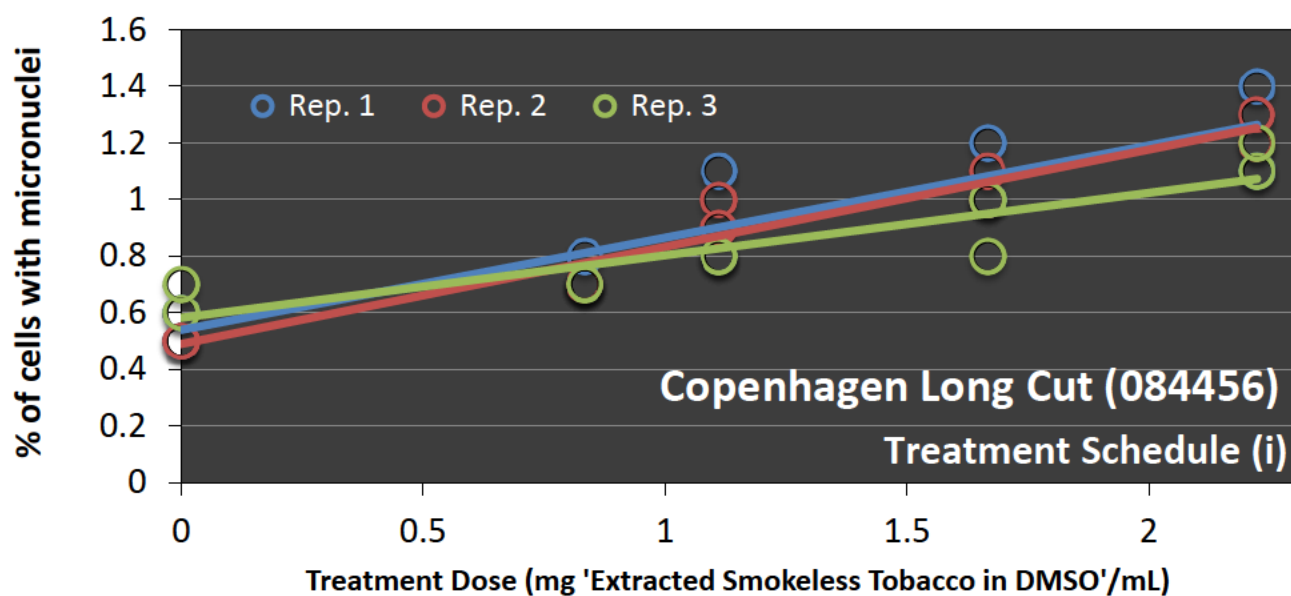
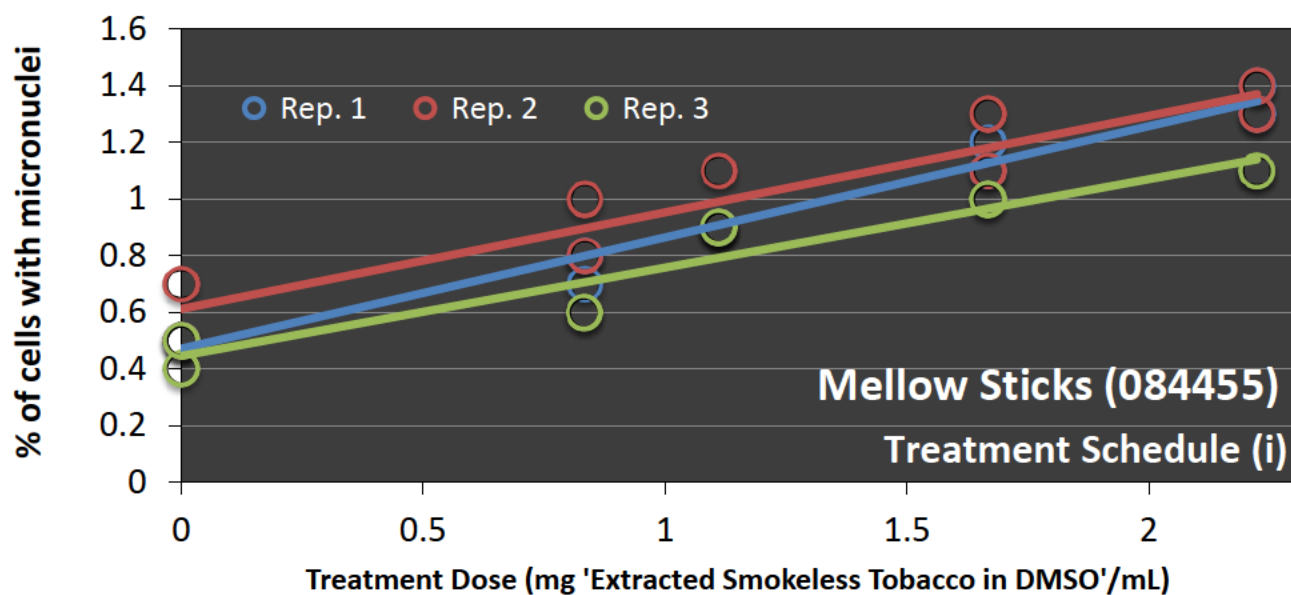
Sample Description	Sample ID	Mean Slope	Homogenous Groupings
2S3	084395	0.185	X
Copenhagen Long Cut	084456	0.185	X
Camel SNUS Frost	084394	0.207	X
Mellow Sticks	084455	0.226	XX
Ariva Wintergreen	084457	0.247	XX
Fresh Strips	084454	0.247	XX
Fresh Orbs	084458	0.333	X

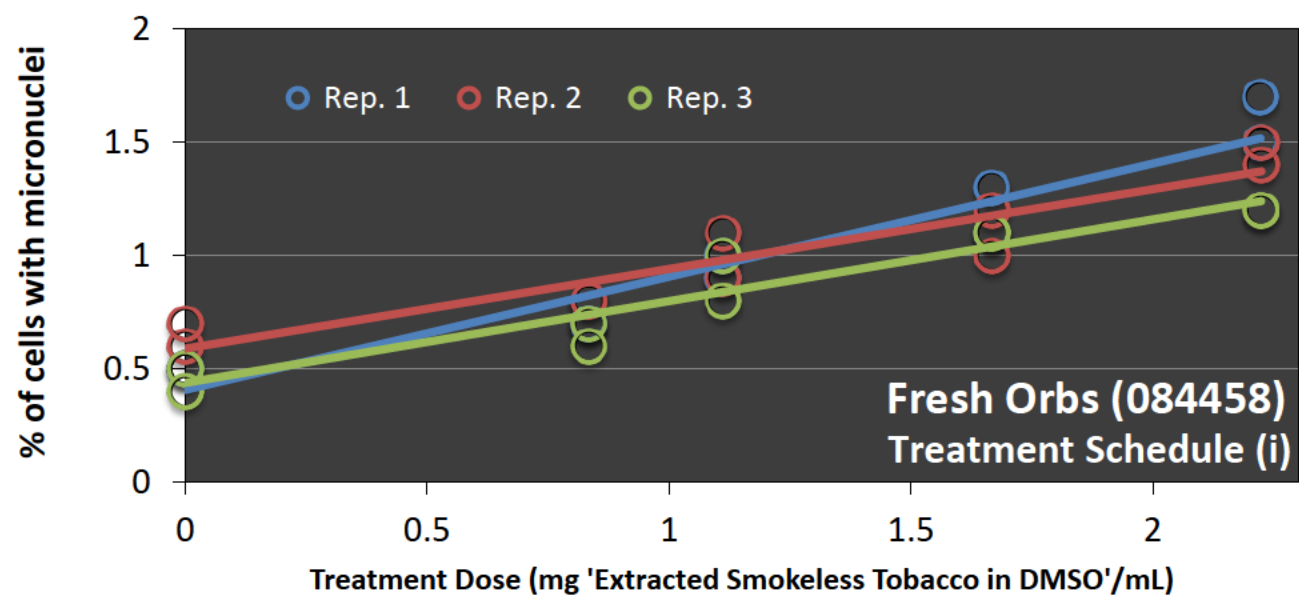
Pairwise T-Test Comparisons of Mean 'Extracted Smokeless Tobacco' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

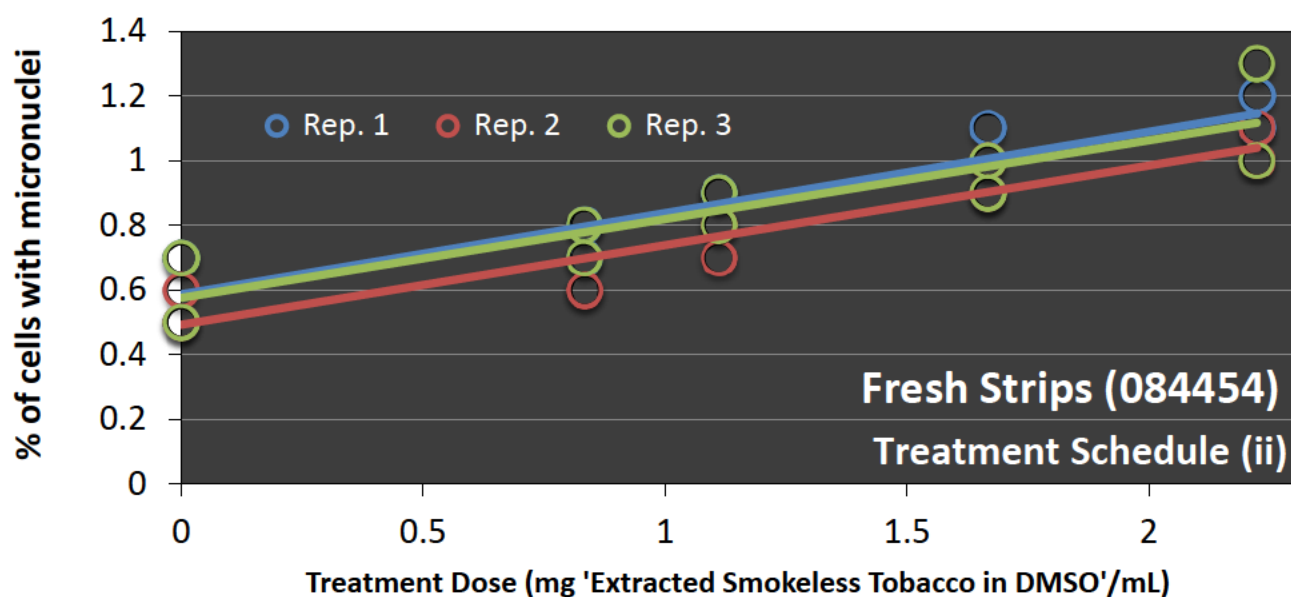
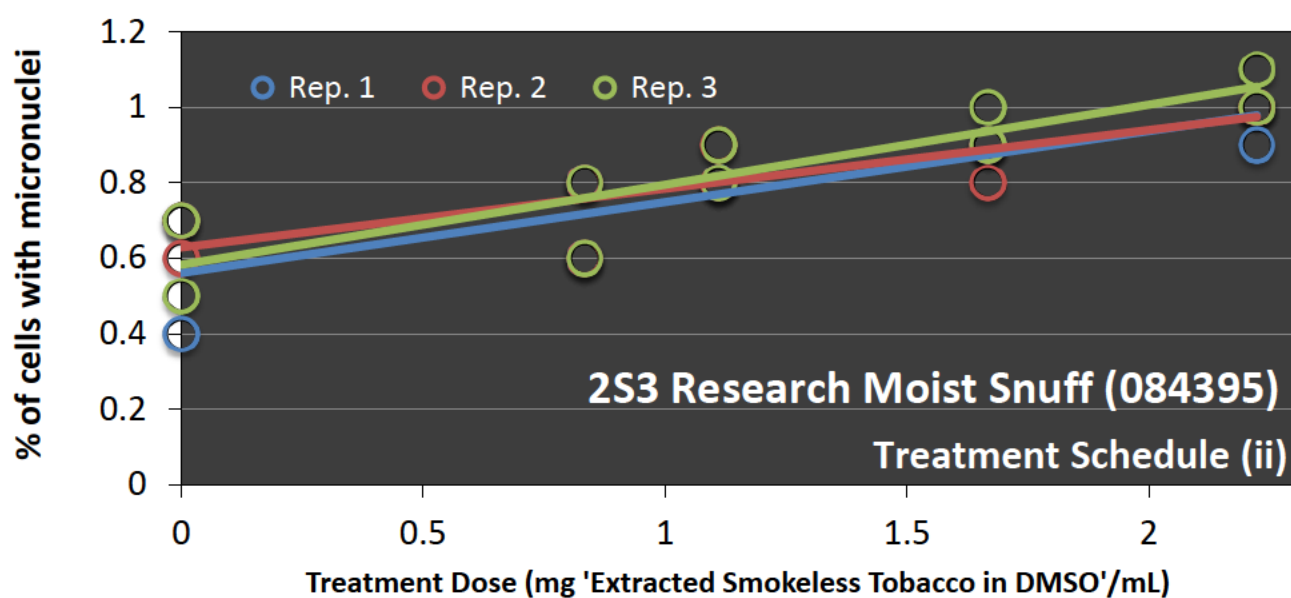
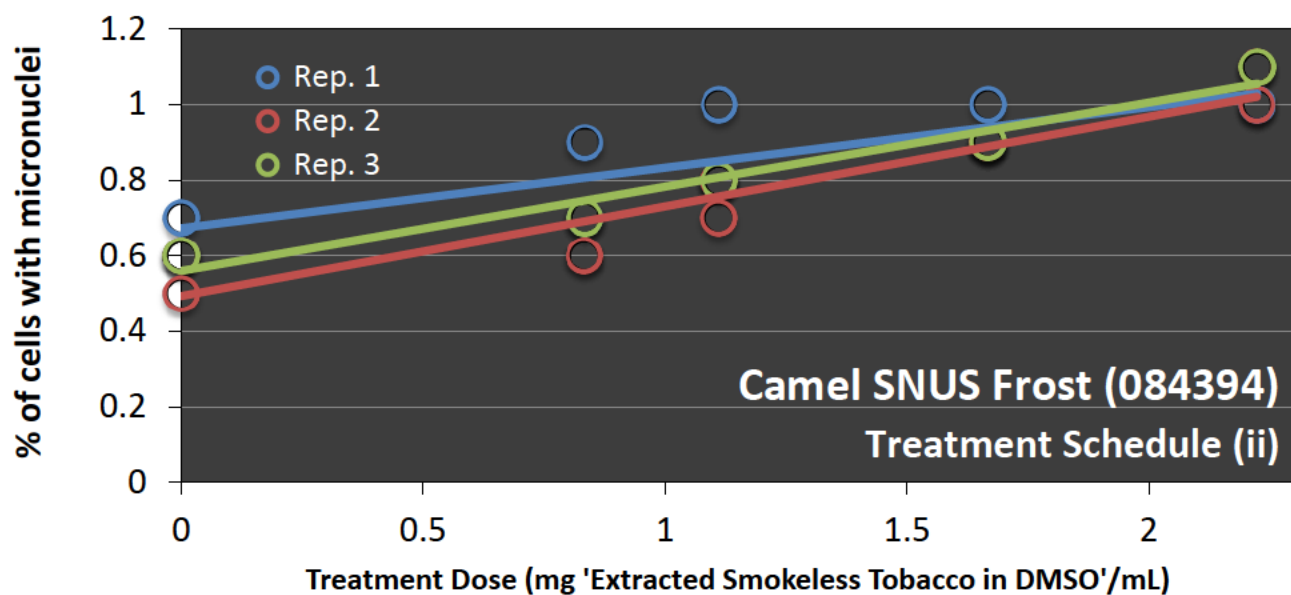
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.5856	0.5896	not significant	0.7573	0.4910	not significant
084394 vs. 084454	4.9378	0.0078	not significant	1.6827	0.1677	not significant
084394 vs. 084455	3.6074	0.0226	not significant	0.5584	0.6063	not significant
084394 vs. 084456	0.9008	0.4186	not significant	0.8882	0.4246	not significant
084394 vs. 084457	1.8376	0.1400	not significant	0.9474	0.3971	not significant
084394 vs. 084458	2.9552	0.0418	not significant	3.7577	0.0198	not significant
084395 vs. 084454	4.4884	0.0109	not significant	3.7376	0.0202	not significant
084395 vs. 084455	3.4941	0.0250	not significant	1.3739	0.2414	not significant
084395 vs. 084456	1.0571	0.3501	not significant	0.0198	0.9851	not significant
084395 vs. 084457	1.9248	0.1266	not significant	1.6054	0.1837	not significant
084395 vs. 084458	3.0222	0.0391	not significant	5.1231	0.0069	not significant
084454 vs. 084455	0.2899	0.7863	not significant	0.8307	0.4528	not significant
084454 vs. 084456	1.4288	0.2263	not significant	11.4848	0.0003	significant
084454 vs. 084457	0.4076	0.7044	not significant	0.0065	0.9951	not significant
084454 vs. 084458	0.9061	0.4161	not significant	3.6050	0.0227	not significant
084455 vs. 084456	1.1594	0.3108	not significant	1.6000	0.1848	not significant
084455 vs. 084457	0.5224	0.6290	not significant	0.4817	0.6552	not significant
084455 vs. 084458	1.0374	0.3581	not significant	3.1005	0.0362	not significant
084456 vs. 084457	1.1546	0.3126	not significant	1.7486	0.1553	not significant
084456 vs. 084458	1.7551	0.1541	not significant	6.0843	0.0037	not significant
084457 vs. 084458	0.2197	0.8369	not significant	2.0505	0.1096	not significant

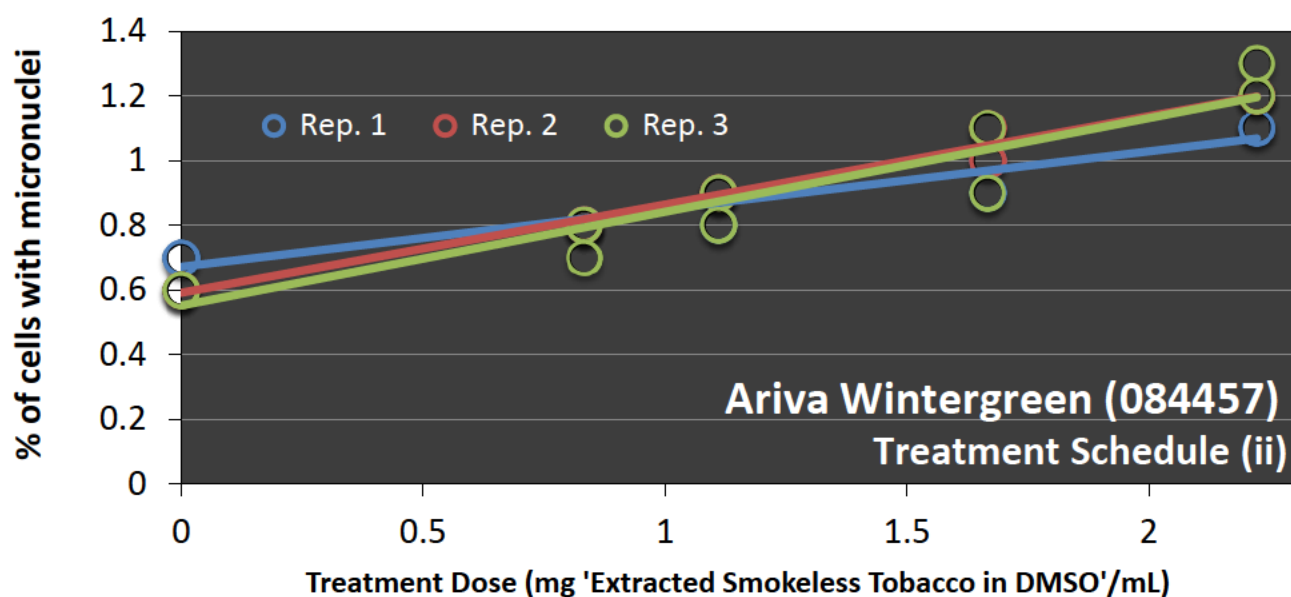
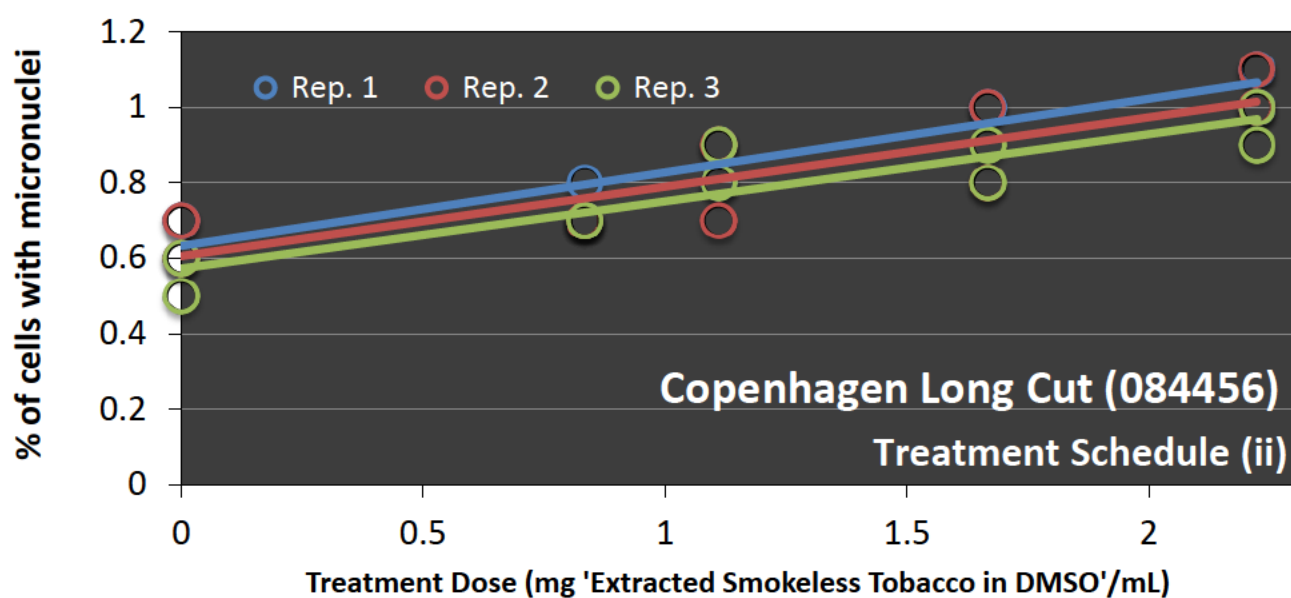
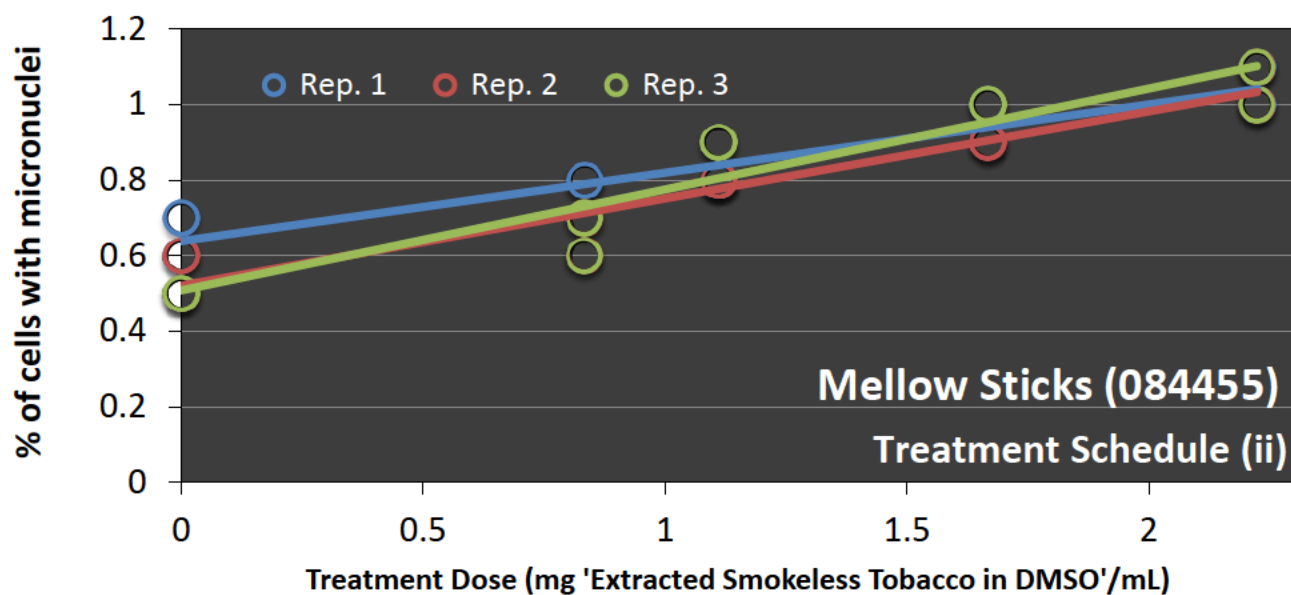
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted smokeless tobacco' slope were detected between Fresh Strips (084454) and Copenhagen Long Cut (084456) under treatment schedule (ii).

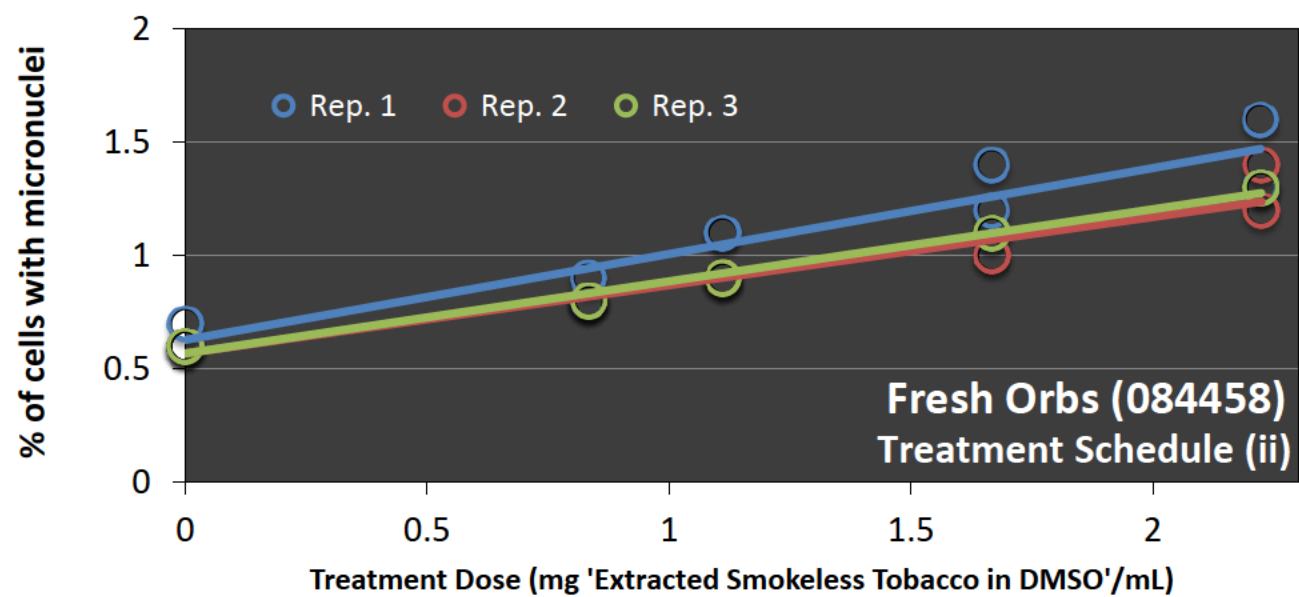


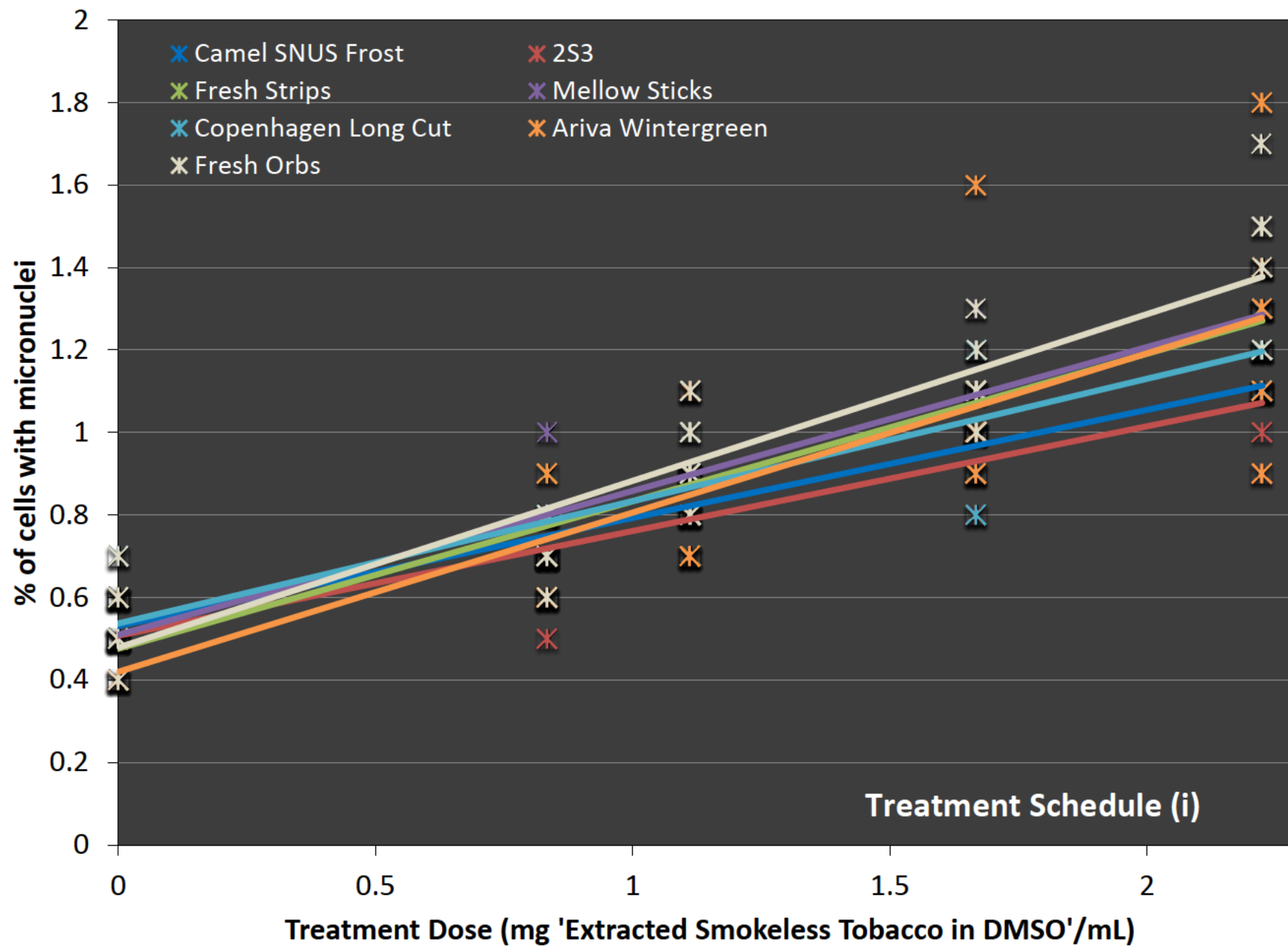


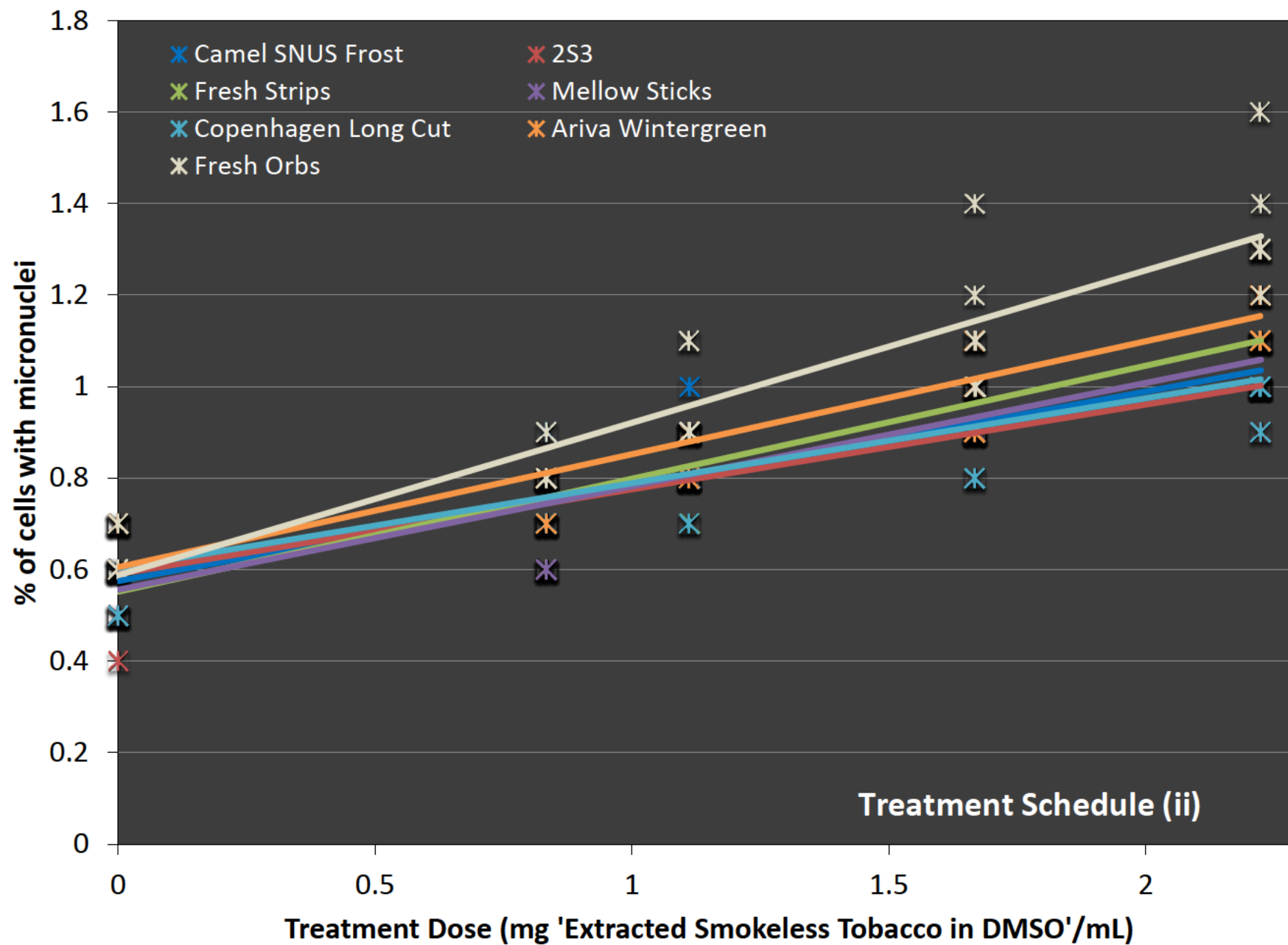












Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of cells with micronuclei/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL)] (ST-H₂O)

Treatment Schedule	Sample ID	Sample Description	% micronucleated cells /(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'ST-H ₂ O' Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard		t-test p-value (H ₀ : mean = 0)		
			(mg 'ST-H ₂ O'/mL)	slope	(mg 'ST-H ₂ O'/mL)	slope	(mg 'ST-H ₂ O'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 1.52	0.387	0 - 1.52	0.393	0 - 1.52	0.372	0.384	0.006	0.358 - 0.41	0.000	significant
Schedule (i)	084395	2S3	0 - 1.02	0.602	0 - 1.02	0.502	0 - 1.02	0.553	0.552	0.029	0.428 - 0.676	0.003	significant
Schedule (i)	084454	Fresh Strips	0 - 1.98	0.400	0 - 1.98	0.440	0 - 1.98	0.366	0.402	0.021	0.311 - 0.494	0.003	significant
Schedule (i)	084455	Mellow Sticks	0 - 2.09	0.418	0 - 2.09	0.363	0 - 2.09	0.332	0.371	0.025	0.263 - 0.48	0.005	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 0.992	0.730	0 - 0.992	0.769	0 - 0.992	0.495	0.665	0.086	0.297 - 1.03	0.016	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 2.14	0.533	0 - 2.14	0.374	0 - 2.14	0.296	0.401	0.070	0.1 - 0.702	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 2.11	0.527	0 - 2.11	0.371	0 - 2.11	0.380	0.426	0.051	0.209 - 0.643	0.014	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 1.52	0.235	0 - 1.52	0.348	0 - 1.52	0.326	0.303	0.035	0.154 - 0.453	0.013	significant
Schedule (ii)	084395	2S3	0 - 1.02	0.408	0 - 1.02	0.338	0 - 1.02	0.461	0.403	0.036	0.249 - 0.556	0.008	significant
Schedule (ii)	084454	Fresh Strips	0 - 1.98	0.283	0 - 1.98	0.277	0 - 1.98	0.274	0.278	0.003	0.267 - 0.289	0.000	significant
Schedule (ii)	084455	Mellow Sticks	0 - 2.09	0.193	0 - 2.09	0.246	0 - 2.09	0.284	0.241	0.027	0.126 - 0.355	0.012	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 0.992	0.436	0 - 0.992	0.412	0 - 0.992	0.399	0.416	0.011	0.369 - 0.462	0.001	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 2.14	0.185	0 - 2.14	0.283	0 - 2.14	0.301	0.256	0.036	0.101 - 0.411	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 2.11	0.400	0 - 2.11	0.317	0 - 2.11	0.336	0.351	0.025	0.243 - 0.459	0.005	significant

One-Way ANOVA of Mean 'Extracted Moisture-Corrected Smokeless Tobacco' Slope Estimates Among Test Samples

Schedule (i)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.216	6	0.036	5.027	0.006
Within Samples	0.100	14	0.007		
Total (Corr.)	0.316	20			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	0.088	6	0.015	6.529	0.002
Within Samples	0.031	14	0.002		
Total (Corr.)	0.119	20			

One-way ANOVA analysis indicates significant differences (at $\alpha = 0.05$) among mean 'Extracted Moisture-Corrected Smokeless Tobacco' specific activity slope estimates for test samples under both Treatment Schedules (i) and (ii).

Evaluation of Ratio (Max ÷ Min) of Standard Deviations of 'Extracted Moisture-Corrected Smokeless Tobacco' Slope Estimates and Corresponding Method of Comparison

Treatment Schedule	Std. Dev. Ratio (Max ÷ Min)	Method of Comparison
Schedule (i)	14.2	ANOVA (equal variance)
Schedule (ii)	14.3	ANOVA (equal variance)

ANOVA-Based Comparisons of Mean 'Extracted Moisture-Corrected Smokeless Tobacco' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

ANOVA-Based Comparison	Schedule (i)			Schedule (ii)		
	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	5.9387	0.0288	not significant	6.6128	0.0222	not significant
084394 vs. 084454	0.0705	0.7945	not significant	0.4261	0.5245	not significant
084394 vs. 084455	0.0329	0.8586	not significant	2.5946	0.1295	not significant
084394 vs. 084456	16.5154	0.0012	significant	8.4440	0.0115	not significant
084394 vs. 084457	0.0600	0.8100	not significant	1.4706	0.2453	not significant
084394 vs. 084458	0.3741	0.5506	not significant	1.5407	0.2349	not significant
084395 vs. 084454	4.7151	0.0476	not significant	10.3961	0.0061	not significant
084395 vs. 084455	6.8558	0.0202	not significant	17.4916	0.0009	significant
084395 vs. 084456	2.6470	0.1260	not significant	0.1118	0.7431	not significant
084395 vs. 084457	4.8044	0.0458	not significant	14.3204	0.0020	significant
084395 vs. 084458	3.3318	0.0894	not significant	1.7696	0.2047	not significant
084454 vs. 084455	0.1998	0.6618	not significant	0.9178	0.3543	not significant
084454 vs. 084456	14.4278	0.0020	significant	12.6638	0.0031	not significant
084454 vs. 084457	0.0004	0.9840	not significant	0.3135	0.5844	not significant
084454 vs. 084458	0.1198	0.7344	not significant	3.5874	0.0791	not significant
084455 vs. 084456	18.0229	0.0008	significant	20.3999	0.0005	significant
084455 vs. 084457	0.1819	0.6762	not significant	0.1585	0.6966	not significant
084455 vs. 084458	0.6289	0.4410	not significant	8.1341	0.0128	not significant
084456 vs. 084457	14.5837	0.0019	significant	16.9625	0.0010	significant
084456 vs. 084458	11.9183	0.0039	not significant	2.7709	0.1182	not significant
084457 vs. 084458	0.1344	0.7194	not significant	6.0219	0.0278	not significant

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted moisture-corrected smokeless tobacco' slope were as follows:

Schedule (i)				Schedule (ii)			
Sample Description	Sample ID	Mean Slope	Homogenous Groupings	Sample Description	Sample ID	Mean Slope	Homogenous Groupings
Mellow Sticks	084455	0.371	X	Mellow Sticks	084455	0.241	X
Camel SNUS Frost	084394	0.384	X	Ariva Wintergreen	084457	0.256	X
Ariva Wintergreen	084457	0.401	X	Fresh Strips	084454	0.278	XX
Fresh Strips	084454	0.402	X	Camel SNUS Frost	084394	0.303	XX
Fresh Orbs	084458	0.426	XX	Fresh Orbs	084458	0.351	XX
2S3	084395	0.552	XX	2S3	084395	0.403	X
Copenhagen Long Cut	084456	0.665	X	Copenhagen Long Cut	084456	0.416	X

