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

***Labstat International ULC
Test Report***



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

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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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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

January 12, 2009

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

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.



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 SMOKE⁵

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)

⁵ 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 Cell Culture Suspension

(b) (4)



4.4 Collection of Total Particulate Matter (TPM)⁶

(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)



⁶ 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)

⁷ 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.

⁸ 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 Cells and Exposure to Test Articles

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4.6.2 Harvesting and Counting of Cells

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4.6.3 Micronucleus Staining and Scoring

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4.7 Method Deviations

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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), *M100_chem_dataCF.xls* (nicotine analysis results for smoked and smokeless tobacco products).

5.1.1 Moisture-Corrected Smokeless Tobacco and Nicotine Dose Basis

(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

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(b) (4)

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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

⁹ 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)

(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

¹⁰ 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 Toxicity

5.2.7.1 Requirement

Section 13.4 of T-503 suggests that the highest concentration of the test article exhibit approximately < 60 percent toxicity.

5.2.7.2 Conclusion

All MN laboratory control assay and test sample assay results that are part of this report showed approximately less than 60% cytotoxicity at the highest concentration of TPM.

6 Genotoxicity Comparisons

6.1 Data Files

The data file 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 file has been labeled *M100_mn_stats.xls*.

6.2 Comparisons Among Tobacco Products

6.2.1 Methodology

(b) (4)

¹² Zar, Jerrold H., *Biostatistical Analysis*. Prentice-Hall Inc. pp. 230-232, 1974.

¹³ Zar, Jerrold H., *Biostatistical Analysis*. Prentice-Hall Inc. pp. 233-234, 1974.

6.2.2 'Extracted Smokeless Tobacco' Dose Basis

6.2.2.1 Results

Schedule & Dose Basis	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Schedule (i) 'ST' Dose	Dose	15.3	1	15.3	1088	< 0.001
	Intercepts	0.603	6	0.100	7.16	< 0.001
	Slopes	0.411	6	0.068	4.88	< 0.001
	TOTAL	16.3	13			
Schedule (ii) 'ST' Dose	Dose	7.88	1	7.88	1282	< 0.001
	Intercepts	0.744	6	0.124	20.2	< 0.001
	Slopes	0.340	6	0.057	9.23	< 0.001
	TOTAL	8.96	13			

The results in the above table indicate that the *analysis of covariance* null hypothesis of equality among linear regression slopes could be rejected¹⁴ for the Schedule (i) and Schedule (ii) response in smokeless tobacco samples expressed per mg "extracted smokeless tobacco". For these treatment schedules, there is strong evidence in the data to suggest that the mean %MN per (mg "extracted smokeless tobacco"/mL) is not equal among the smokeless tobacco test products. Subsequent applications of the Student-Newman Keul multiple comparison procedure ($\alpha = 0.05$) for differences in product genotoxicity yielded the following results:

Schedule & Dose Basis	Sample Description	% MN per (mg 'ST'/mL)		Homogenous Groupings	
		Slope	Std. Err.		
Schedule (i) 'ST' Dose	Fresh Orbs	0.449	0.030	X	
	Ariva Wintergreen	0.411	0.045	X	X
	Fresh Strips	0.391	0.024	X	X
	Mellow Sticks	0.361	0.029	X	X
	Copenhagen Long Cut	0.321	0.022		X
	Camel SNUS Frost	0.288	0.018		X
	2S3	0.283	0.024		X

Strain & Dose Basis	Sample Description	% MN per (mg 'ST'/mL)		Homogenous Groupings	
		Slope	Std. Err.		
Schedule (ii) 'ST' Dose	Fresh Orbs	0.366	0.025	X	
	Fresh Strips	0.286	0.023		X
	Ariva Wintergreen	0.269	0.014		X
	Mellow Sticks	0.247	0.014		X
	Camel SNUS Frost	0.222	0.019		X
	Copenhagen Long Cut	0.210	0.016		X
	2S3	0.198	0.020		X

¹⁴ Statistical significance is dependent upon the choice of p. In this case, the cut-off p-value was set at 0.005.

6.2.2.2 Conclusions

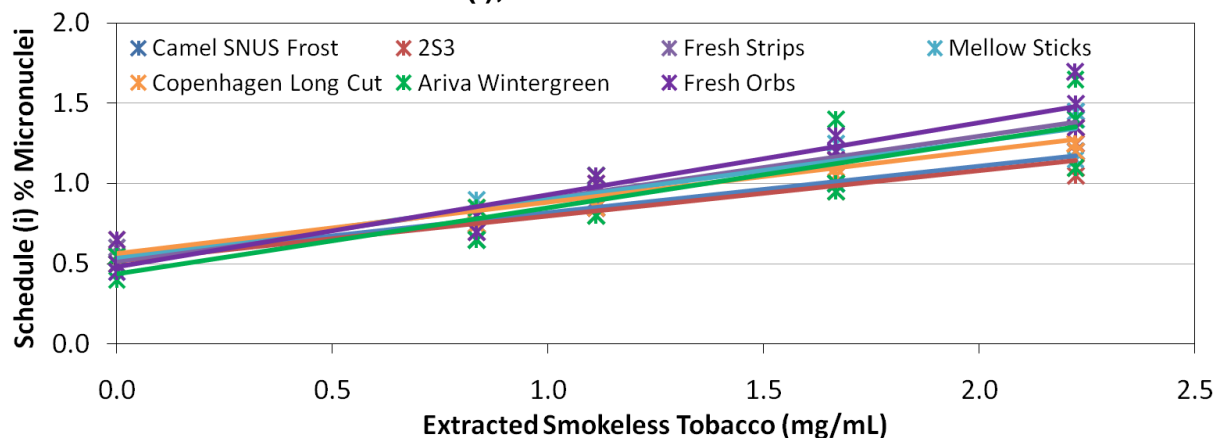
The multiple comparison results indicate that significant¹⁵ differences may exist amongst the average pooled linear regression slope estimate from triplicate assays of smokeless tobacco products expressed on an „Extracted Smokeless Tobacco“ basis [%MN per (mg „extracted smokeless tobacco“/mL)] for the following smokeless tobacco test brands under the two micronucleus assay treatment schedules:

Schedule (i), ‘Extracted Smokeless Tobacco’ Dose Basis

⇒ The multiple comparison results identified the following sets of smokeless tobacco test products, with dose basis „Extracted Smokeless Tobacco“, for which the pooled linear regression slopes under treatment schedule (i) were comparable.

- {Fresh Strips (084454), Mellow Sticks (084455), Ariva Wintergreen (084457), Fresh Orbs (084458)}
- {Camel SNUS Frost (084394), 2S3 (084395), Fresh Strips (084454), Mellow Sticks (084455), Copenhagen Long Cut (084456), Ariva Wintergreen (084457)}

Linear Dose-Response for Pooled Replicate Assays of Smokeless Tobacco Products: Schedule (i), ‘Extracted Smokeless Tobacco’ Dose



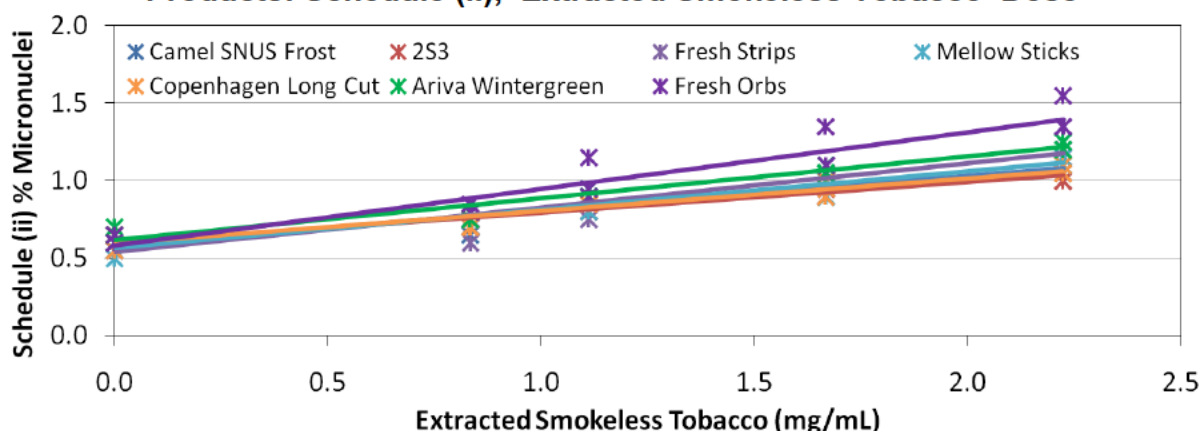
¹⁵ Statistical significance is dependent upon the choice of p. In this case, the cut-off p-value was set at 0.05.

Schedule (ii), 'Extracted Smokeless Tobacco' Dose Basis

⇒ The multiple comparison results identified the following sets of smokeless tobacco test products, with dose basis „Extracted Smokeless Tobacco“, for which the pooled linear regression slopes under treatment schedule (ii) were comparable.

- {Fresh Orbs (084458)}
- {Camel SNUS Frost (084394), 2S3 (084395), Fresh Strips (084454), Mellow Sticks (084455), Copenhagen Long Cut (084456), Ariva Wintergreen (084457)}

Linear Dose-Response for Pooled Replicate Assays of Smokeless Tobacco Products: Schedule (ii), 'Extracted Smokeless Tobacco' Dose



6.2.3 'Extracted Moisture-Corrected Smokeless Tobacco' Dose Basis

6.2.3.1 Results

Schedule & Dose Basis	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Schedule (i) 'ST-H ₂ O' Dose	Dose	14.4	1	14.4	1025	< 0.001
	Intercepts	1.46	6	0.244	17.4	< 0.001
	Slopes	0.432	6	0.072	5.14	< 0.001
	TOTAL	16.3	13			
Schedule (ii) 'ST-H ₂ O' Dose	Dose	7.98	1	7.98	1299	< 0.001
	Intercepts	0.724	6	0.121	19.6	< 0.001
	Slopes	0.257	6	0.043	6.99	< 0.001
	TOTAL	8.96	13			

The results in the above table indicate that the *analysis of covariance* null hypothesis of equality among linear regression slopes could be rejected¹⁶ for the Schedule (i) and Schedule (ii) response in smokeless tobacco test samples expressed per mg "extracted moisture-corrected smokeless tobacco". For these treatment schedules, there is strong evidence in the data to suggest that the mean %MN per (mg „extracted moisture-corrected smokeless tobacco"/mL) is not equal among all smokeless tobacco test products. Subsequent applications of the Student-Newman Keul multiple comparison procedure ($\alpha = 0.05$) for differences in product genotoxicity yielded the following results:

¹⁶ Statistical significance is dependent upon the choice of p. In this case, the cut-off p-value was set at 0.005.

Schedule & Dose Basis	Sample Description	% MN per (mg 'ST-H ₂ O'/mL)		Homogenous Groupings		
		Slope	Std. Err.			
Schedule (i) 'ST-H ₂ O' Dose	Copenhagen Long Cut	0.719	0.050	X		
	2S3	0.615	0.052	X	X	
	Fresh Orbs	0.473	0.031		X	X
	Fresh Strips	0.440	0.027		X	X
	Ariva Wintergreen	0.427	0.047		X	X
	Camel SNUS Frost	0.423	0.026			X
	Mellow Sticks	0.384	0.031			X

Schedule & Dose Basis	Sample Description	% MN per (mg 'ST-H ₂ O'/mL)		Homogenous Groupings		
		Slope	Std. Err.			
Schedule (ii) 'ST-H ₂ O' Dose	Copenhagen Long Cut	0.470	0.036	X		
	2S3	0.430	0.044	X	X	
	Fresh Orbs	0.386	0.026	X	X	
	Camel SNUS Frost	0.325	0.028		X	X
	Fresh Strips	0.322	0.025		X	X
	Ariva Wintergreen	0.280	0.014			X
	Mellow Sticks	0.263	0.015			X

6.2.3.2 Conclusions

The multiple comparison results indicate that significant¹⁷ differences may exist amongst the average pooled linear regression slope estimate from triplicate assays of smokeless tobacco products expressed on an „Extracted Moisture-Corrected Smokeless Tobacco“ basis [%MN per (mg „extracted moisture-corrected smokeless tobacco“/mL)] for the following smokeless tobacco test brands under the two micronucleus assay treatment schedules:

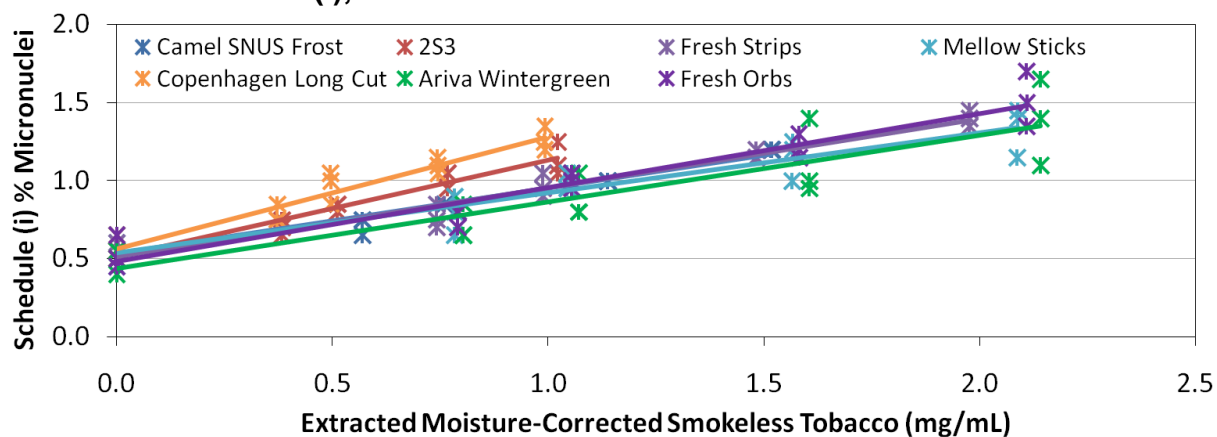
Schedule (i), 'Extracted Moisture-Corrected Smokeless Tobacco' Dose Basis

⇒ The multiple comparison results identified the following sets of smokeless tobacco test products, with dose basis „Extracted Moisture-Corrected Smokeless Tobacco“, for which the pooled linear regression slopes under treatment schedule (i) were comparable.

- {2S3 (084395), Copenhagen Long Cut (084456)}
- {2S3 (084395), Fresh Strips (084454), Ariva Wintergreen (084457), Fresh Orbs (084458)}
- {Camel SNUS Frost (084394), Fresh Strips (084454), Mellow Sticks (084455), Ariva Wintergreen (084457), Fresh Orbs (084458)}

¹⁷ Statistical significance is dependent upon the choice of p. In this case, the cut-off p-value was set at 0.05.

Linear Dose-Response for Pooled Replicate Assays of Smokeless Tobacco Products: Schedule (i), 'Extracted Moisture-Corrected Smokeless Tobacco' Dose

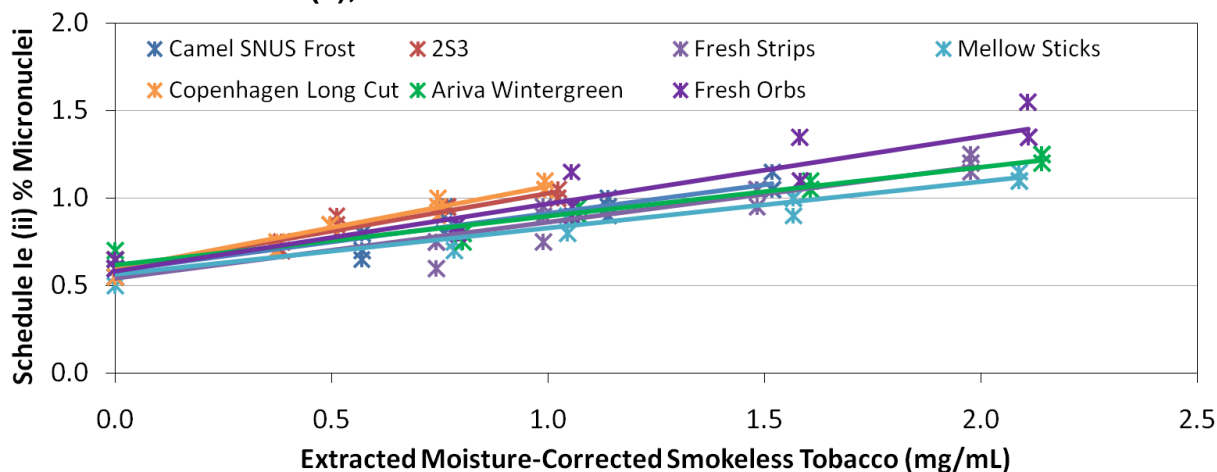


Schedule (ii), 'Extracted Moisture-Corrected Smokeless Tobacco' Dose Basis

⇒ The multiple comparison results identified the following sets of smokeless tobacco test products, with dose basis „Extracted Moisture-Corrected Smokeless Tobacco“, for which the pooled linear regression slopes under treatment schedule (ii) were comparable.

- { 2S3 (084395), Copenhagen Long Cut (084456), Fresh Orbs (084458)}
- {Camel SNUS Frost (084394), 2S3 (084395), Fresh Strips (084454), Fresh Orbs (084458)}
- {Camel SNUS Frost (084394), Fresh Strips (084454), Mellow Sticks (084455), Ariva Wintergreen (084457)}

Linear Dose-Response for Pooled Replicate Assays of Smokeless Tobacco Products: Schedule (ii), 'Extracted Moisture-Corrected Smokeless Tobacco' Dose



6.2.4 'Nicotine' Dose Basis

6.2.4.1 Results

Schedule & Dose Basis	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Schedule (i) 'Nicotine' Dose	Dose	6.09	1	6.09	351	< 0.001
	Intercepts	10.1	7	1.45	83.6	< 0.001
	Slopes	10.8	7	1.54	88.9	< 0.001
	TOTAL	27.0	15			
Schedule (ii) 'Nicotine' Dose	Dose	2.51	1	2.51	319	< 0.001
	Intercepts	6.91	7	0.987	125	< 0.001
	Slopes	5.29	7	0.756	96.2	< 0.001
	TOTAL	14.7	15			

The results in the above table indicate that the *analysis of covariance* null hypothesis of equality among linear regression slopes could be rejected¹⁸ for the Schedule (i) and Schedule (ii) response in smokeless tobacco samples expressed per mg "nicotine in smokeless tobacco" and smoked tobacco samples expressed per mg "nicotine in TPM". For these treatment schedules, there is strong evidence in the data to suggest that the mean %MN per (mg nicotine/mL) is not equal among the smoked and smokeless tobacco test products. Subsequent applications of the Student-Newman Keul multiple comparison procedure ($\alpha = 0.05$) for differences in product genotoxicity yielded the following results:

Schedule & Dose Basis	Sample Description	% MN per (mg 'Nicotine'/mL)		Homogenous Groupings			
		Slope	Std. Err.				
Schedule (i) 'Nicotine' Dose	Fresh Orbs	199	15	X			
	Kentucky Reference 2R4F	117	8		X		
	Fresh Strips	109	7		X		
	Mellow Sticks	87.0	6.0			X	
	Ariva Wintergreen	73.1	8.1			X	
	Copenhagen Long Cut	25.9	1.7				X
	Camel SNUS Frost	22.3	1.4				X
	2S3	20.8	1.7				X

Schedule & Dose Basis	Sample Description	% MN per (mg 'Nicotine'/mL)		Homogenous Groupings			
		Slope	Std. Err.				
Schedule (ii) 'Nicotine' Dose	Fresh Orbs	160	13	X			
	Fresh Strips	79.4	6.5		X		
	Kentucky Reference 2R4F	77.5	4.4		X		
	Mellow Sticks	56.2	4.4			X	
	Ariva Wintergreen	47.9	2.4			X	
	Camel SNUS Frost	17.2	1.5				X
	Copenhagen Long Cut	16.9	1.3				X
	2S3	14.5	1.5				X

¹⁸ Statistical significance is dependent upon the choice of p. In this case, the cut-off p-value was set at 0.005.

6.2.4.2 Conclusions

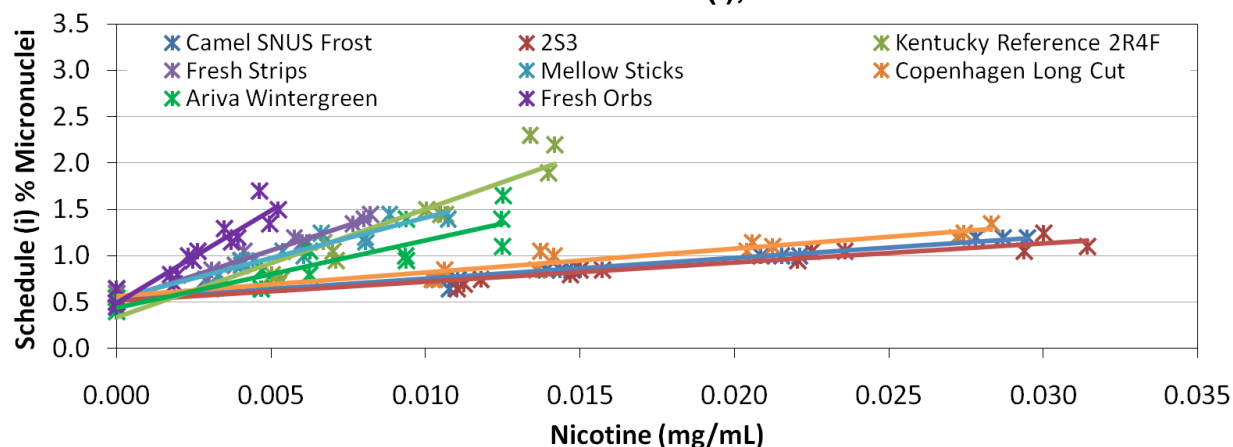
The multiple comparison results indicate that significant¹⁹ differences may exist amongst the average pooled linear regression slope estimate from triplicate assays of smokeless tobacco products expressed on an „Nicotine“ basis [%MN per (mg „nicotine in smokeless tobacco“/mL)] and smoked tobacco products expressed on an „Nicotine in TPM“ basis [%MN per (mg „nicotine in TPM“/mL)] for the following test products under the two micronucleus assay treatment schedules:

Schedule (i), ‘Nicotine’ Dose Basis

⇒ The multiple comparison results identified the following sets of smokeless and smoked tobacco products, with dose basis „Nicotine“, for which the pooled linear regression slopes under treatment schedule (i) were comparable.

- {Fresh Orbs (084458)}
- {Kentucky Reference 2R4F (084396), Fresh Strips (084454)}
- {Mellow Sticks (084455), Ariva Wintergreen (084457)}
- {Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456)}

Linear Dose-Response for Pooled Replicate Assays of Smoked and Smokeless Tobacco Products: Schedule (i), ‘Nicotine’ Dose



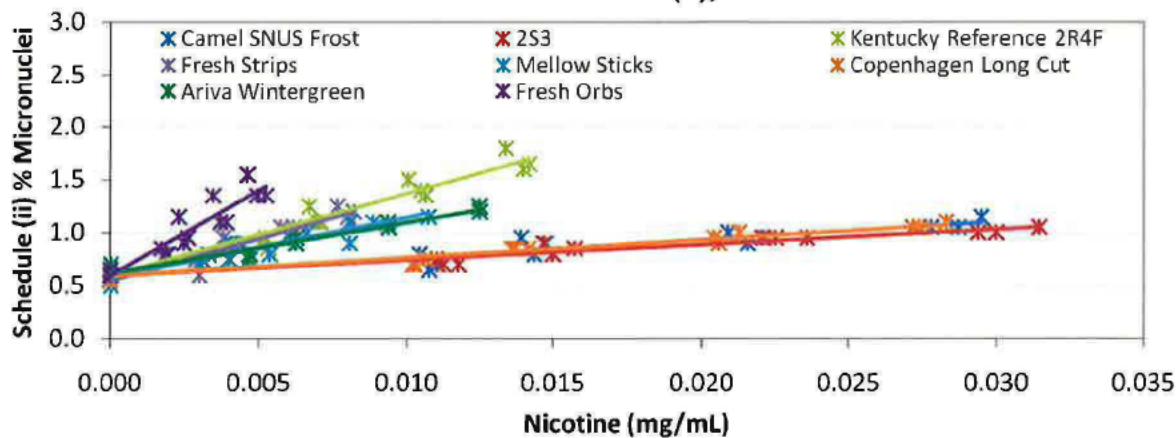
¹⁹ Statistical significance is dependent upon the choice of p. In this case, the cut-off p-value was set at 0.05.

Schedule (ii), 'Nicotine' Dose Basis

⇒ The multiple comparison results identified the following sets of smokeless and smoked tobacco products, with dose basis 'Nicotine', for which the pooled linear regression slopes under treatment schedule (ii) were comparable.

- {Fresh Orbs (084458)}
- {Kentucky Reference 2R4F (084396), Fresh Strips (084454)}
- {Mellow Sticks (084455), Ariva Wintergreen (084457)}
- {Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456)}

Linear Dose-Response for Pooled Replicate Assays of Smoked and Smokeless Tobacco Products: Schedule (ii), 'Nicotine' Dose



7 Attribution

7.1 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

7.2 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

A handwritten signature in black ink that reads "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/QLSearchForm.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

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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.

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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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**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
Colchicine	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
	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

Controls

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

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

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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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**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

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

**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

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 ($\times 10^5$) per mL)		Negative Control (Cells ($\times 10^5$) 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		$\geq 90\%$	
control	2	28-Nov-08	Schedule (i)	-S9	3	27	1.96		7.88		$\geq 90\%$	
control	3	04-Dec-08	Schedule (i)	-S9	3	27	1.96		6.40		$\geq 90\%$	
control	4	04-Dec-08	Schedule (i)	-S9	3	27	1.96		7.28		$\geq 90\%$	
control	5	05-Dec-08	Schedule (i)	-S9	3	27	2.08		7.72		$\geq 90\%$	
control	6	05-Dec-08	Schedule (i)	-S9	3	27	2.08		9.60		$\geq 90\%$	
control	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04		7.56		$\geq 90\%$	
control	2	11-Dec-08	Schedule (ii)	+S9	3	27	2.00		7.24		$\geq 90\%$	
control	3	12-Dec-08	Schedule (ii)	+S9	3	27	2.12		8.36		$\geq 90\%$	
control	4	12-Dec-08	Schedule (ii)	+S9	3	27	1.92		8.04		$\geq 90\%$	
control	5	17-Dec-08	Schedule (ii)	+S9	3	27	1.96		7.52		$\geq 90\%$	
control	6	17-Dec-08	Schedule (ii)	+S9	3	27	2.04		7.36		$\geq 90\%$	

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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****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.

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

			% MNC /(µg 'Nicotine in CSC'/mL) (KR 2R4F) or % MNC /(µg 'Extracted Nicotine in DMSO'/mL)										
Treatment Schedule	Sample ID	Sample Description	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)	
			(µg 'Nic.'/mL)	slope	(µg 'Nic.'/mL)	slope	(µg '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)	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 Sticks	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 Sticks	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)

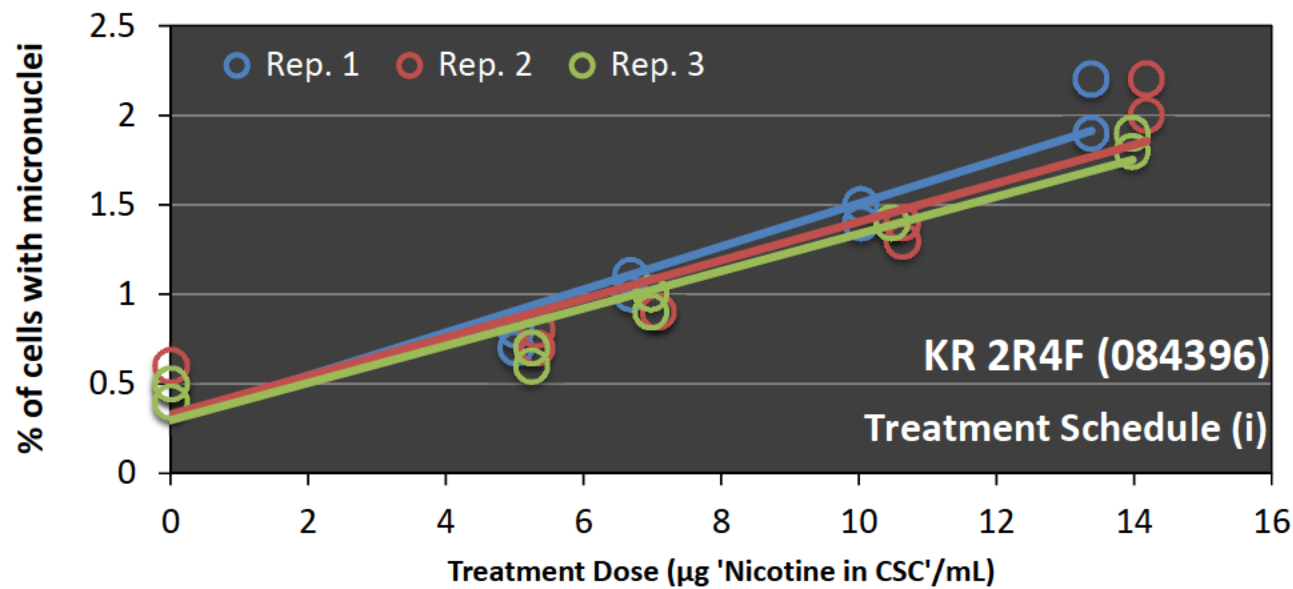
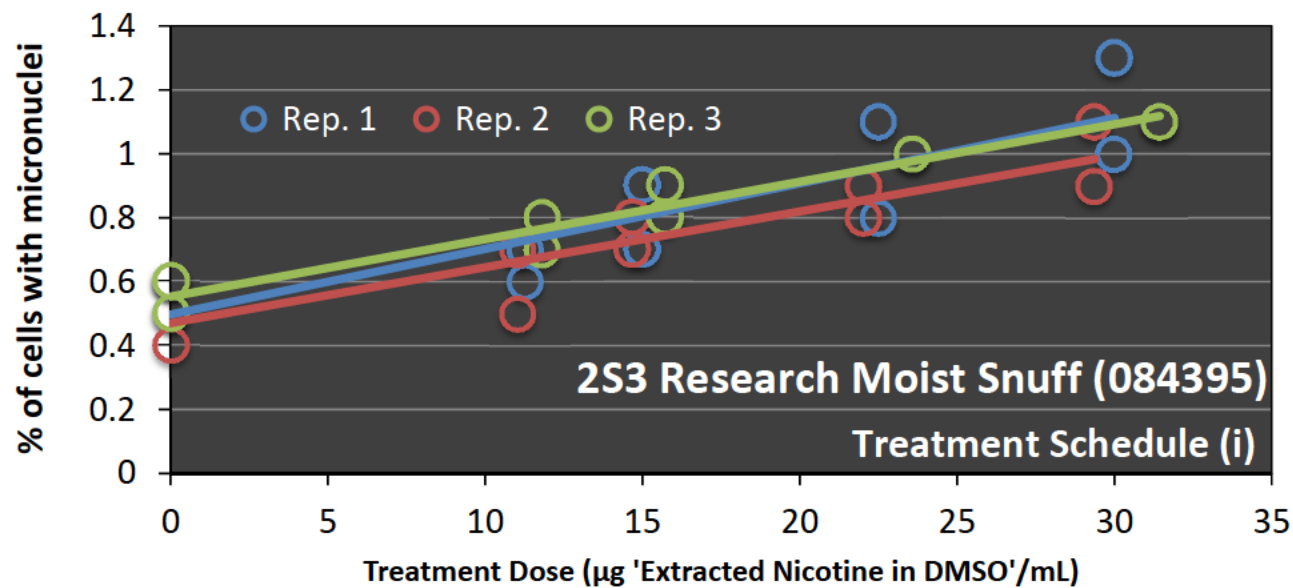
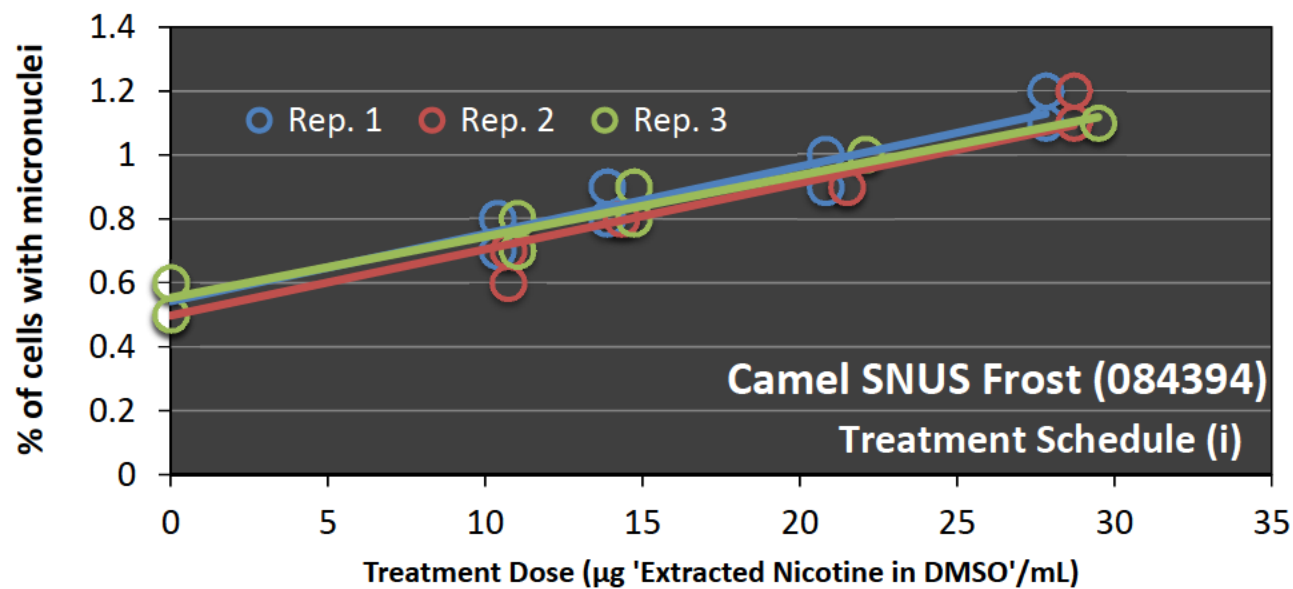
{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456), Ariva Wintergreen (084457), Fresh Orbs (084458)}

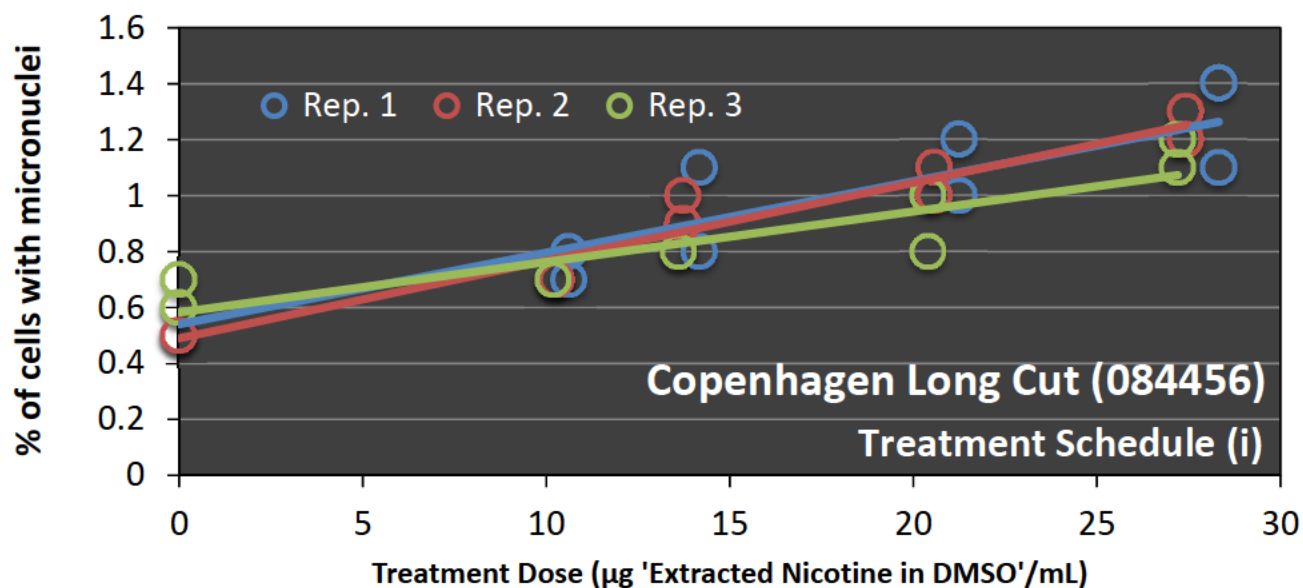
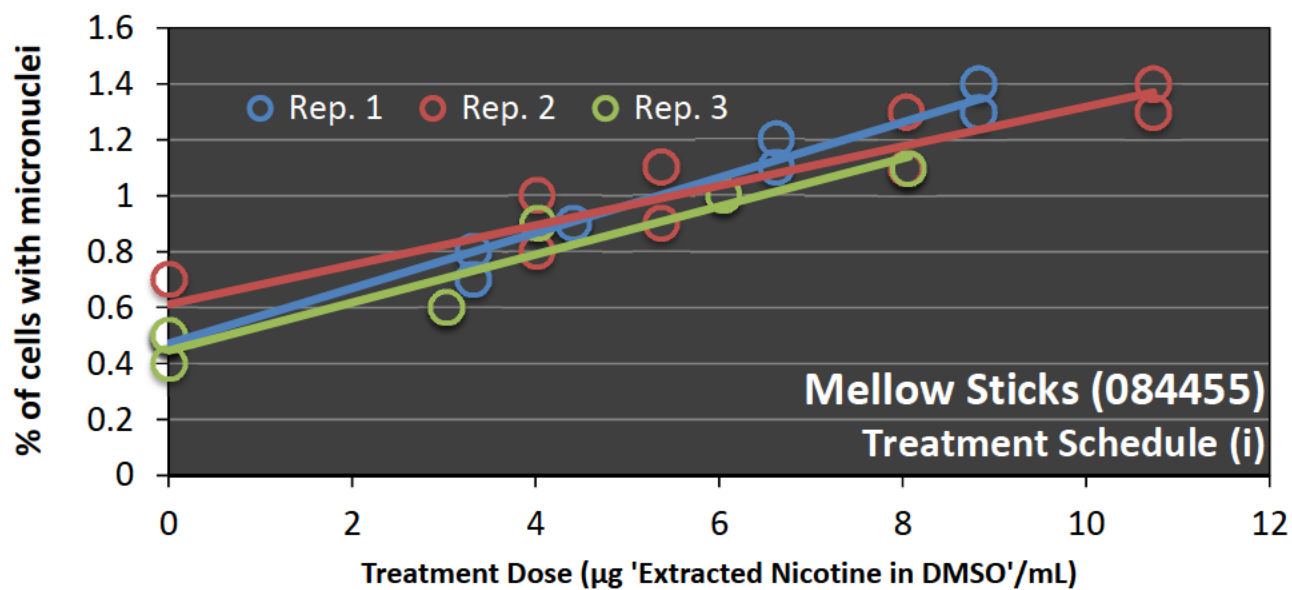
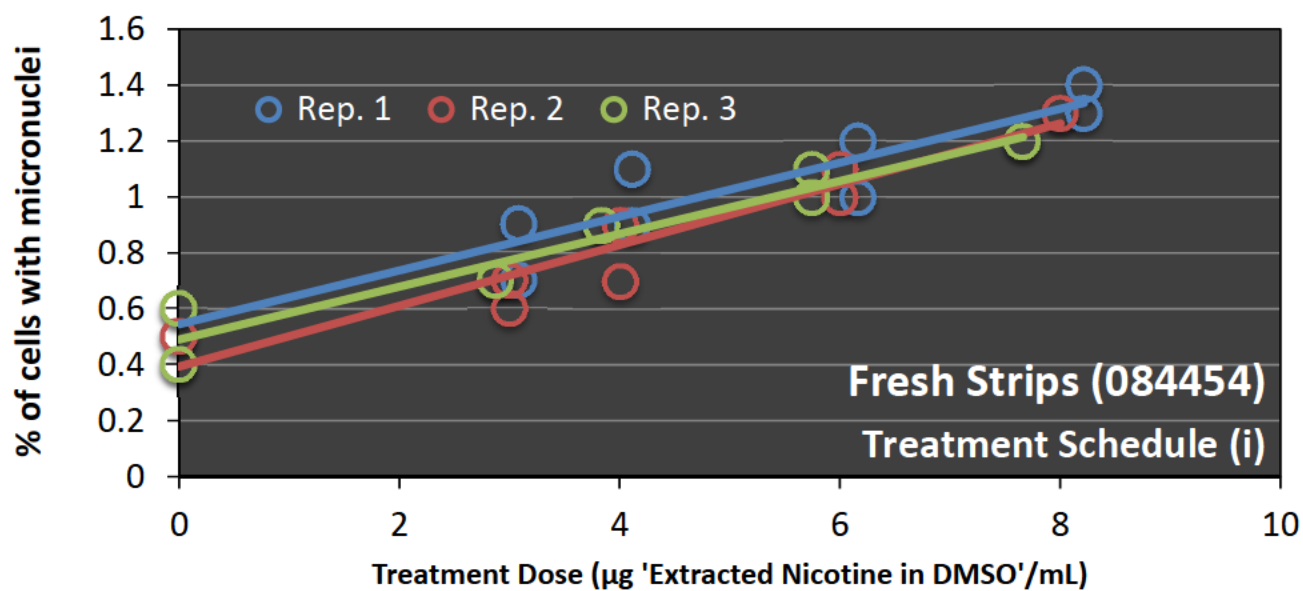
Pairwise T-test Comparisons of Smokeless Tobacco Mean 'Extracted Nicotine in DMSO' Slope to Control Brand KR 2R4F (084396) Mean 'Nicotine in CSC' Slope using Bonferroni-adjusted p-values

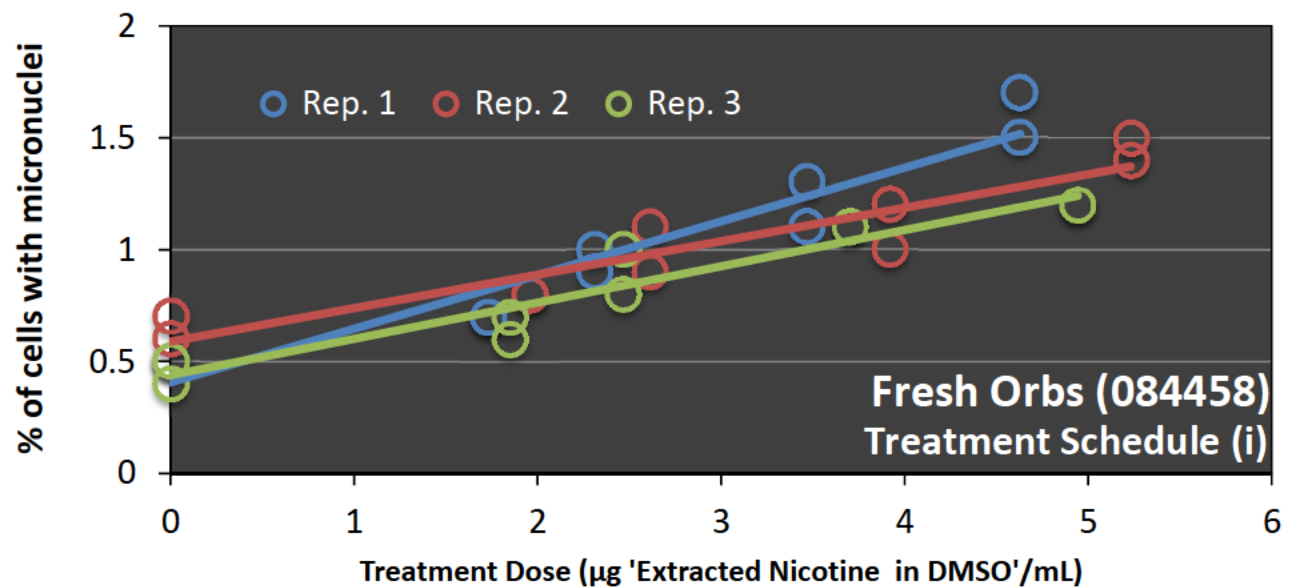
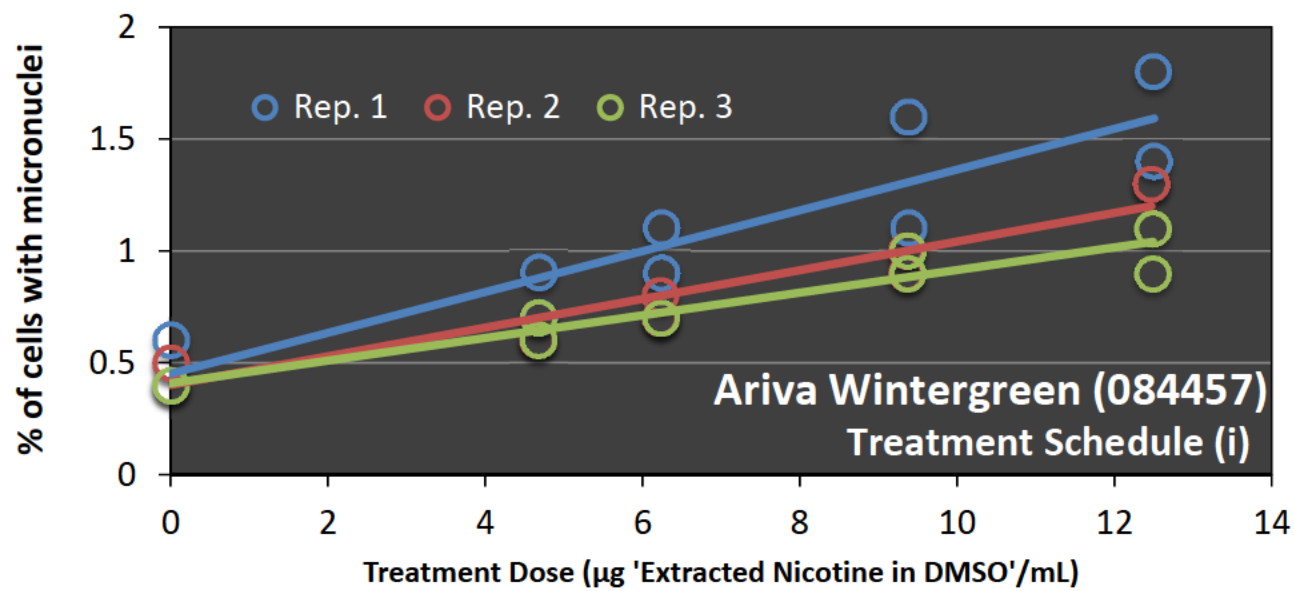
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	18.2889	5.3E-05	significant	20.9526	3.1E-05	significant
084395 vs. 084396	18.4326	5.1E-05	significant	24.7207	1.6E-05	significant
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

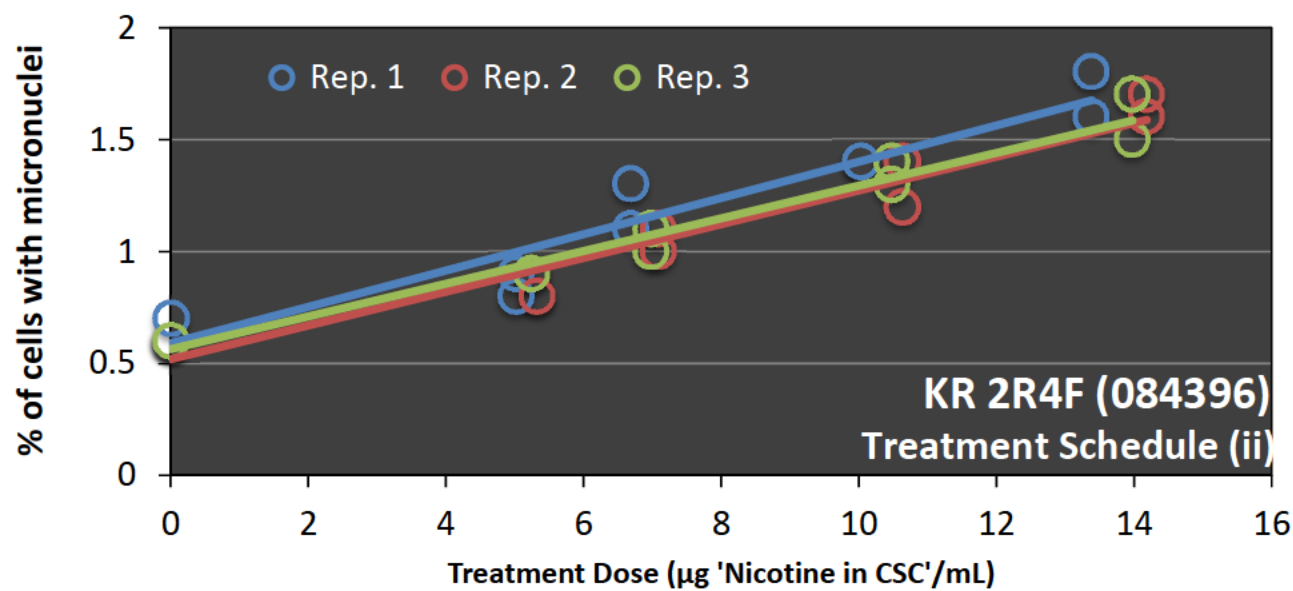
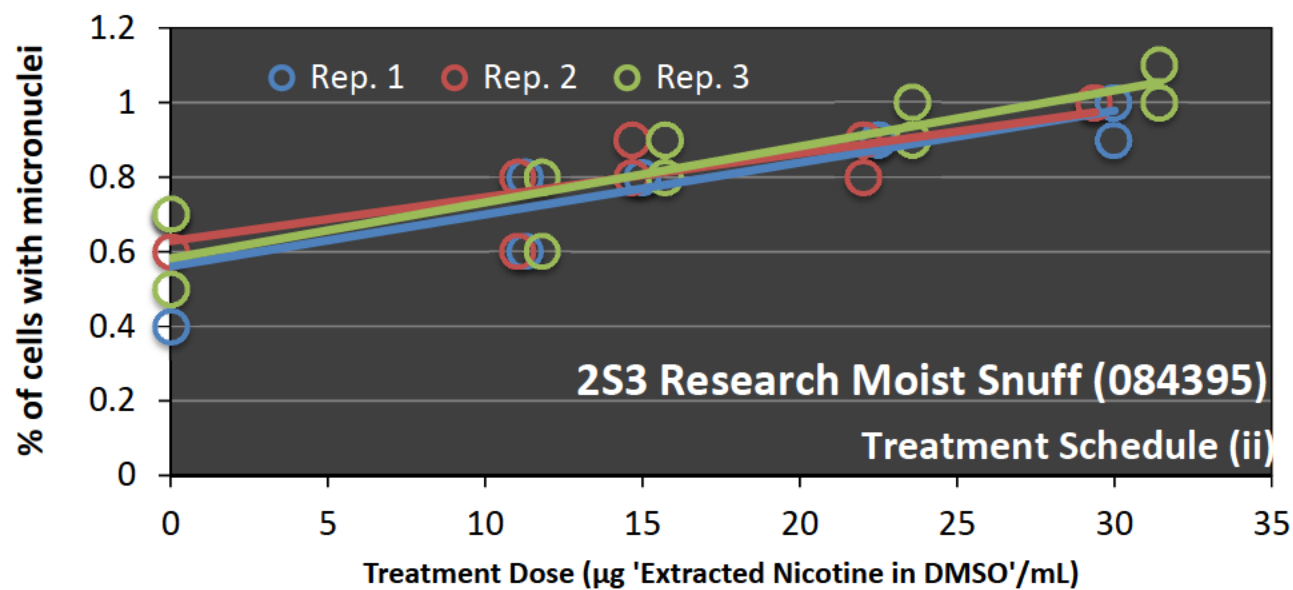
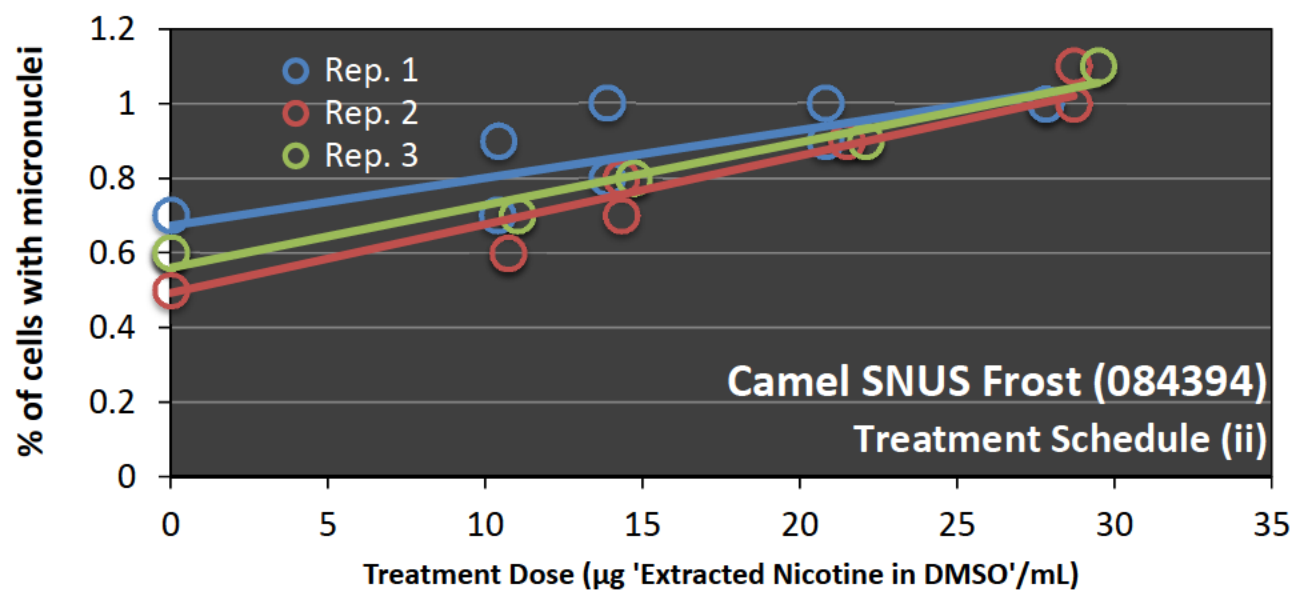
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences were detected between the mean 'nicotine in CSC' slope of the KR 2R4F (084396) smoked tobacco samples and the mean 'extracted nicotine in DMSO' slope of the following smokeless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

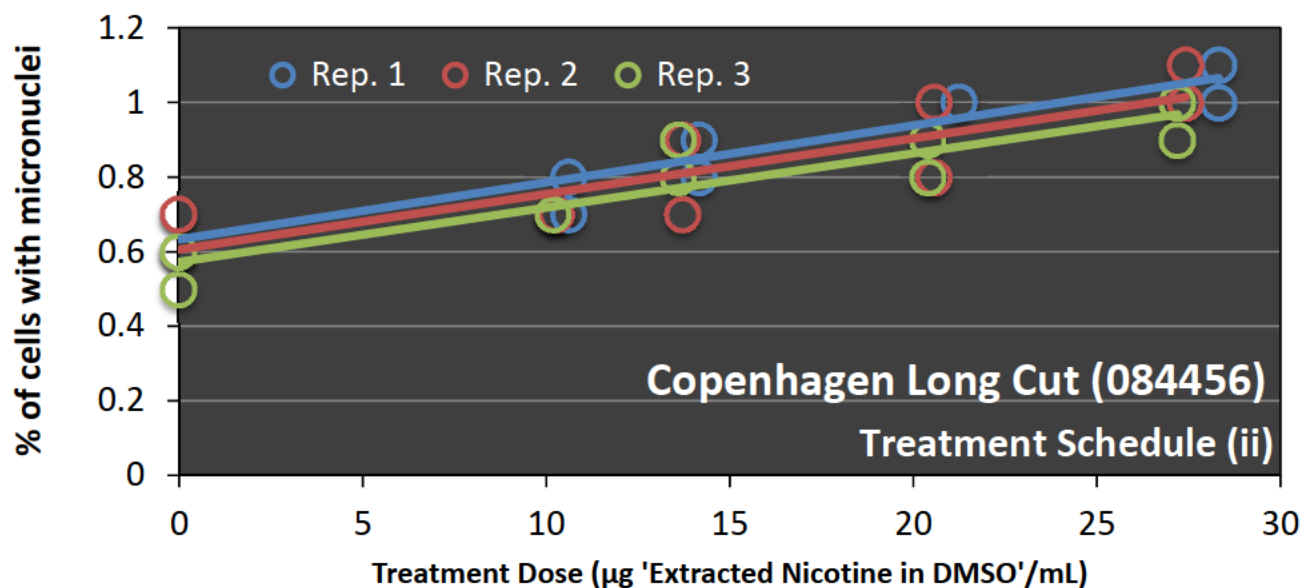
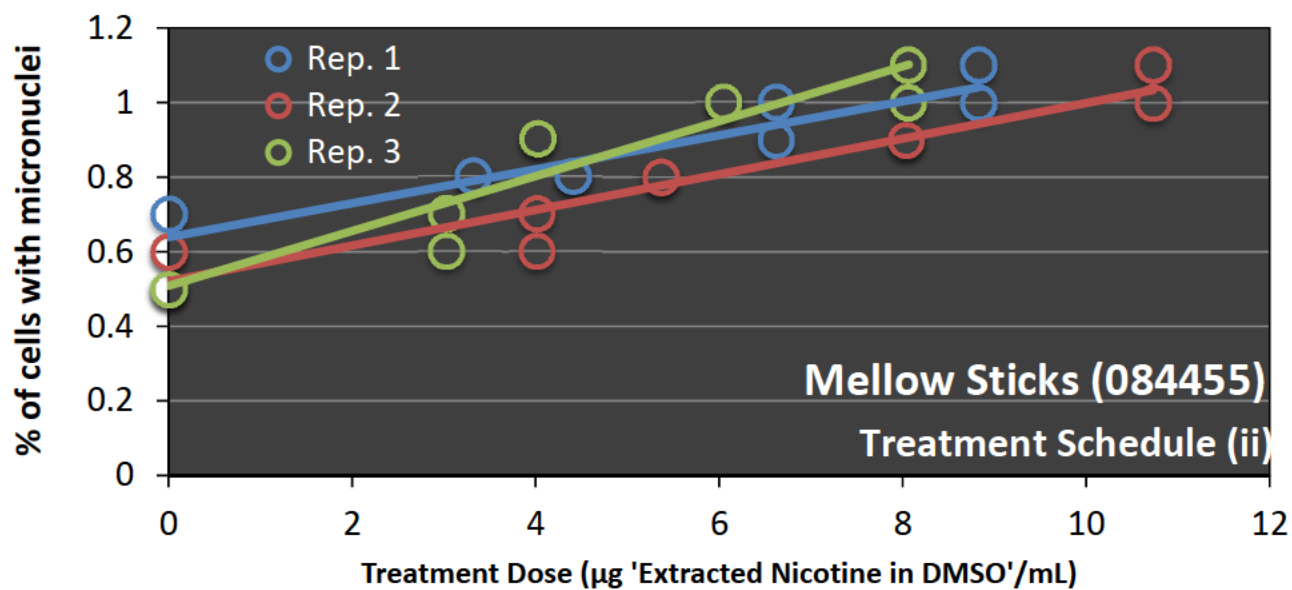
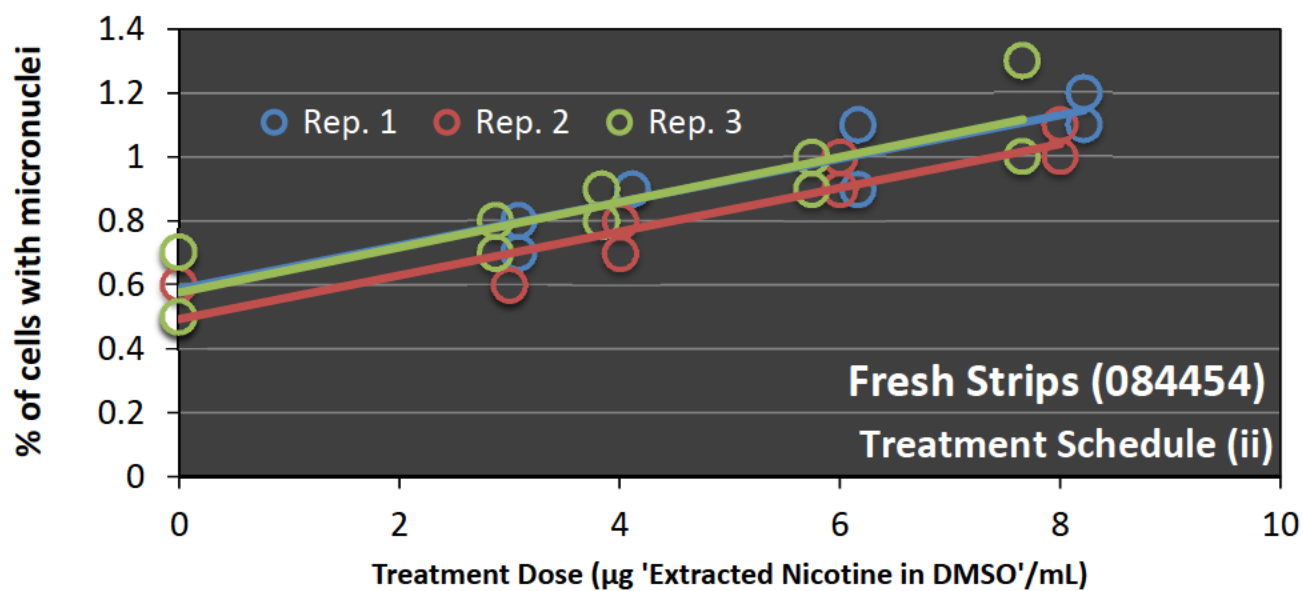
{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456)}

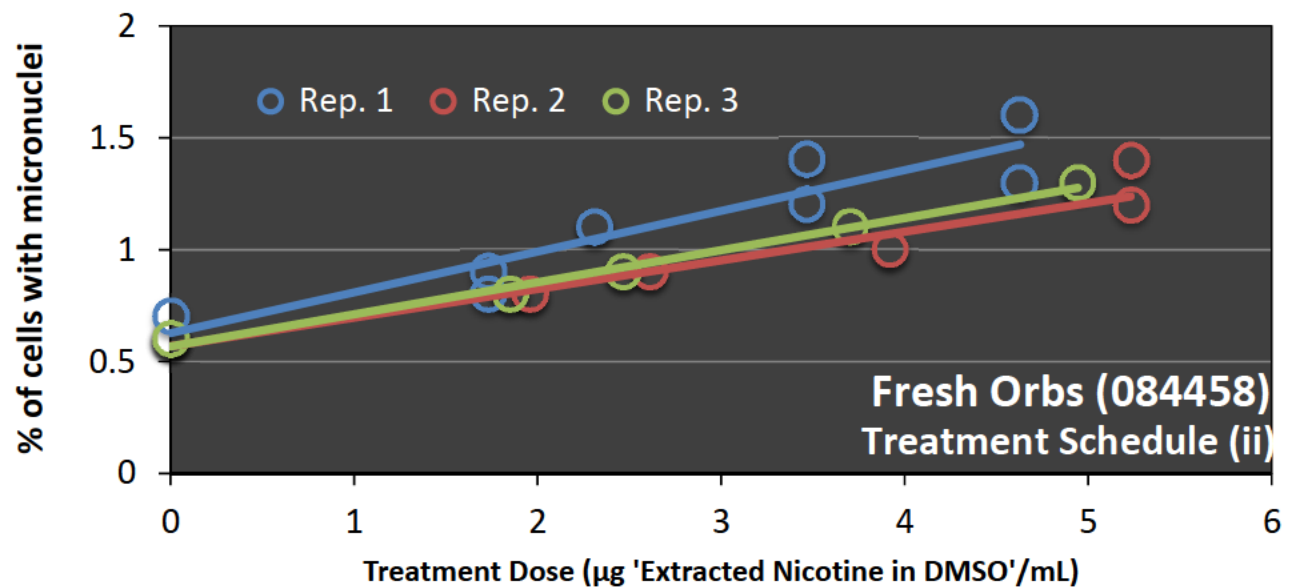
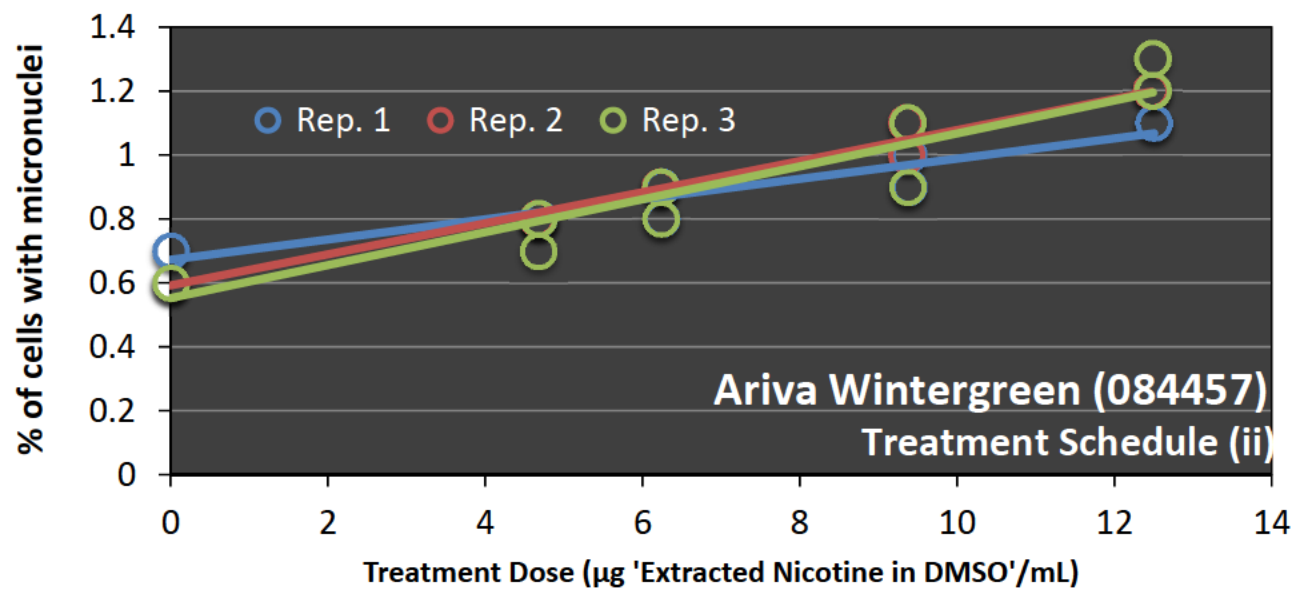


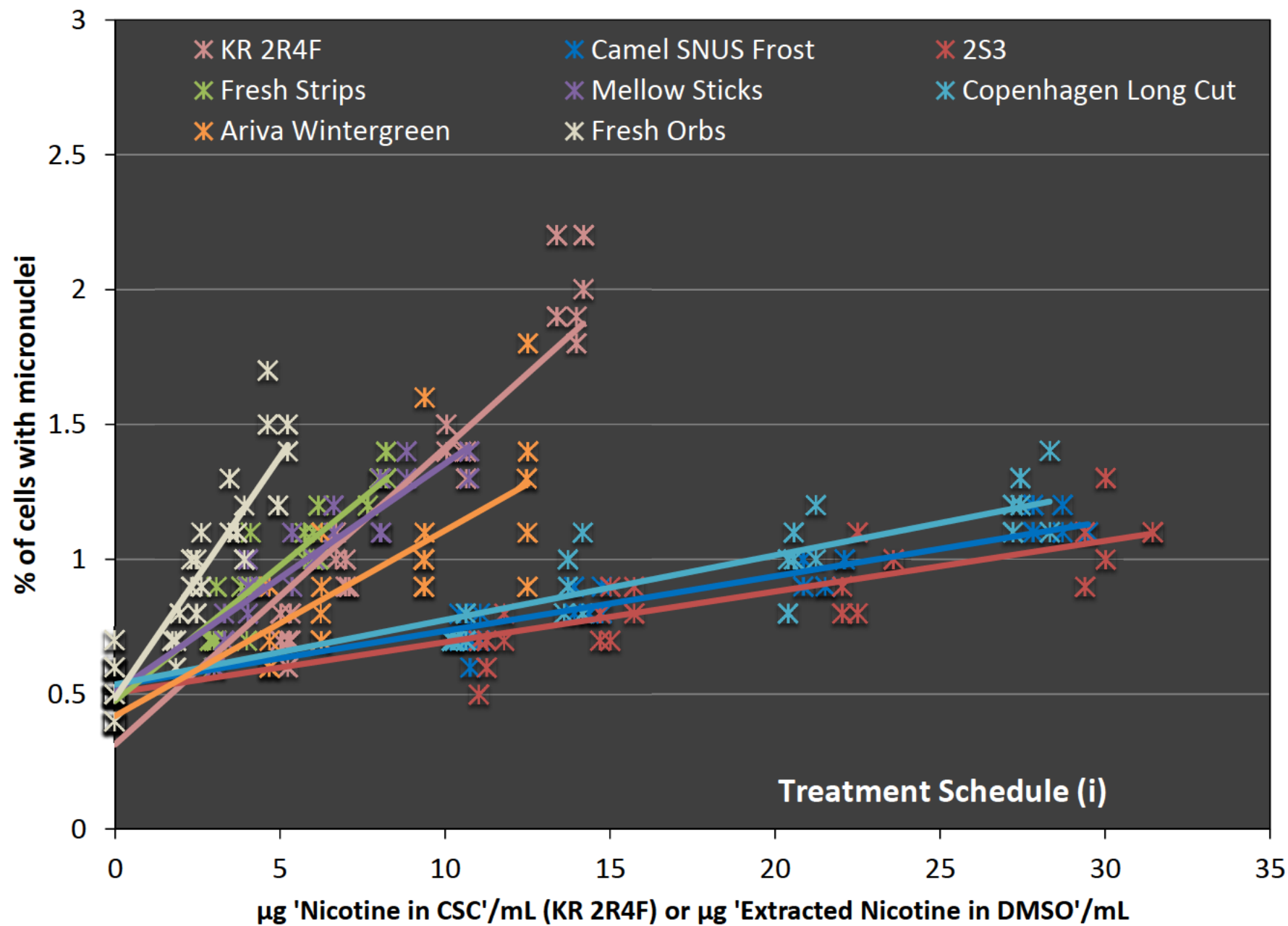


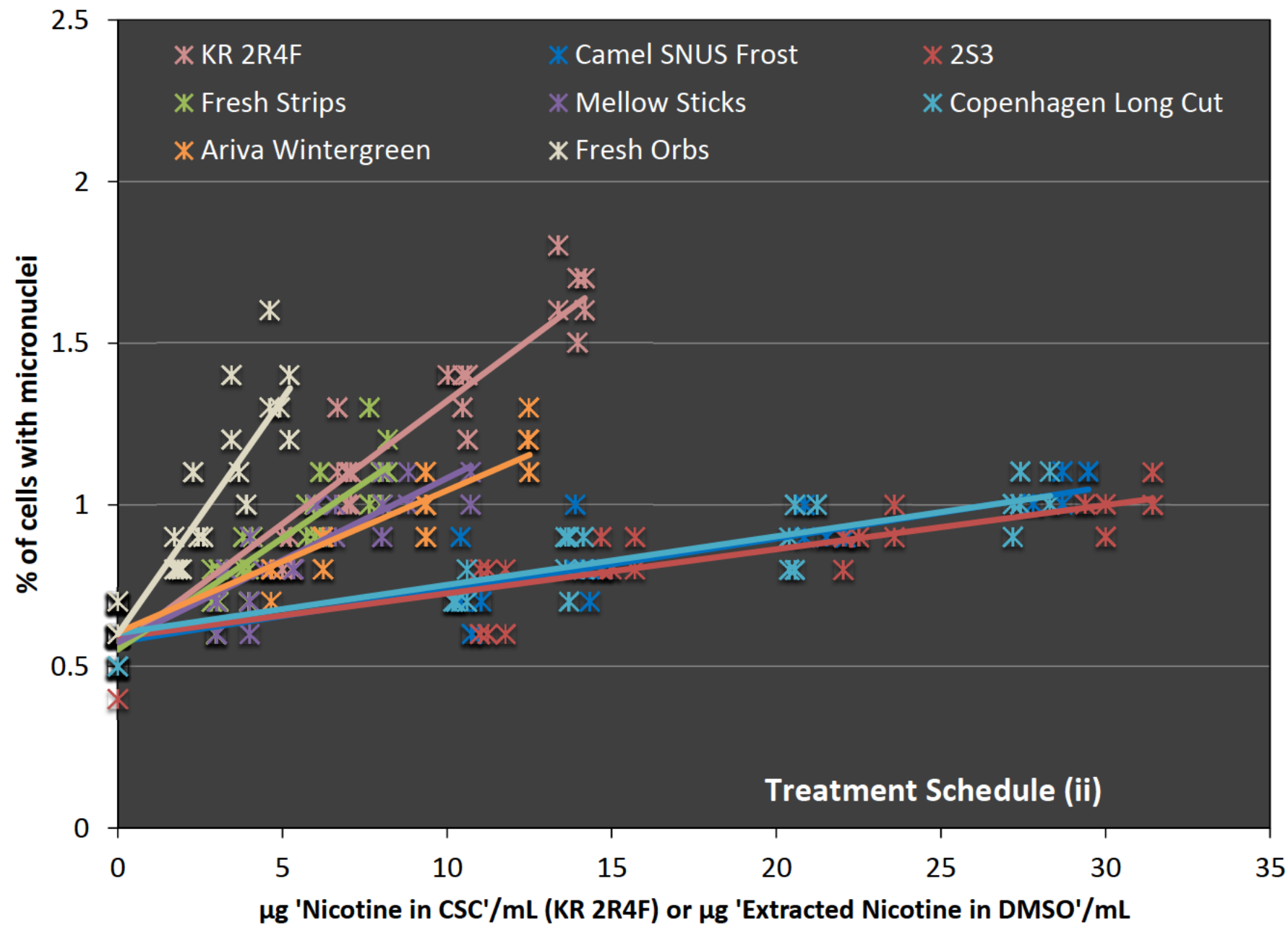






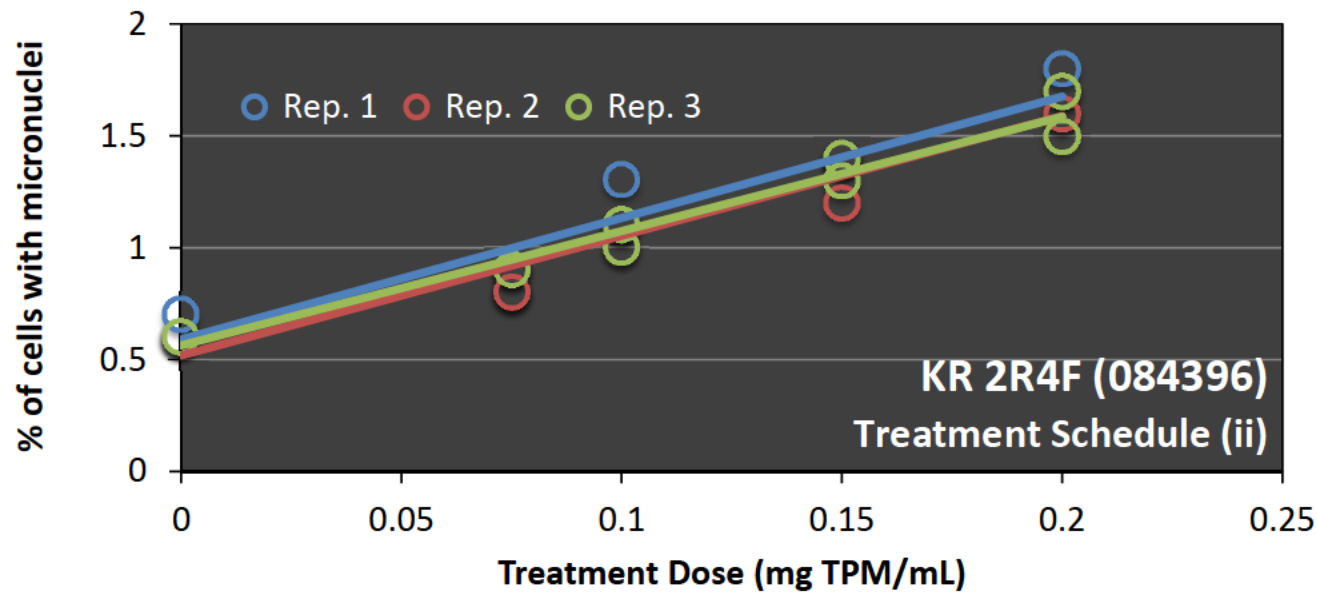
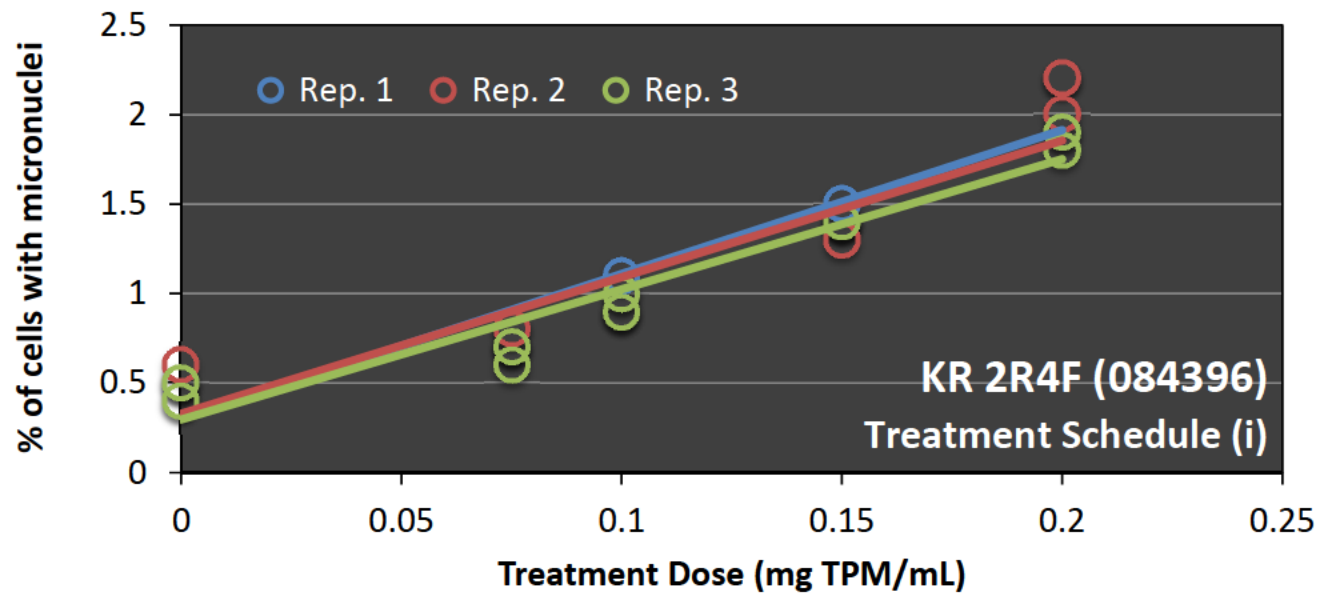


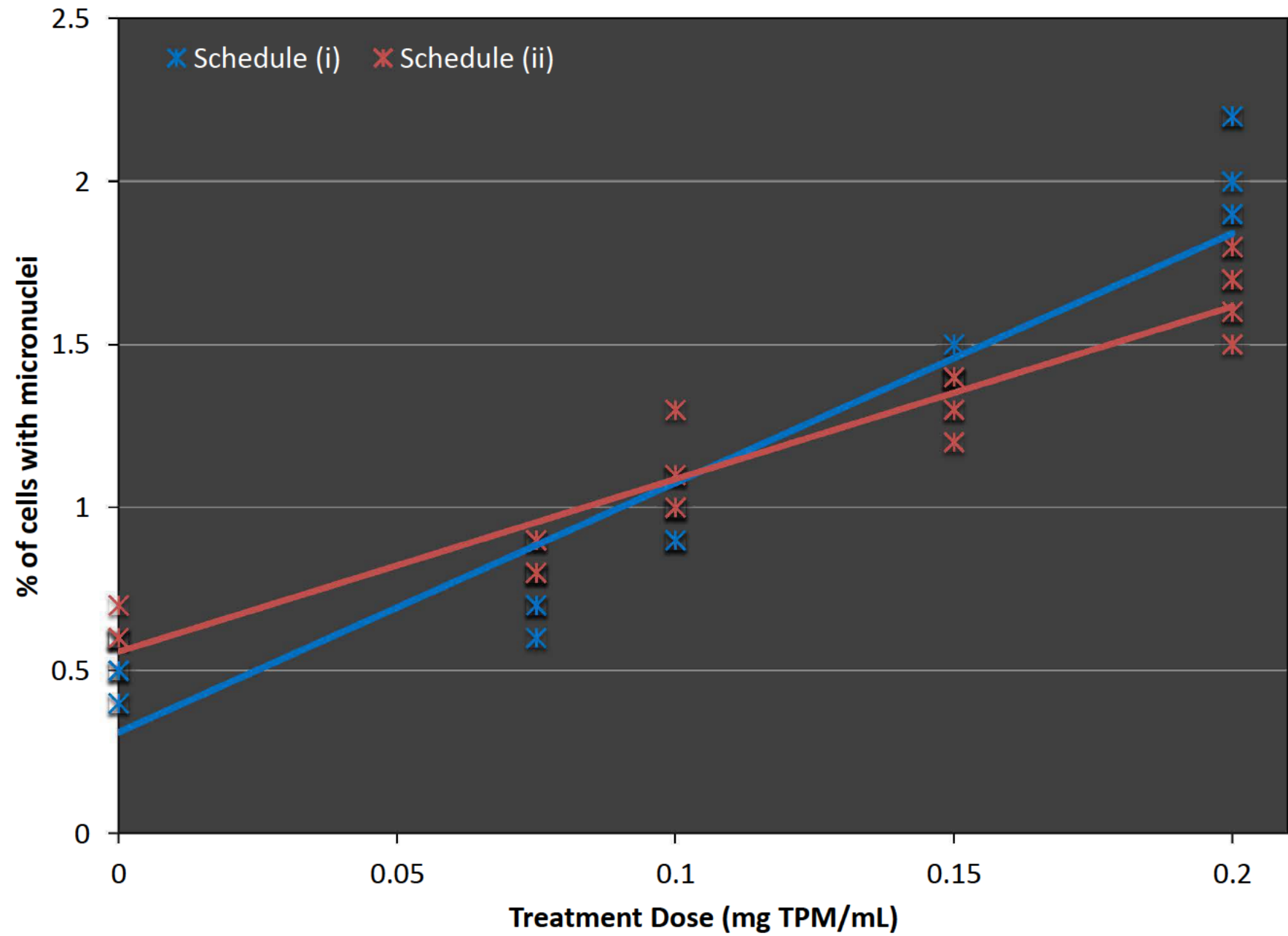




Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/(mg TPM/mL)]

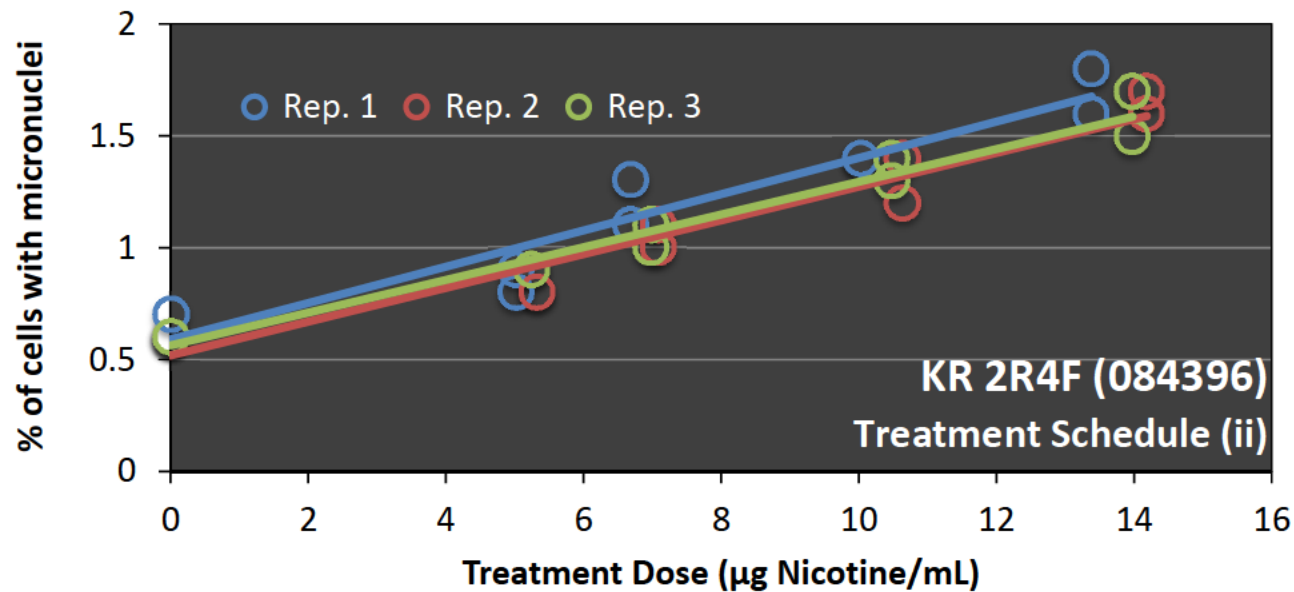
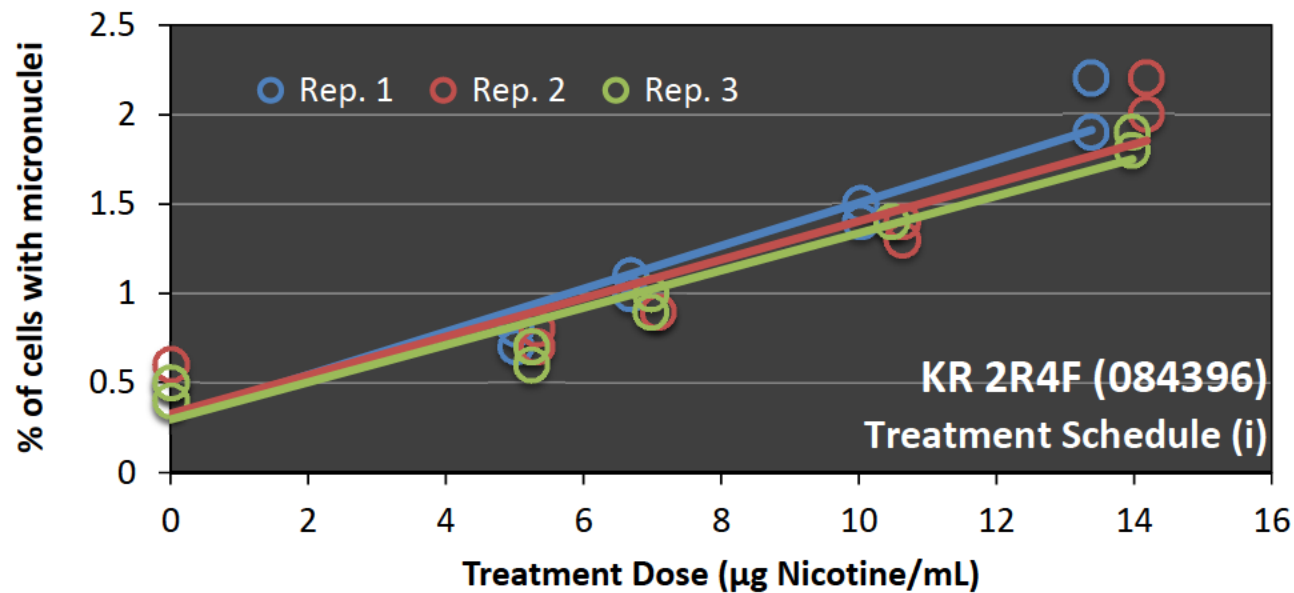
Treatment Schedule	Sample ID	Sample Description	% micronucleated cells/(mg TPM/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate TPM Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard		t-test p-value (H ₀ : mean = 0)		
			(mg TPM/mL)	slope	(mg TPM/mL)	slope	(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

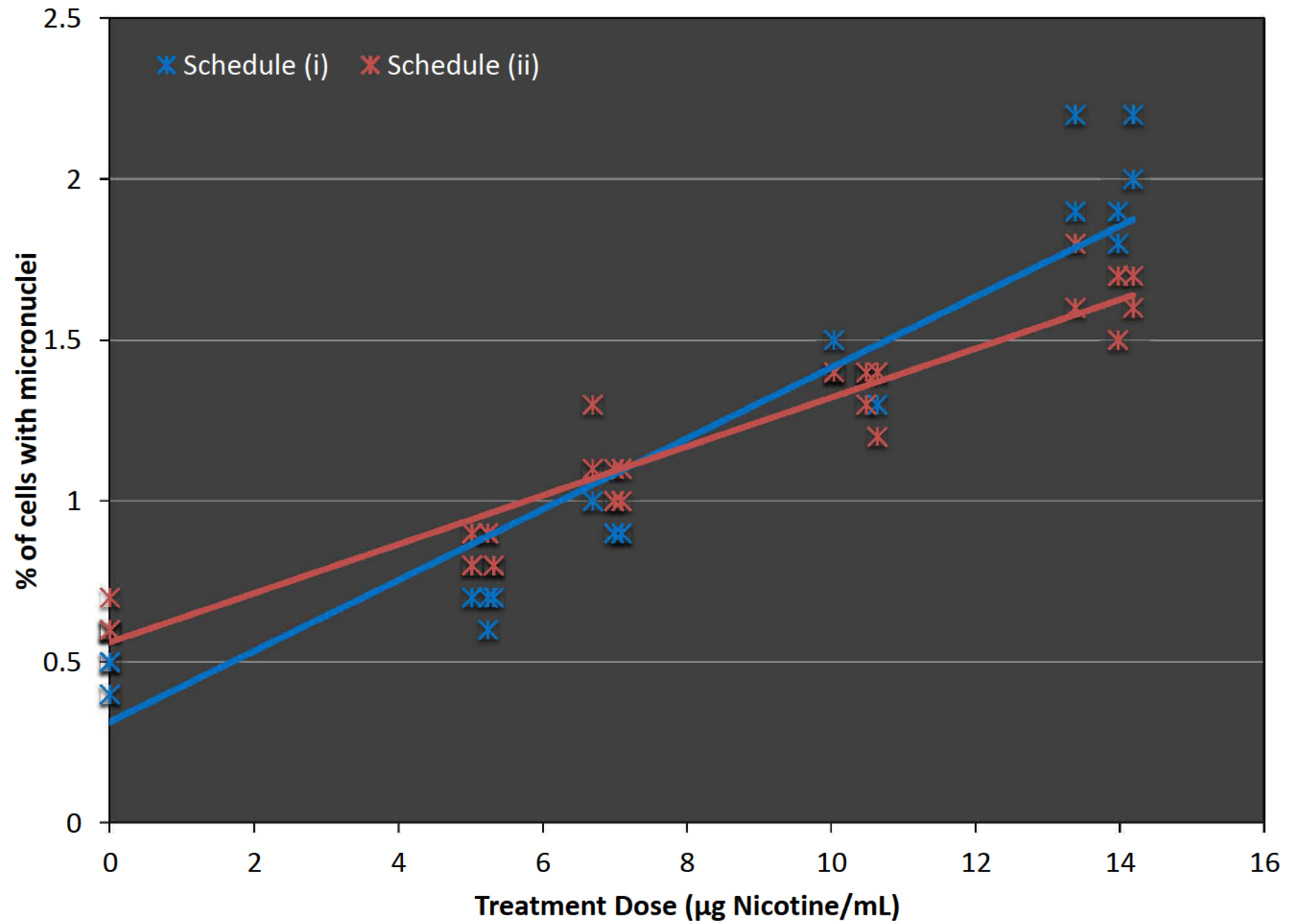




Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/(μ g Nicotine/mL)]

			% 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 /(μg '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)		
			(μg 'Nic.'/mL)	slope	(μg 'Nic.'/mL)	slope	(μg '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 Sticks	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 Sticks	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			

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).

Evaluation of Ratio (Max ÷ Min) of Standard Deviations
of 'Extracted Nicotine' 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 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

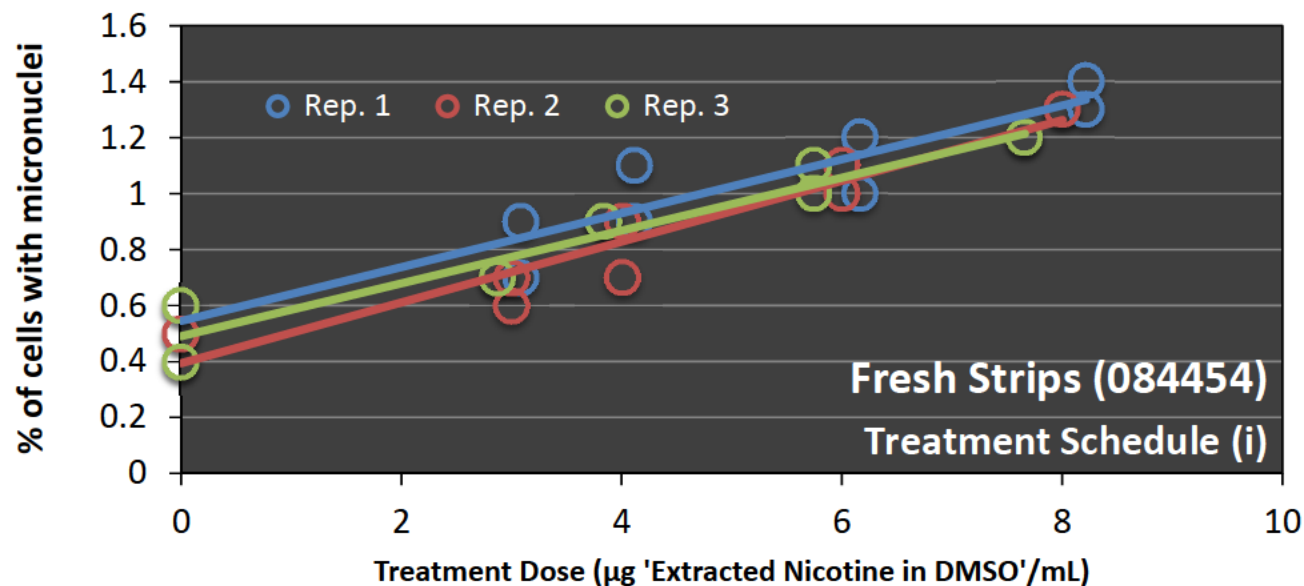
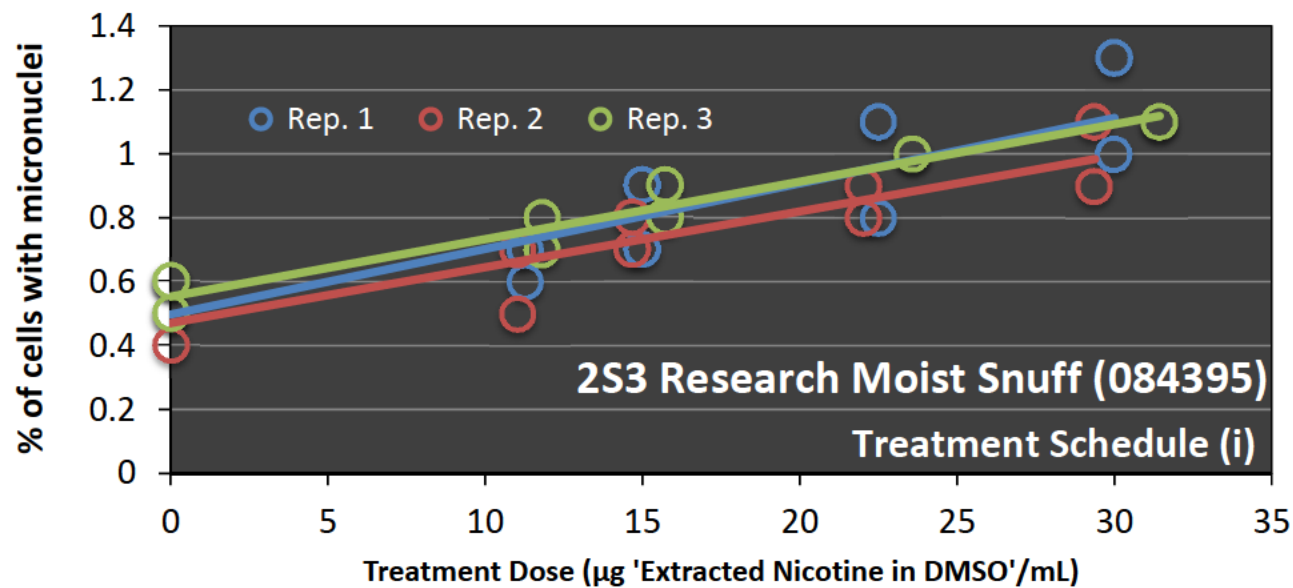
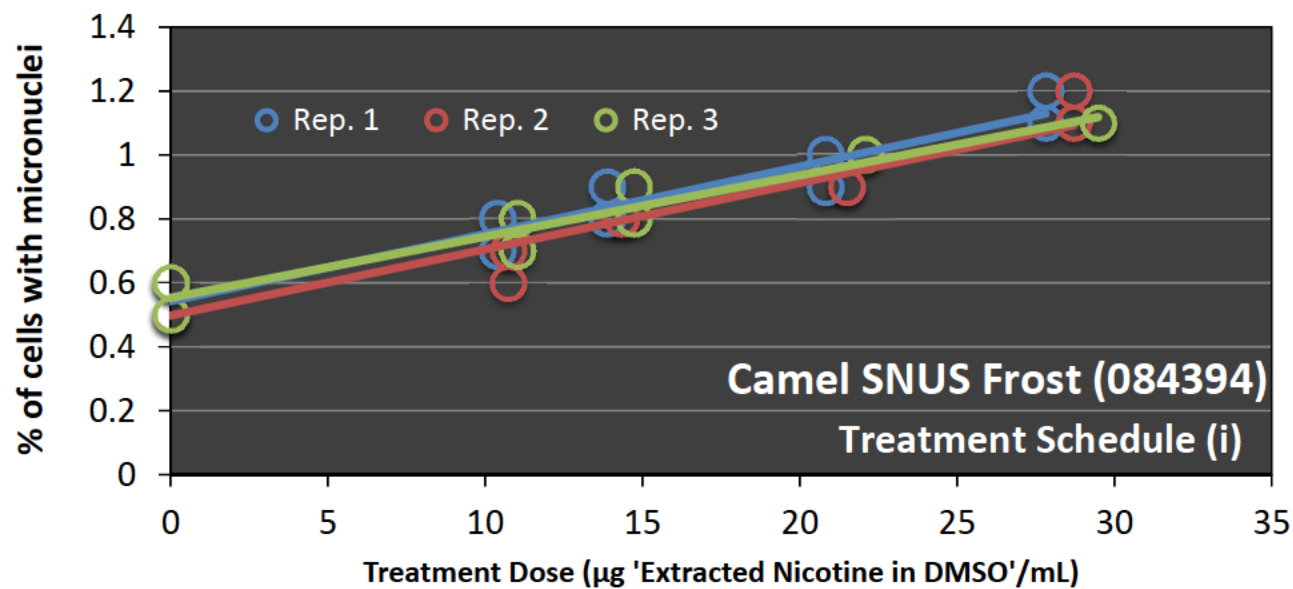
Pairwise T-test Comparisons of Mean 'Extracted Nicotine' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

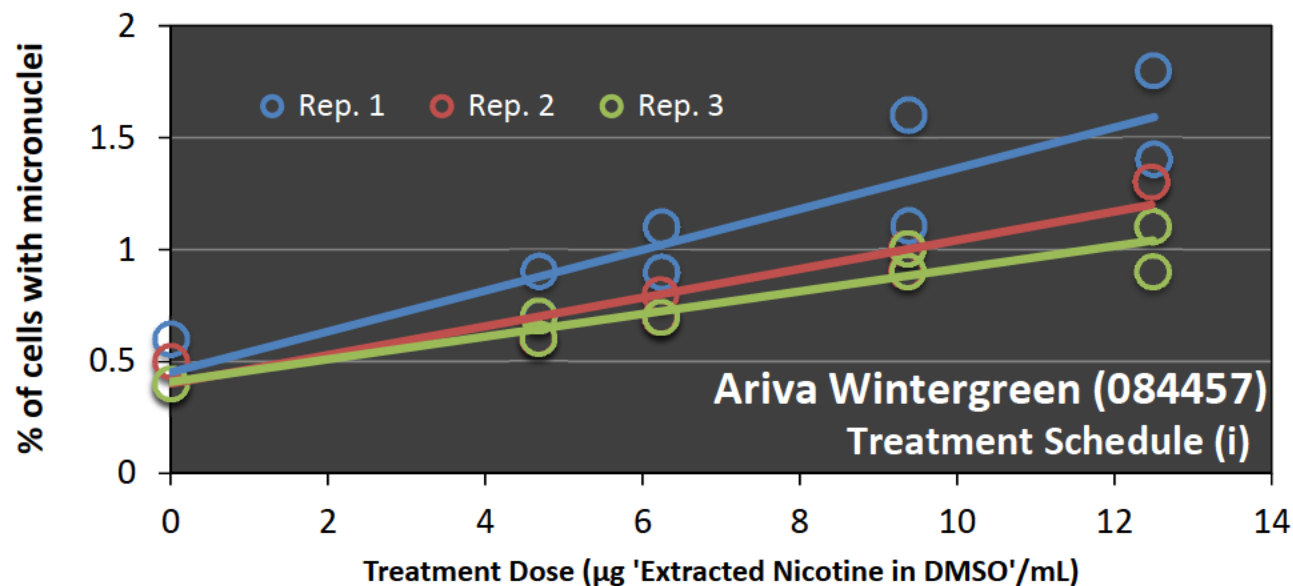
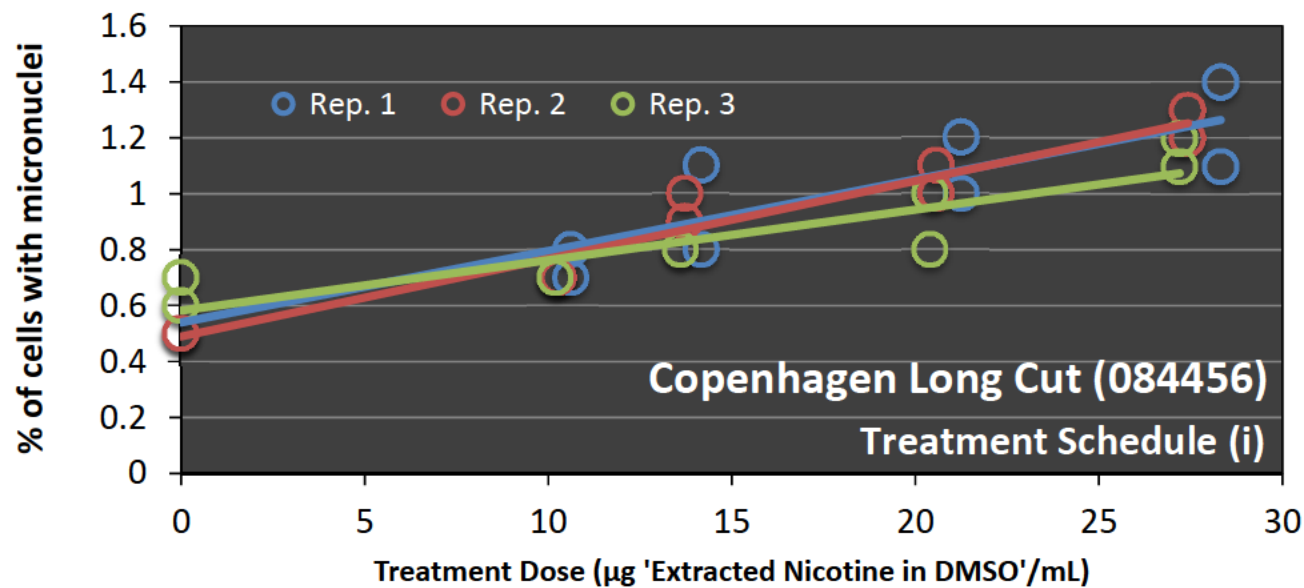
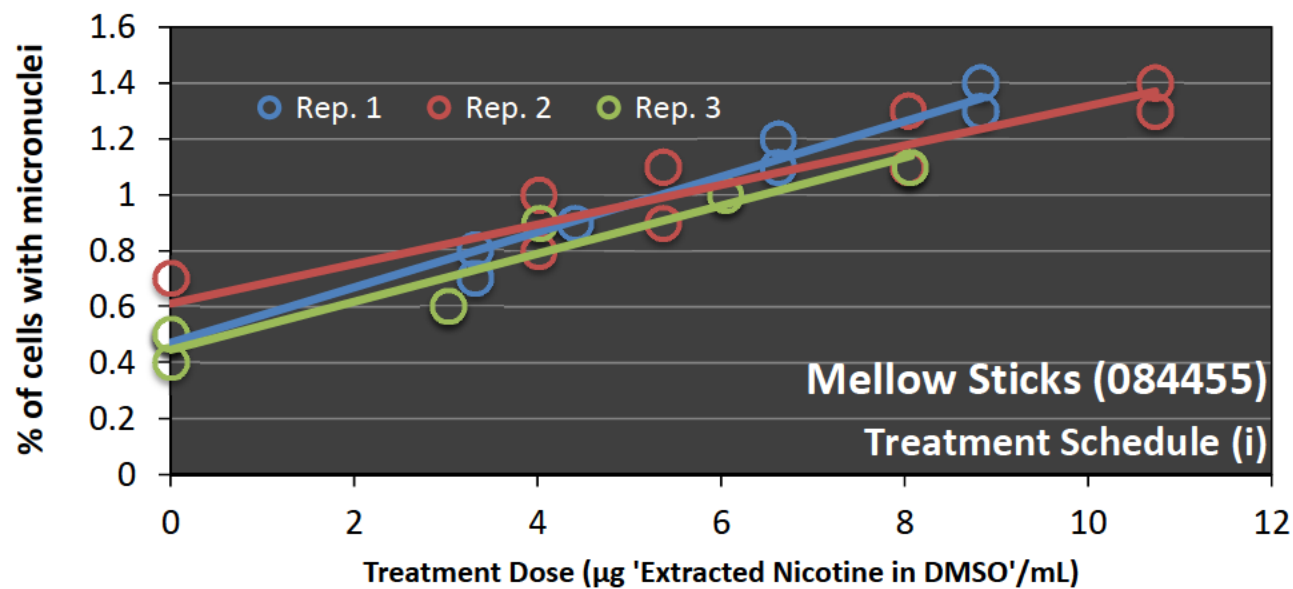
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	1.525	0.2019	not significant	1.281	0.2694	not significant
084394 vs. 084454	17.687	0.0001	significant	28.635	0.0000	significant
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

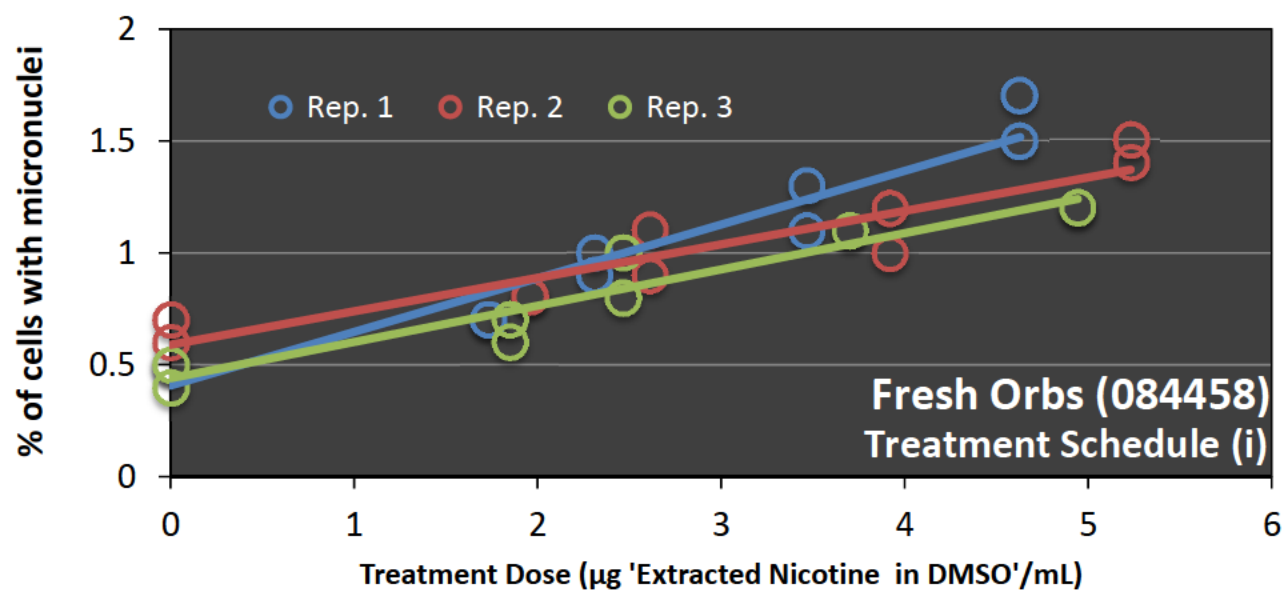
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were detected between:

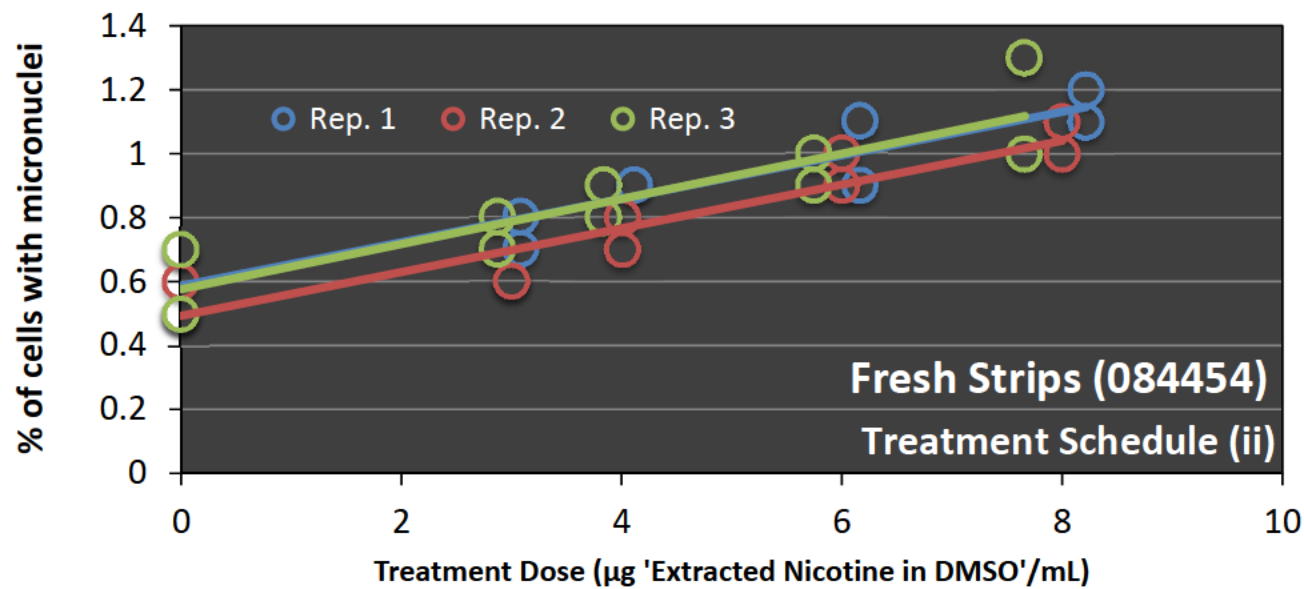
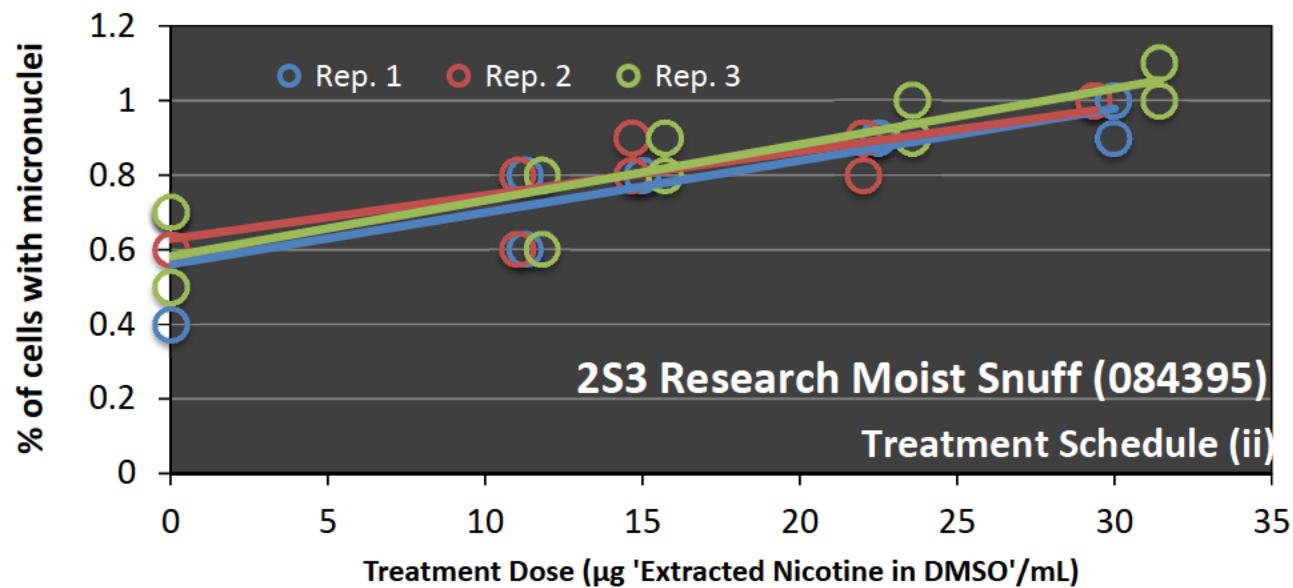
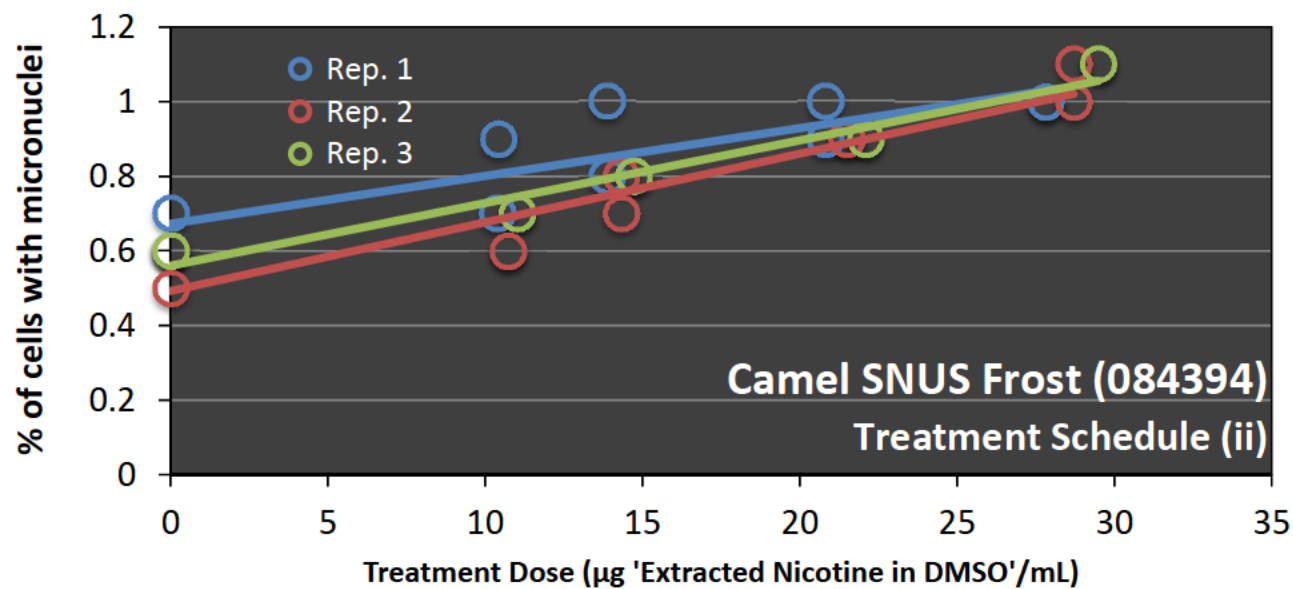
Fresh Strips (084454) as well as Mellow Sticks (084455) and each of {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)} under treatment schedule (i).

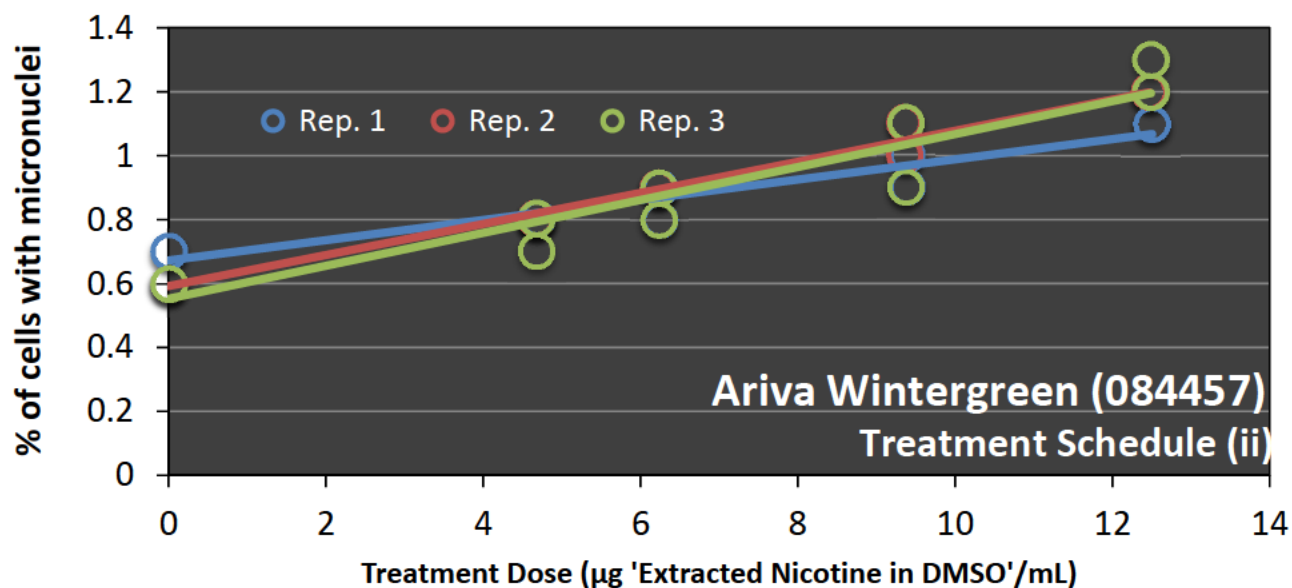
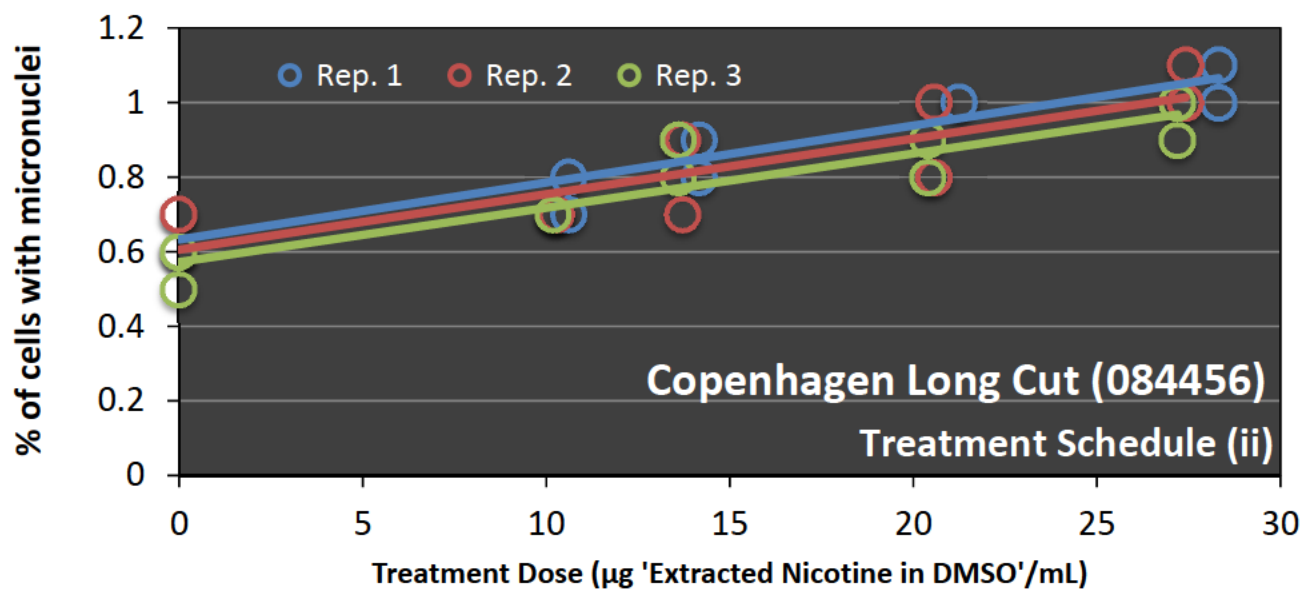
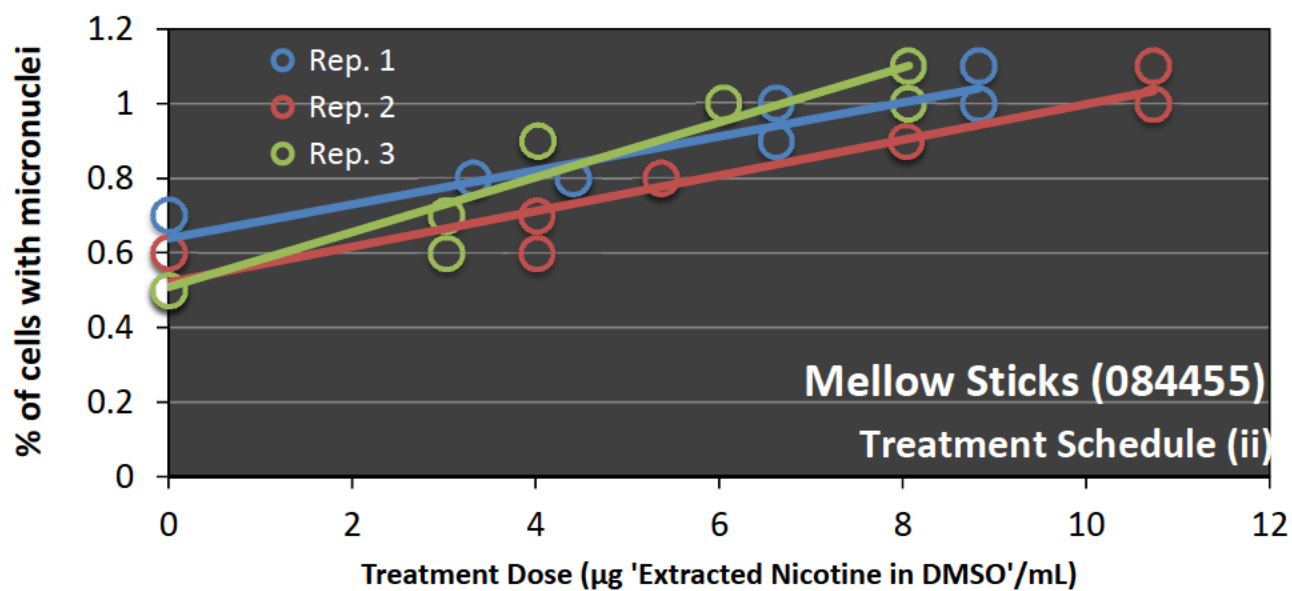
Fresh Strips (084454) as well as Fresh Orbs (084458) and each of {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)} under treatment schedule (ii).

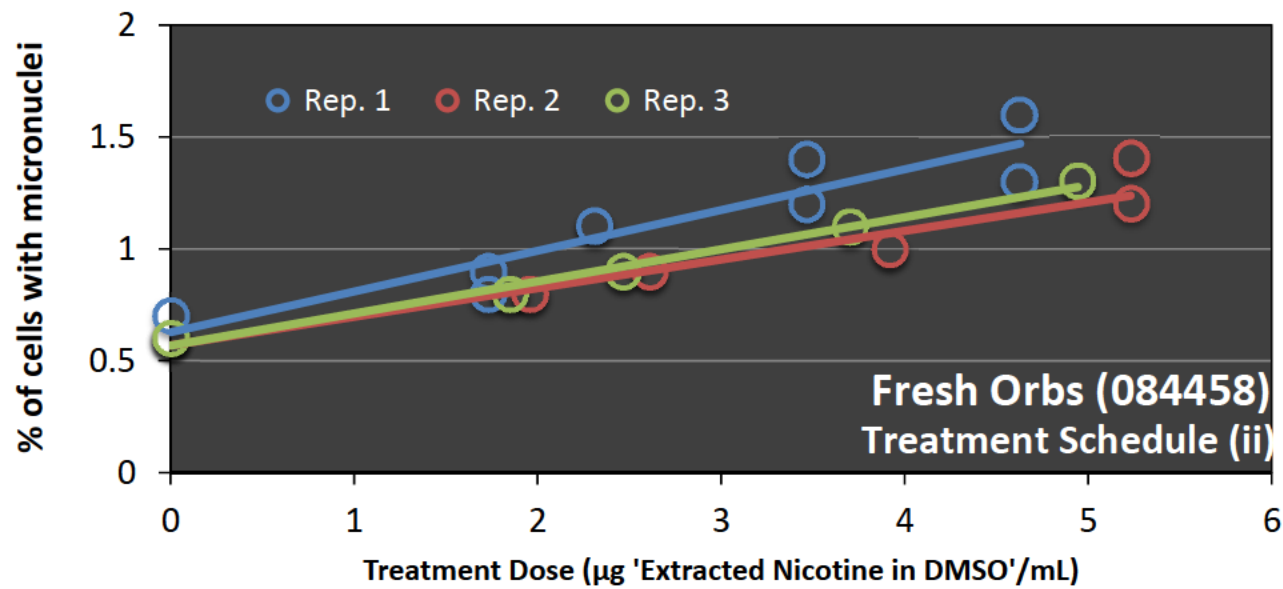


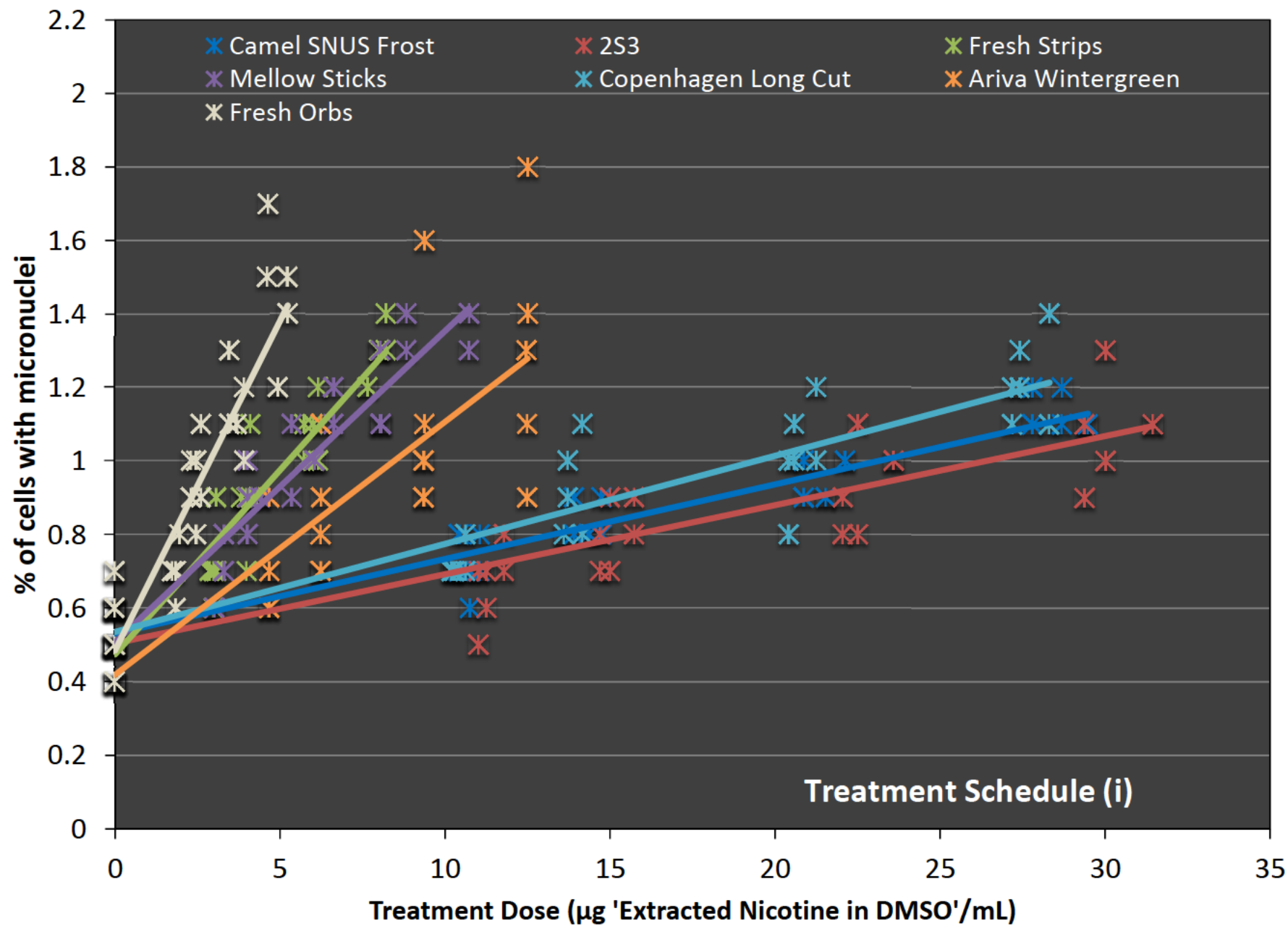


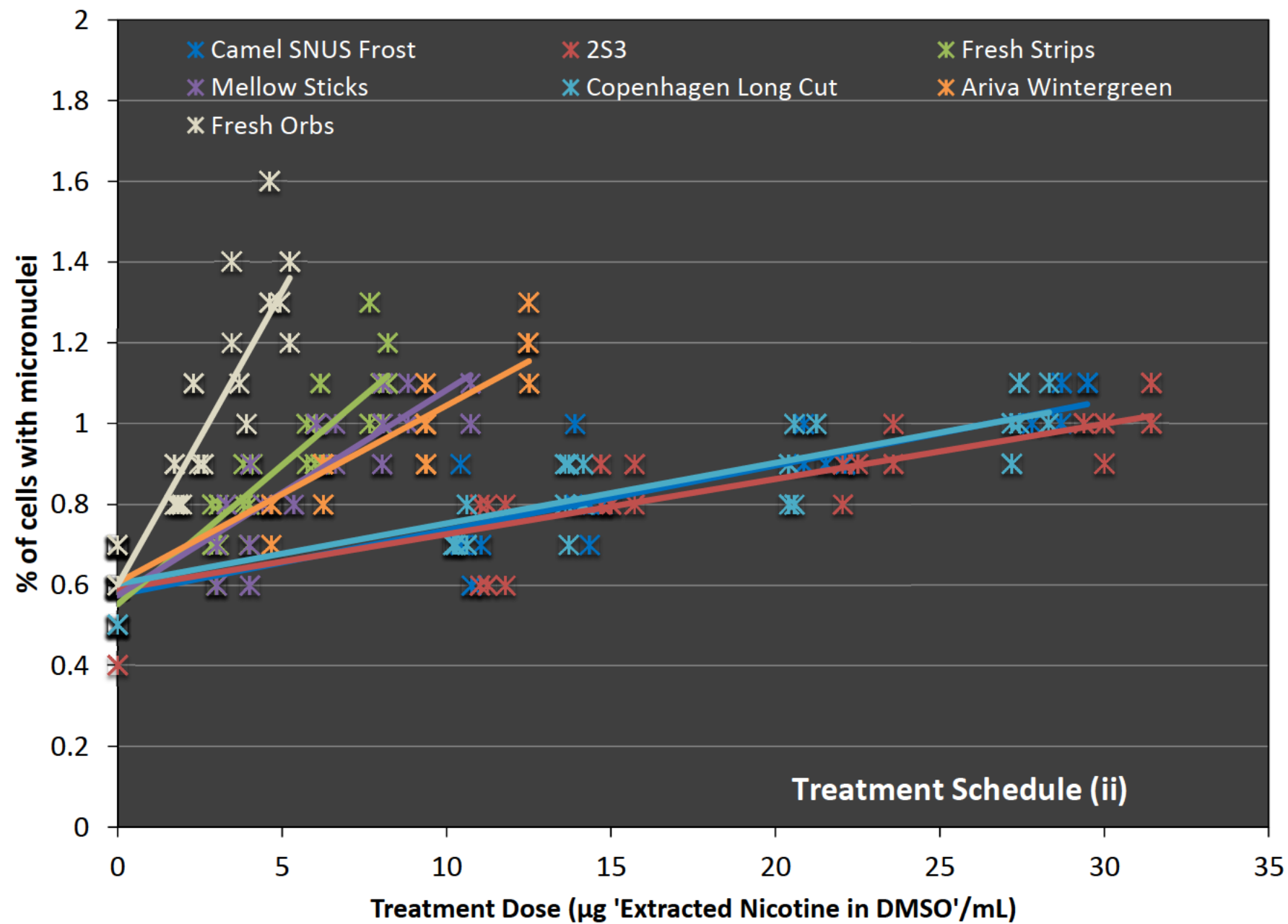












Treatment Schedule (ii)

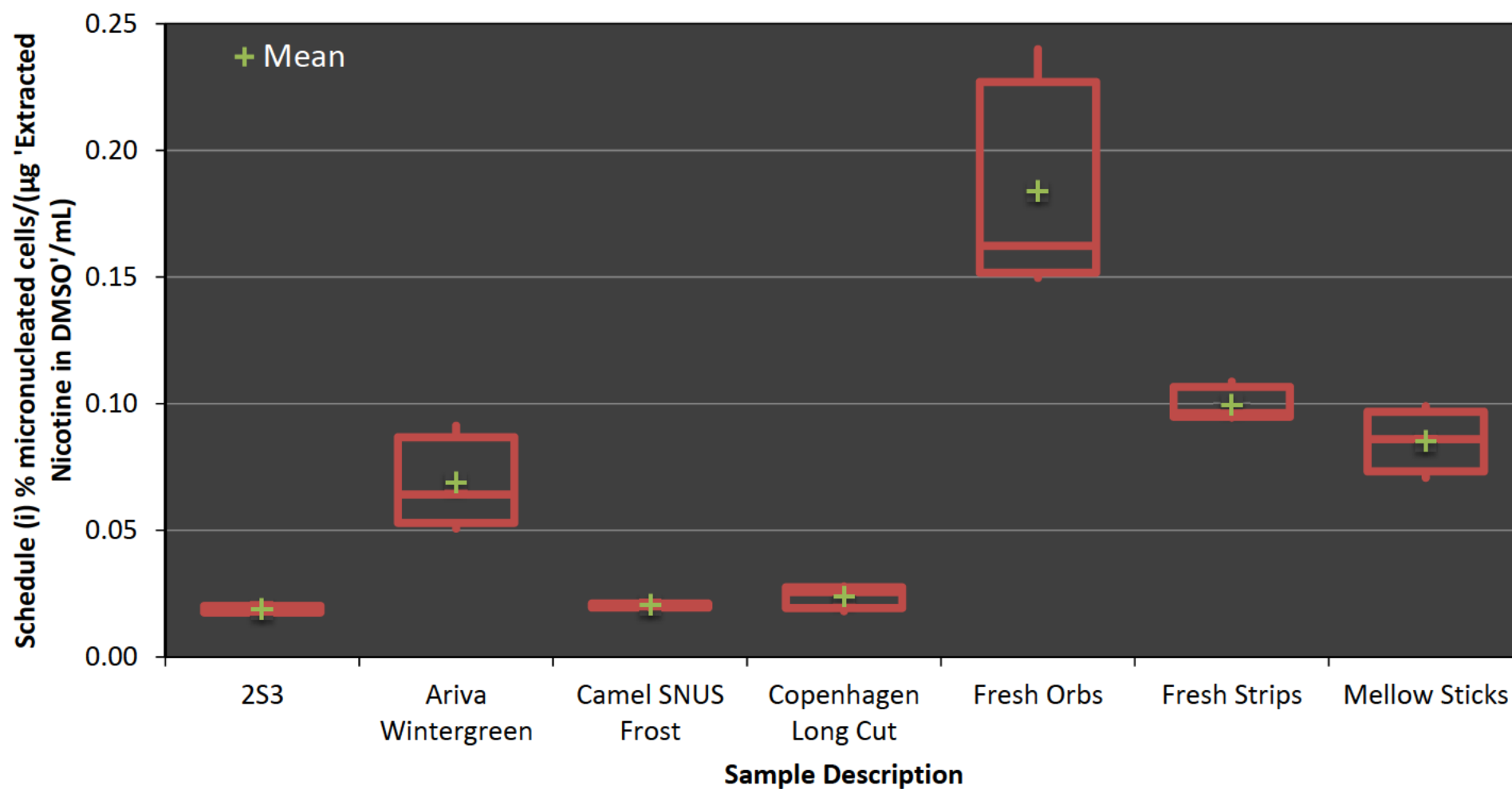
Test **Describe - Comparative**

Performed by

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

Date

4 February 2011



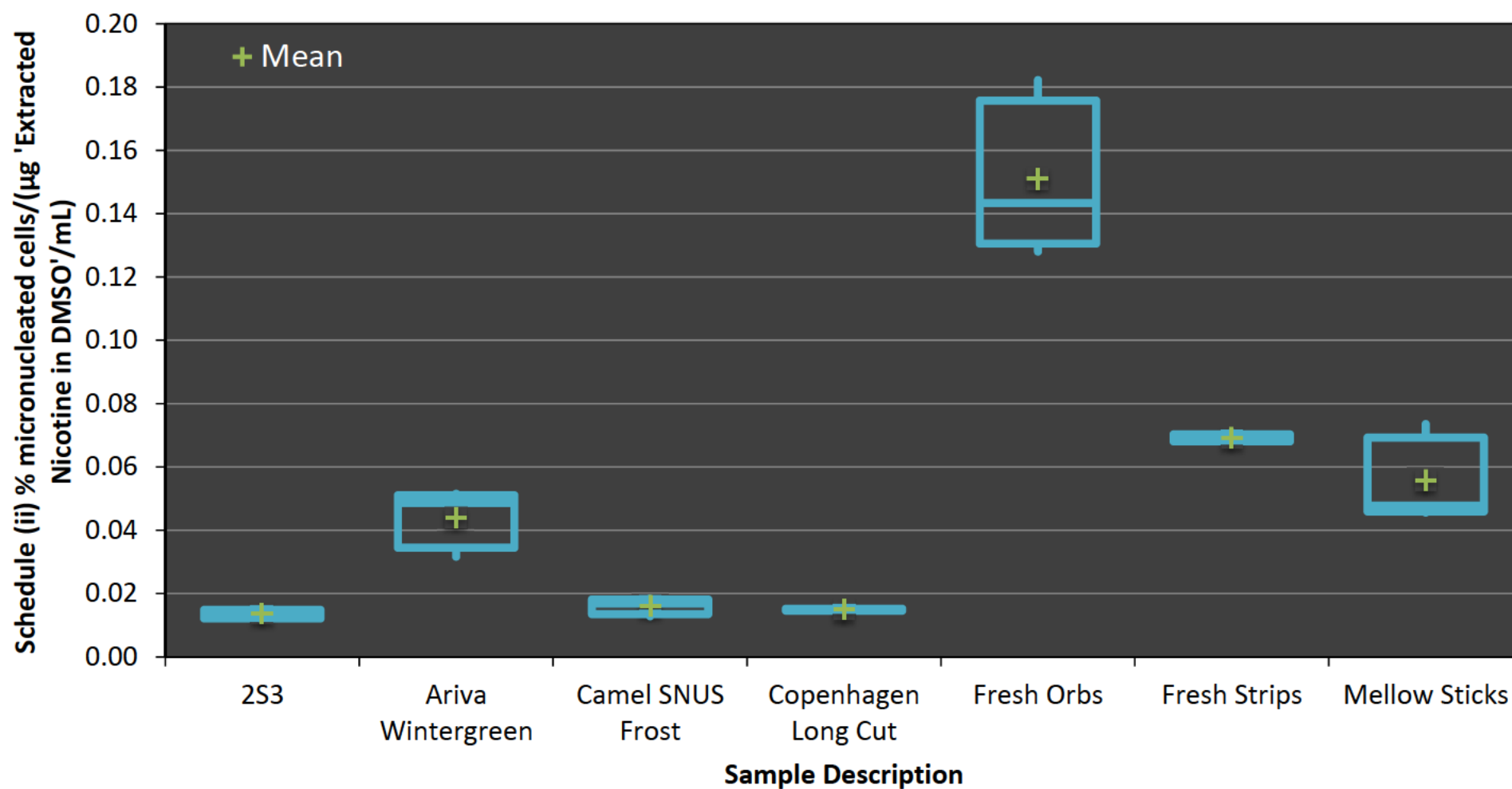
Test Describe - Comparative

Performed by

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

Date

4 February 2011



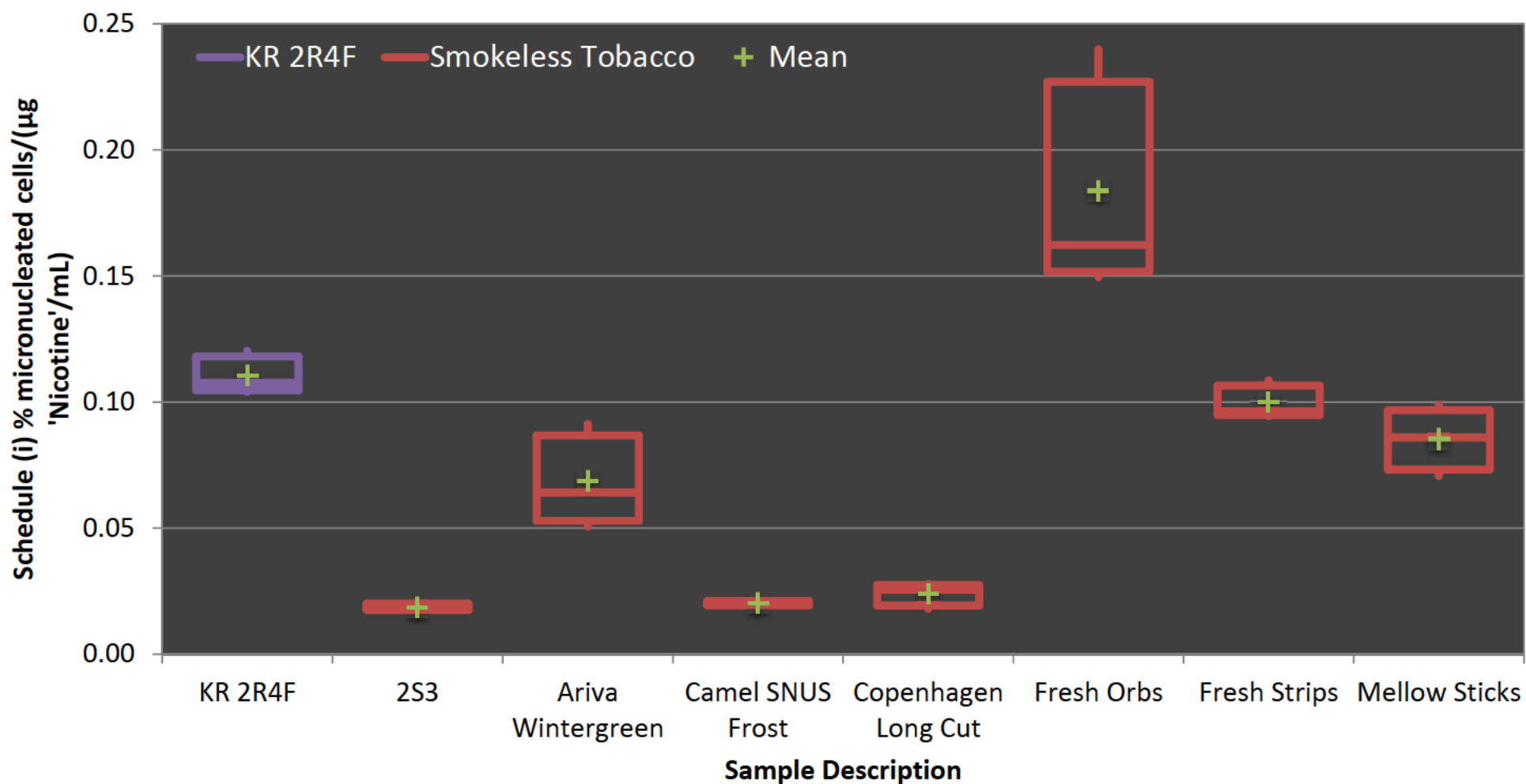
Test Describe - Comparative

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 Desc

Date

4 February 2011



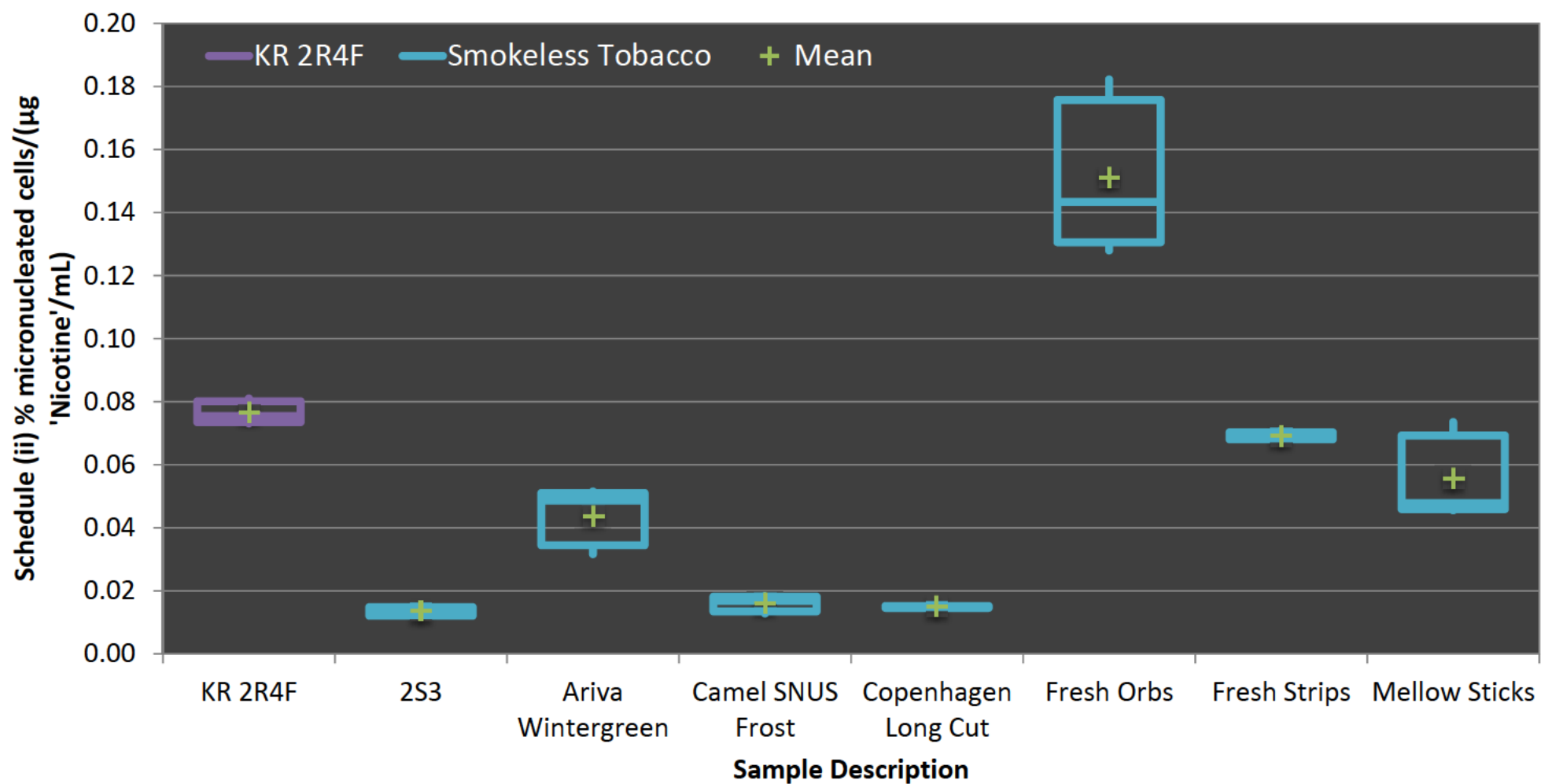
Test Describe - Comparative

Performed by

Schedule (ii) % micronucleated cells/(μg 'Nicotine in CSC'/mL) (KR 2R4F) and % micronucleated cells/(μg '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
[% of mononucleated cells with micronuclei/(mg 'Extracted Smokeless Tobacco in DMSO'/mL)] (ST)

			% micronucleated cells/(mg 'Extracted Smokeless Tobacco in DMSO'/mL)										
Treatment Schedule	Sample ID	Sample Description	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):

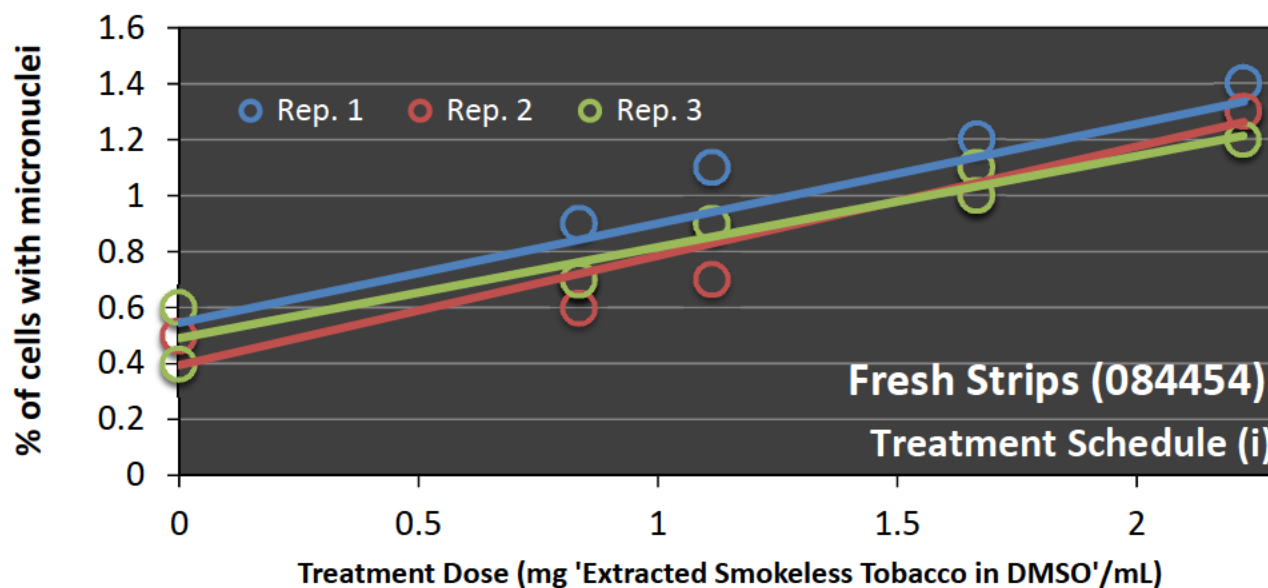
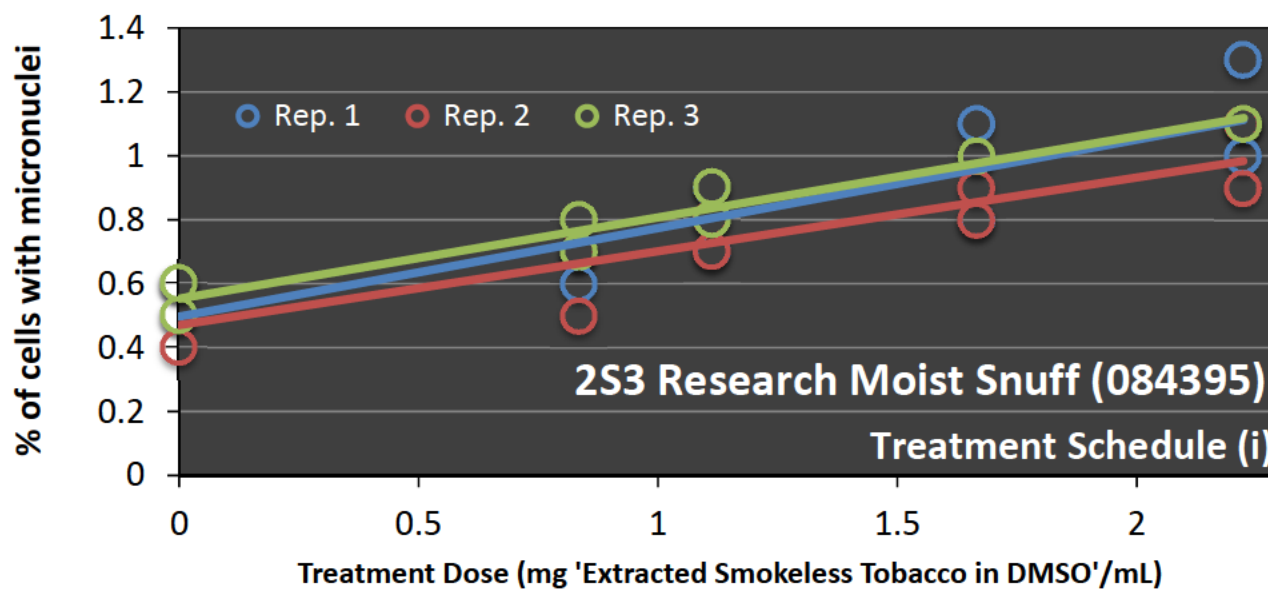
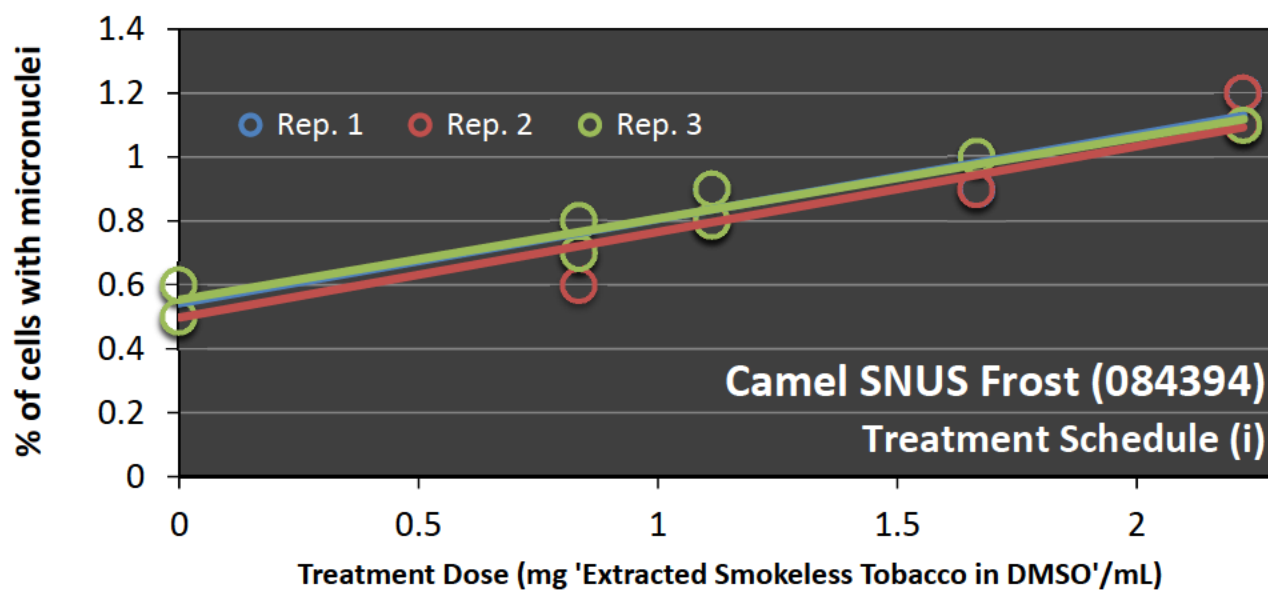
Schedule (ii)

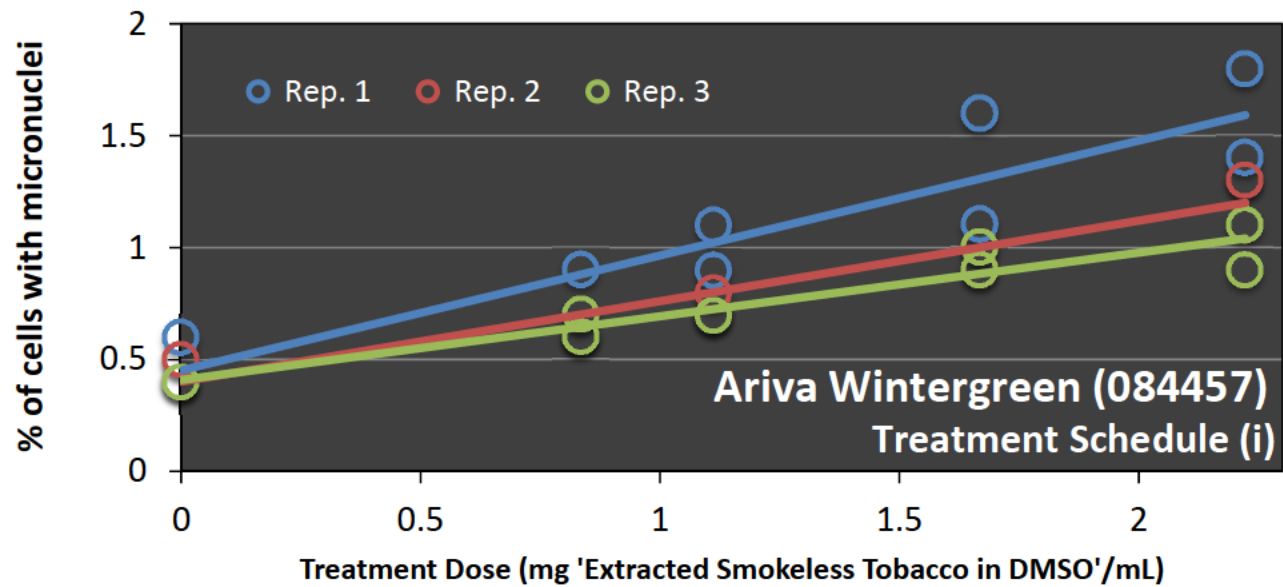
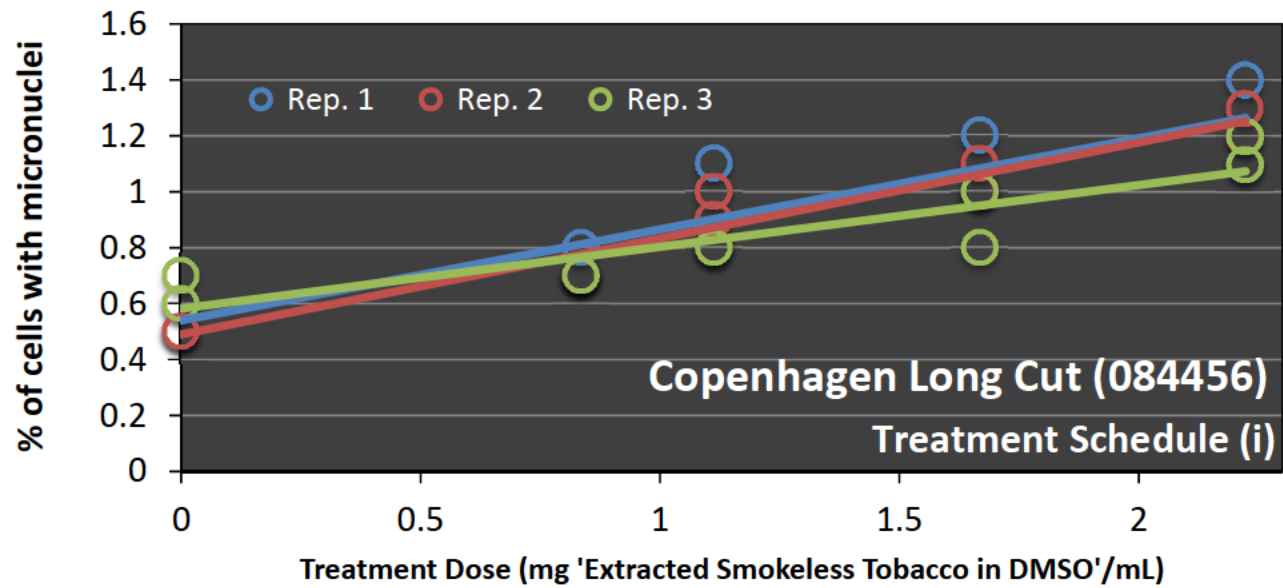
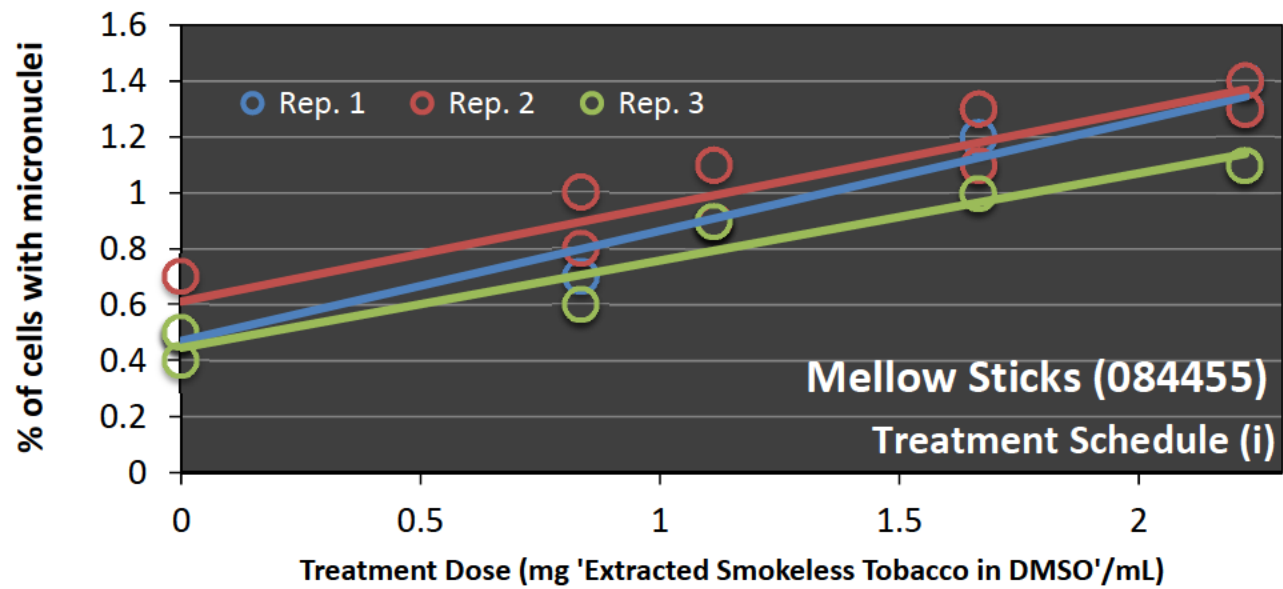
Sample Description	Sample ID	Mean Slope	Homogenous Groupings
2S3	084395	0.185	X
Copenhagen Long Cut	084456	0.185	X
Camel SNUS Frost	084394	0.207	X
Mellow Sticks	084455	0.226	XX
Ariva Wintergreen	084457	0.247	XX
Fresh Strips	084454	0.247	XX
Fresh Orbs	084458	0.333	X

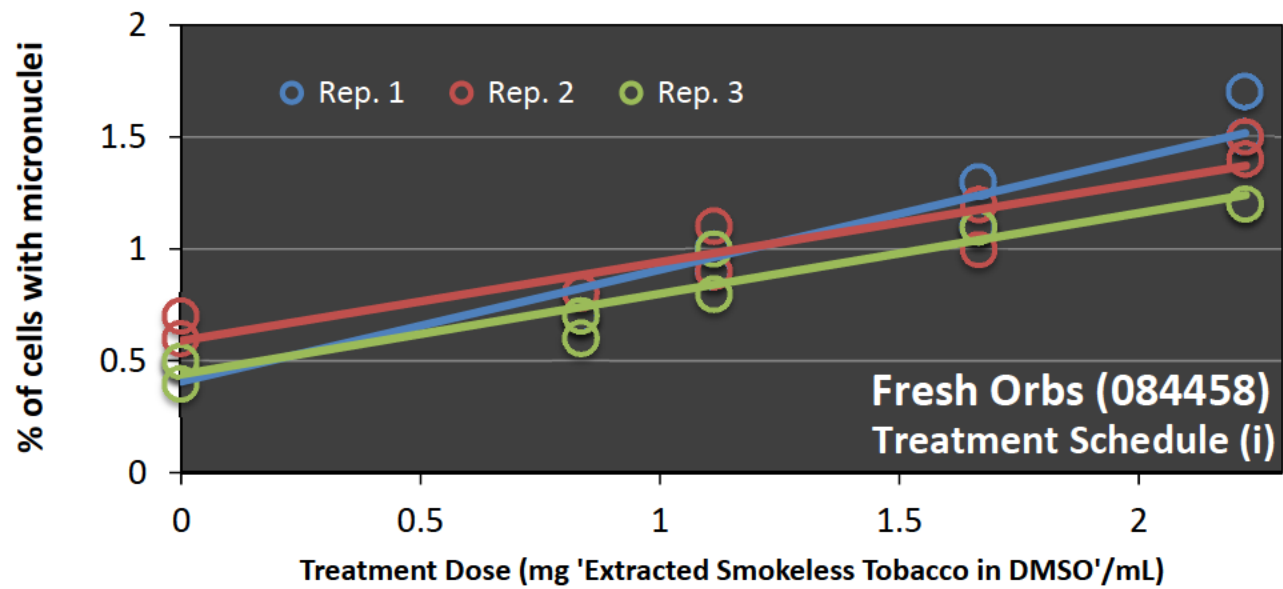
Pairwise T-Test Comparisons of Mean 'Extracted Smokeless Tobacco' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

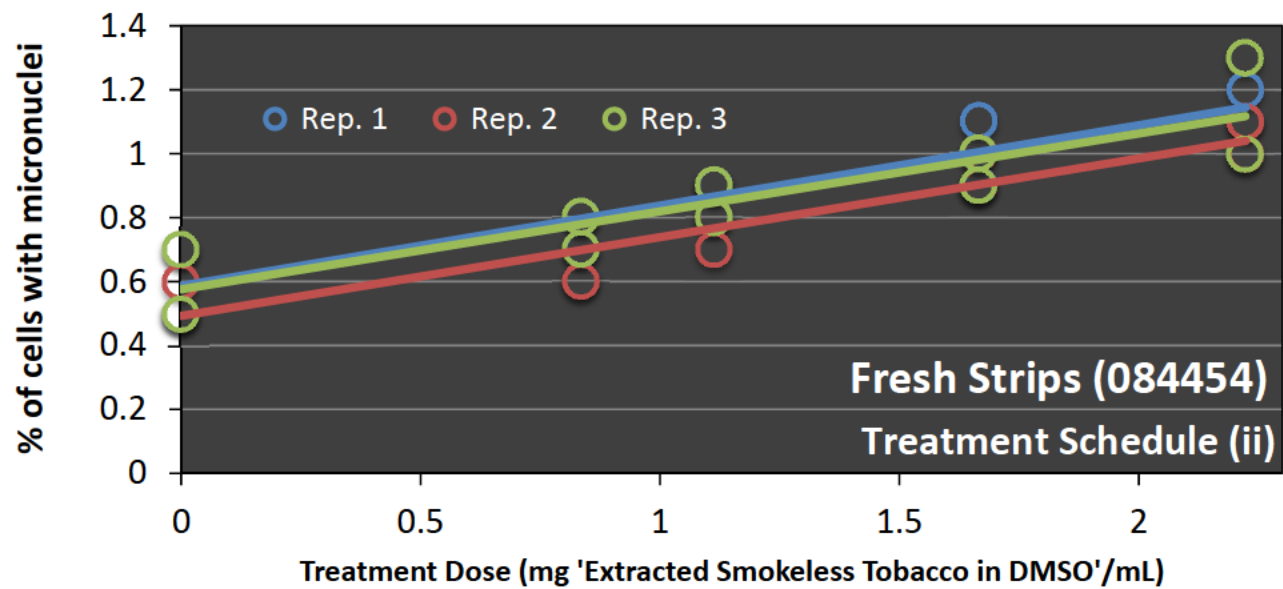
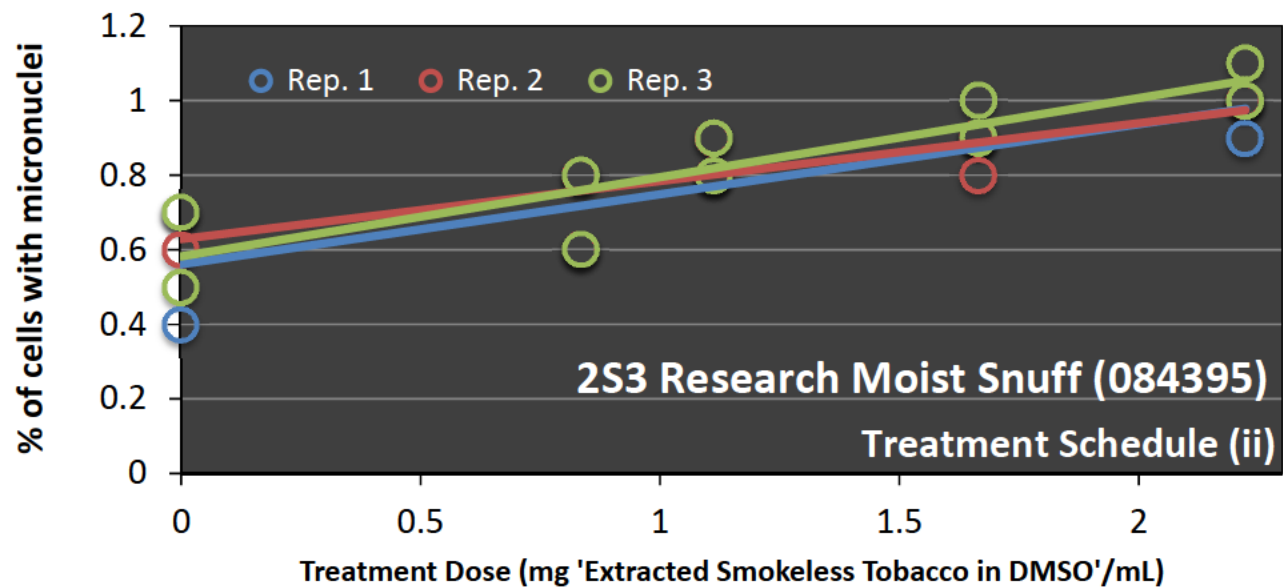
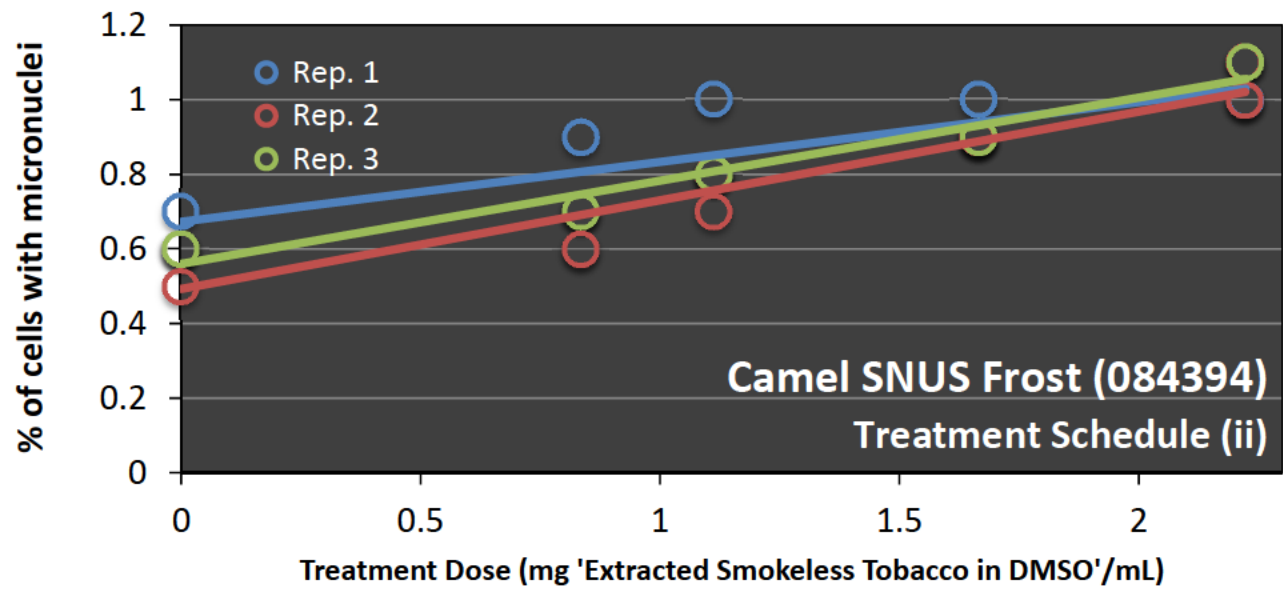
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.5856	0.5896	not significant	0.7573	0.4910	not significant
084394 vs. 084454	4.9378	0.0078	not significant	1.6827	0.1677	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

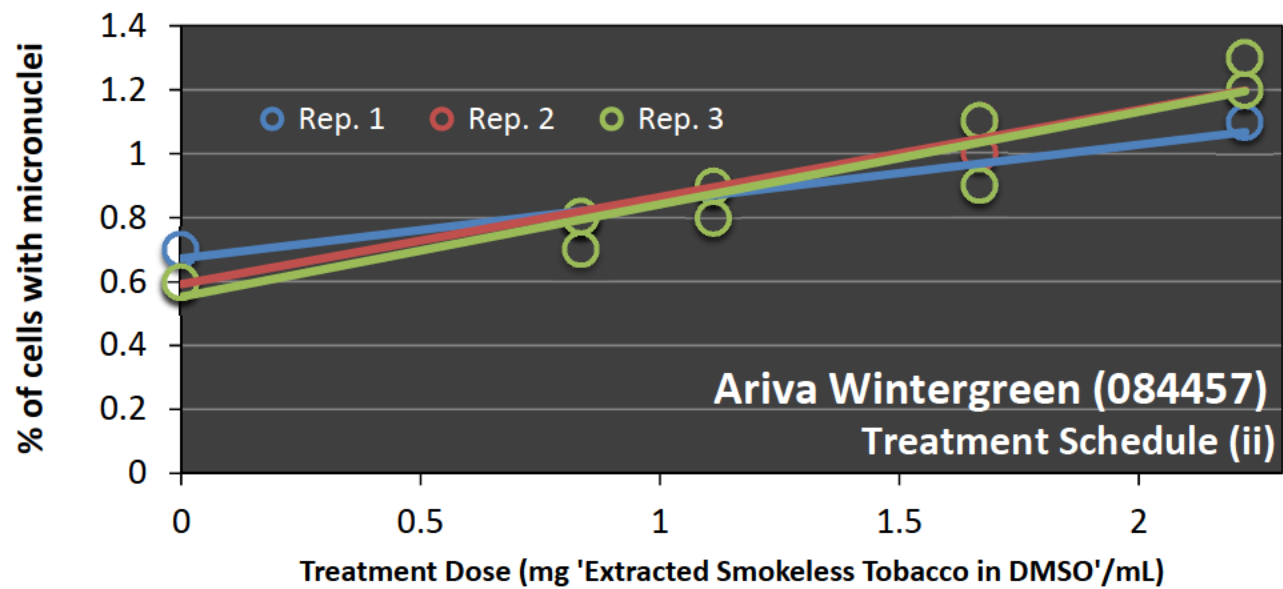
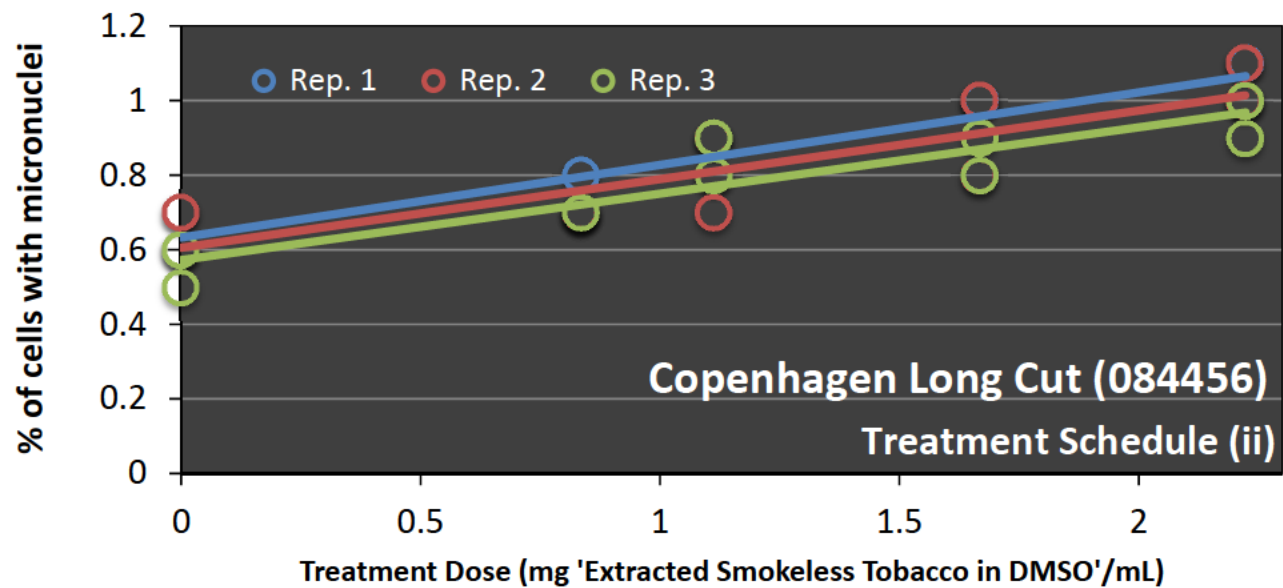
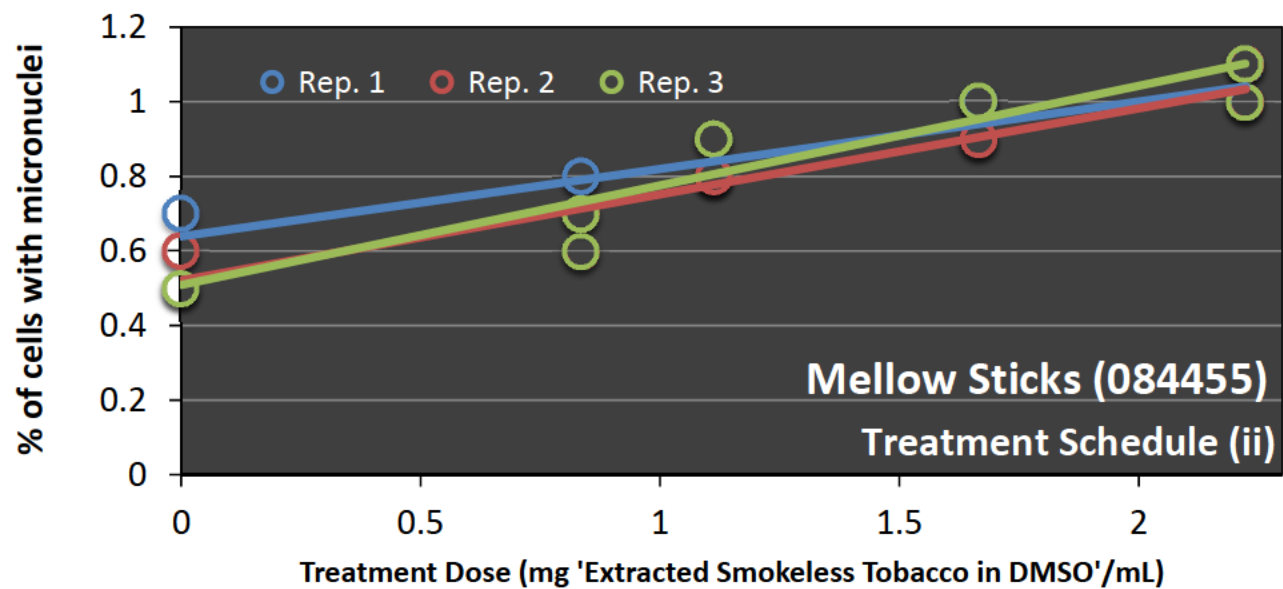
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted smokeless tobacco' slope were detected between Fresh Strips (084454) and Copenhagen Long Cut (084456) under treatment schedule (ii).

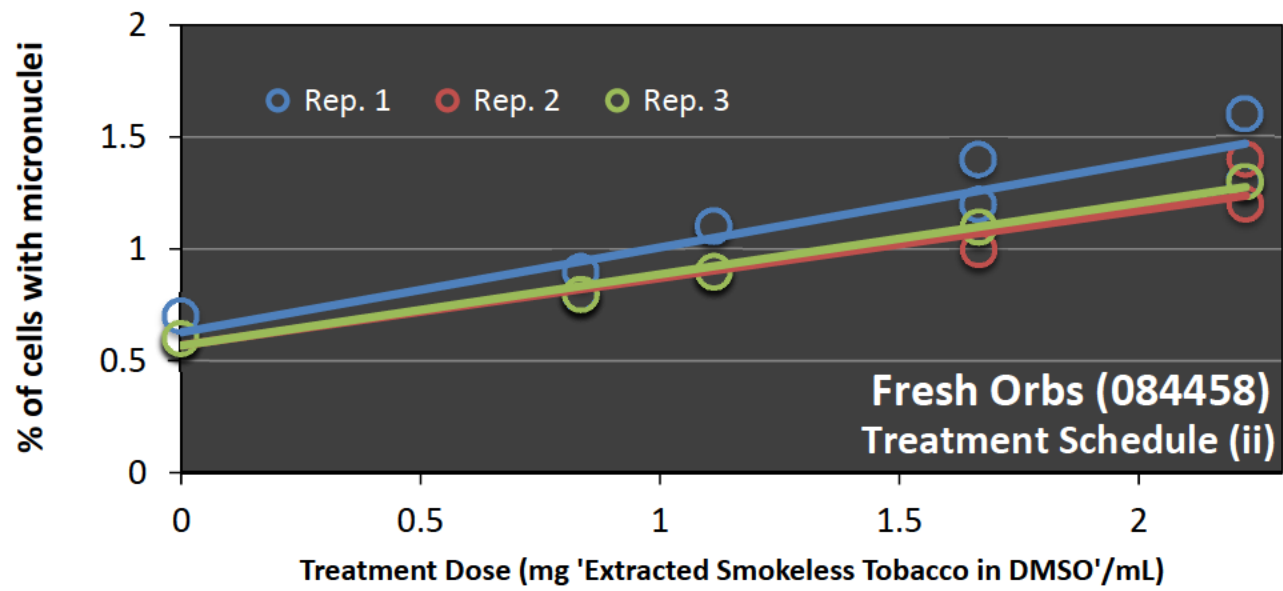


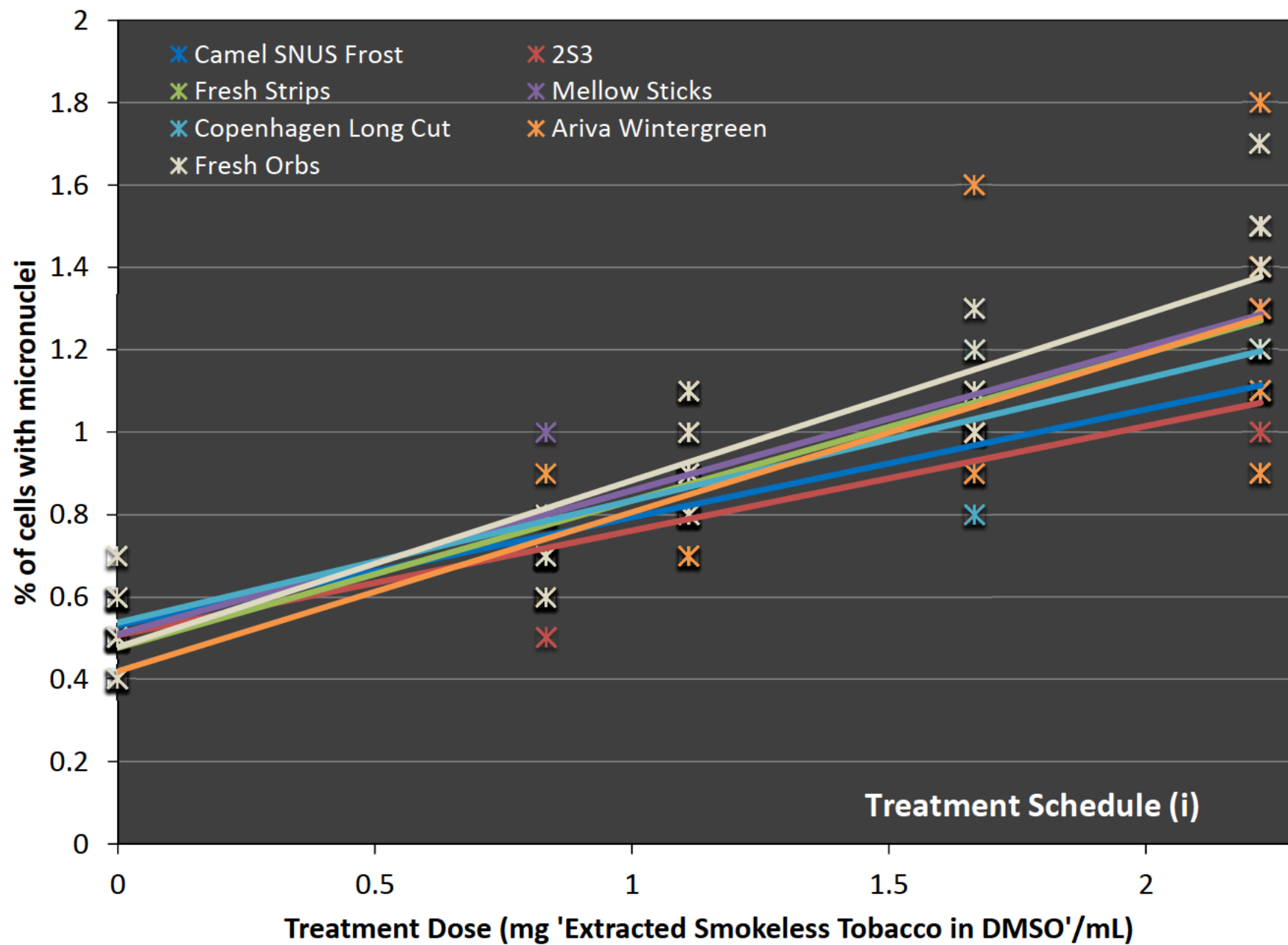


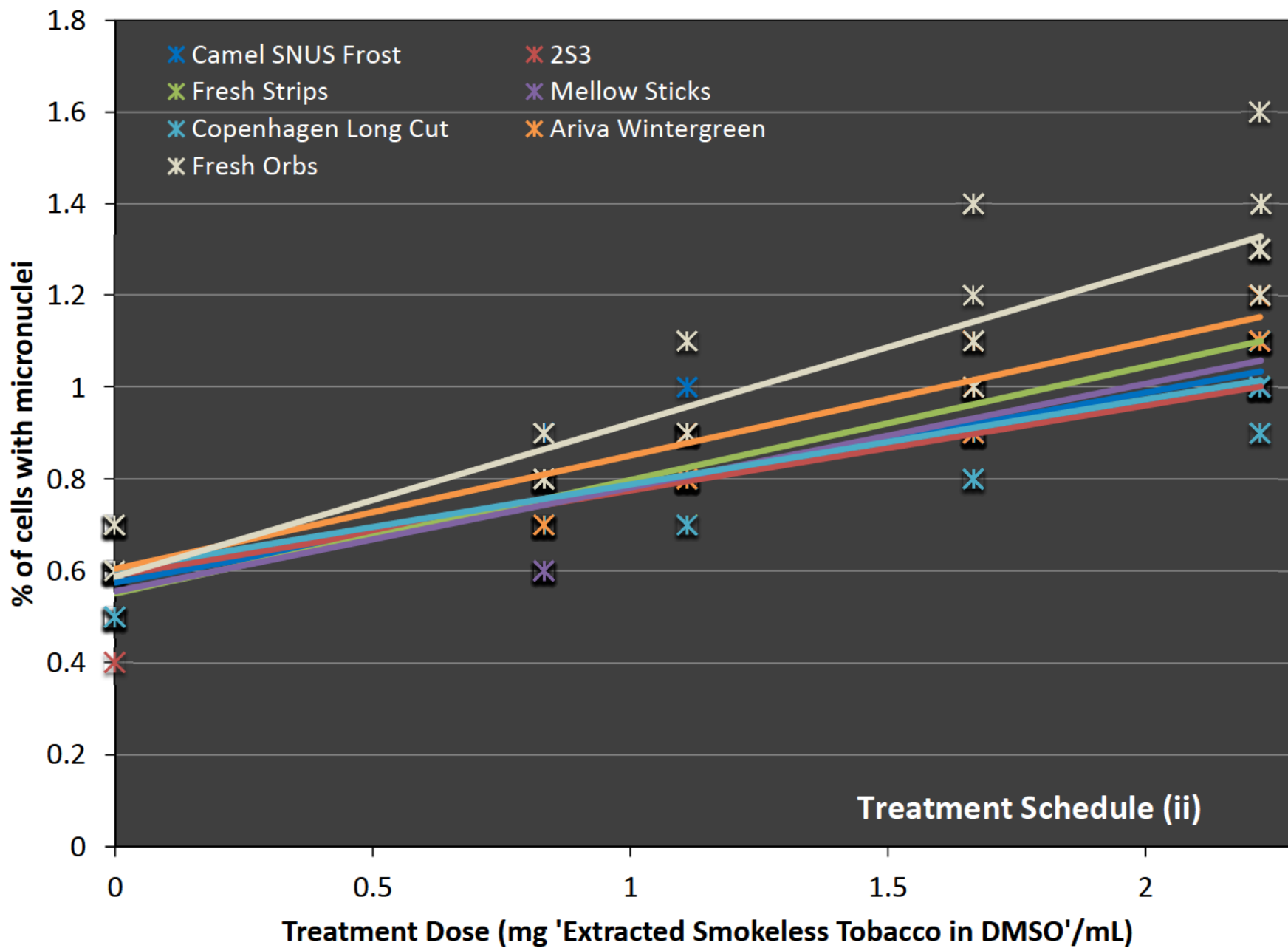












Treatment Schedule (ii)

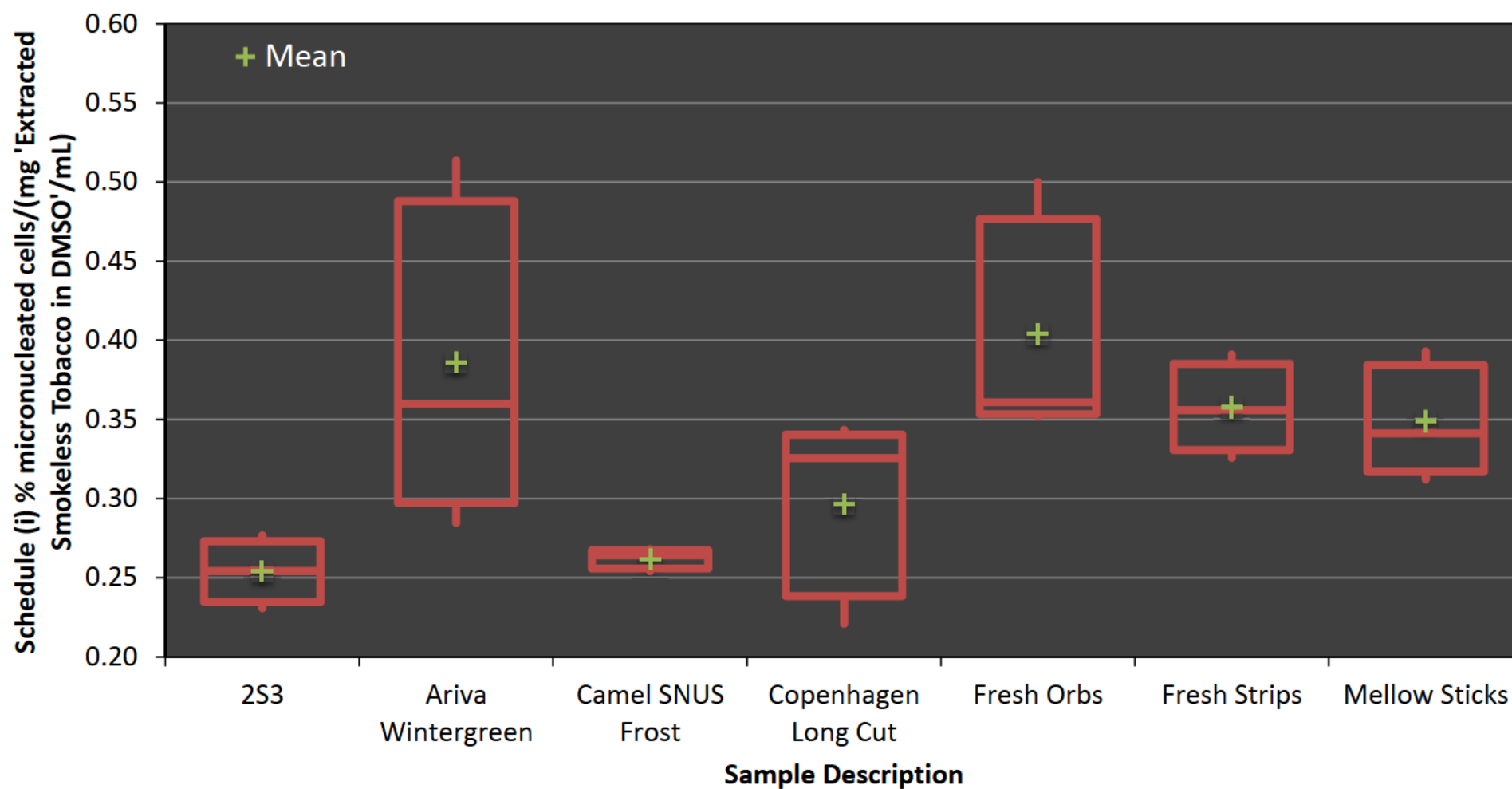
Test **Describe - Comparative**

Performed by

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

Date

2 November 2009



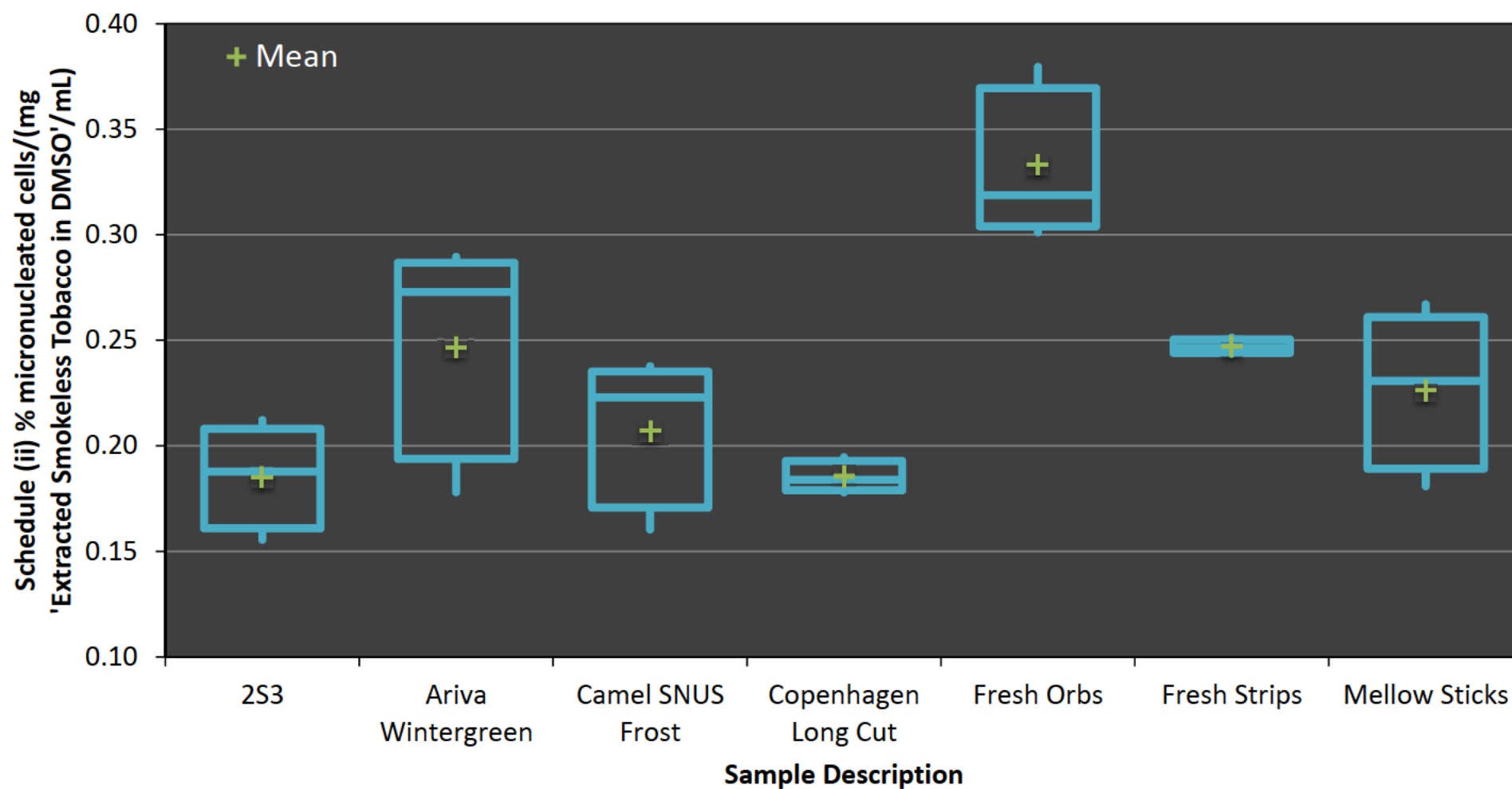
Test Describe - Comparative

Performed by

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

Date

2 November 2009



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

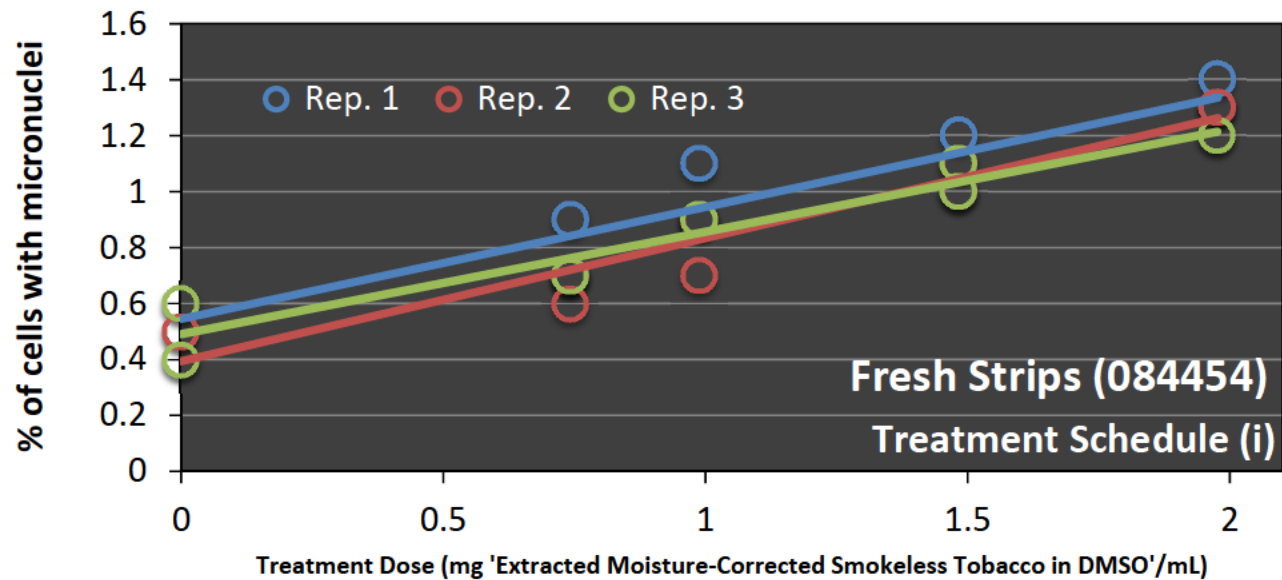
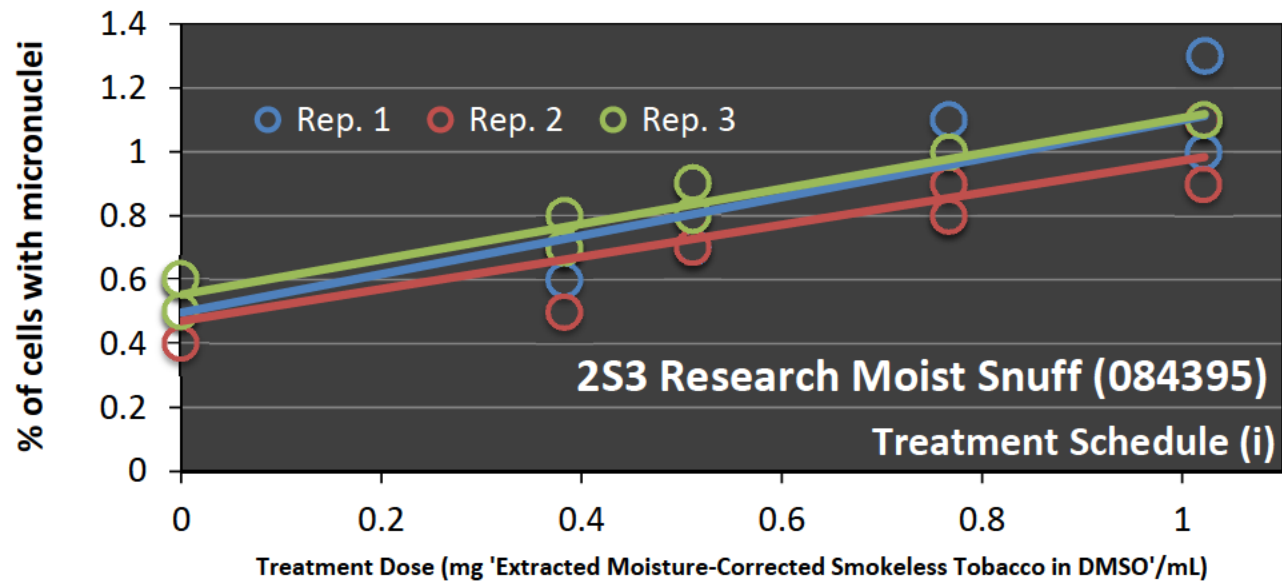
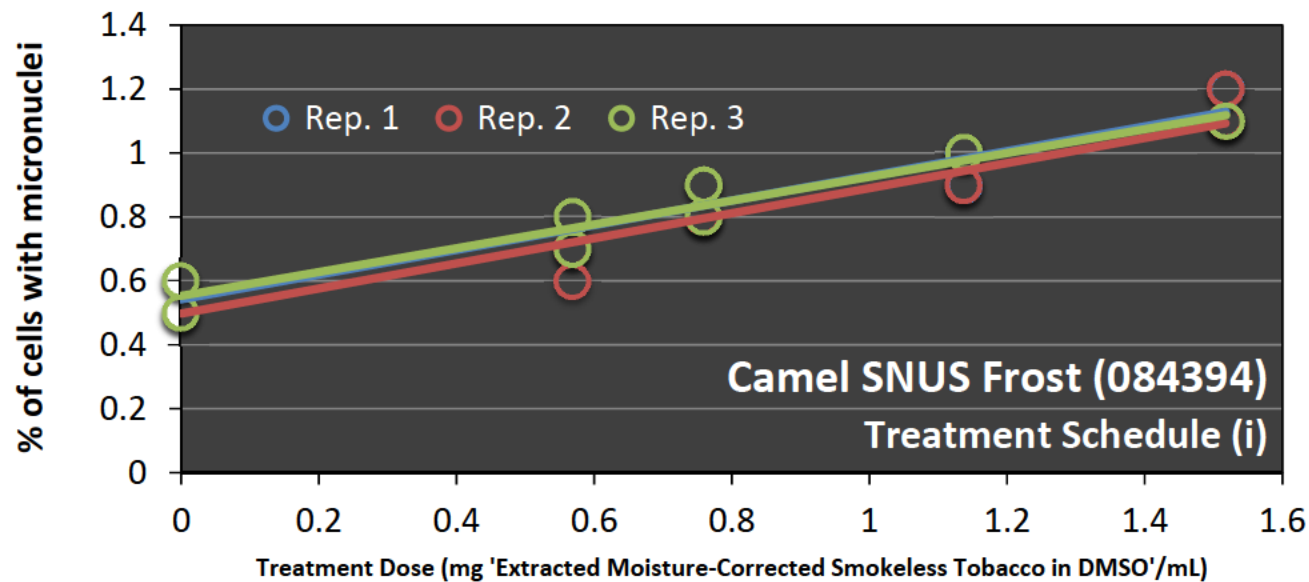
ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted moisture-corrected smokeless tobacco' slope were as follows:

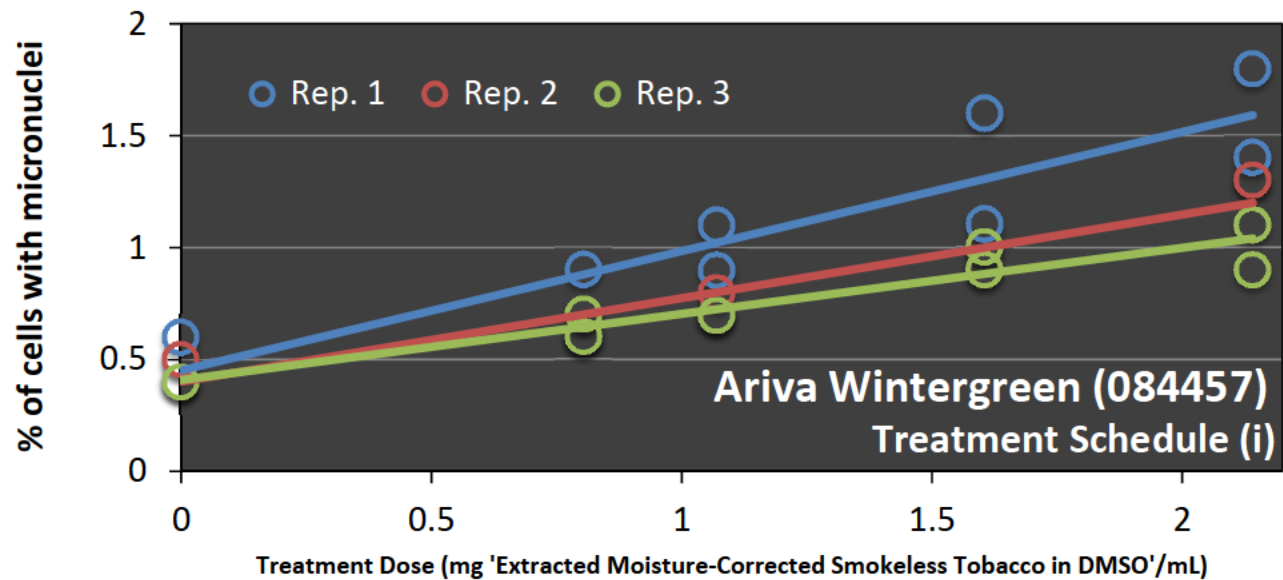
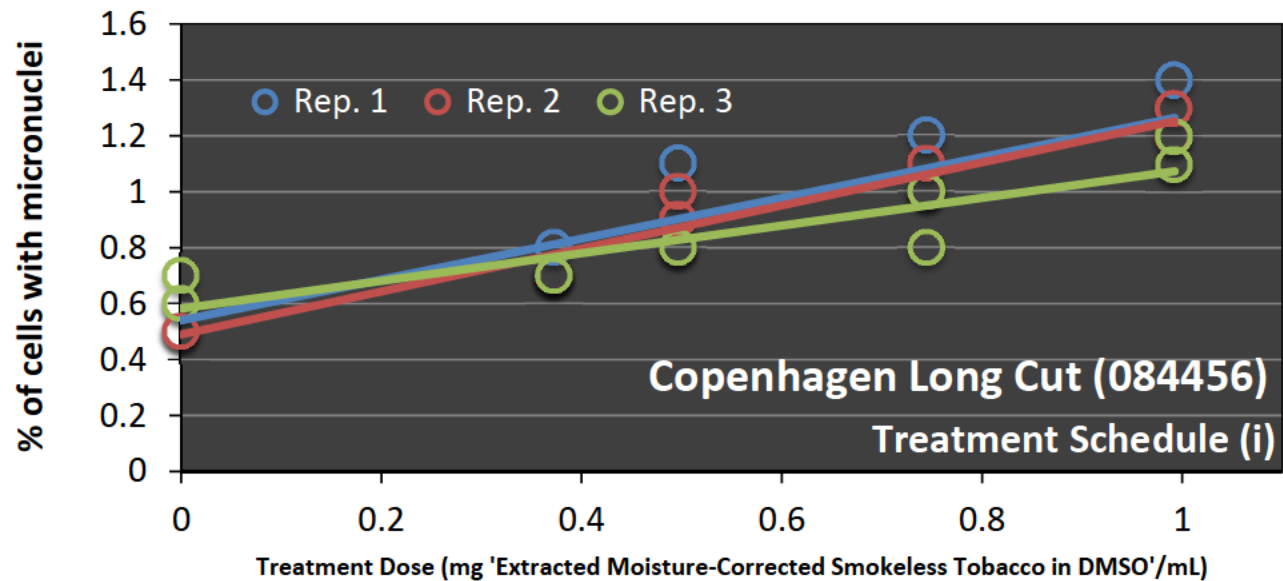
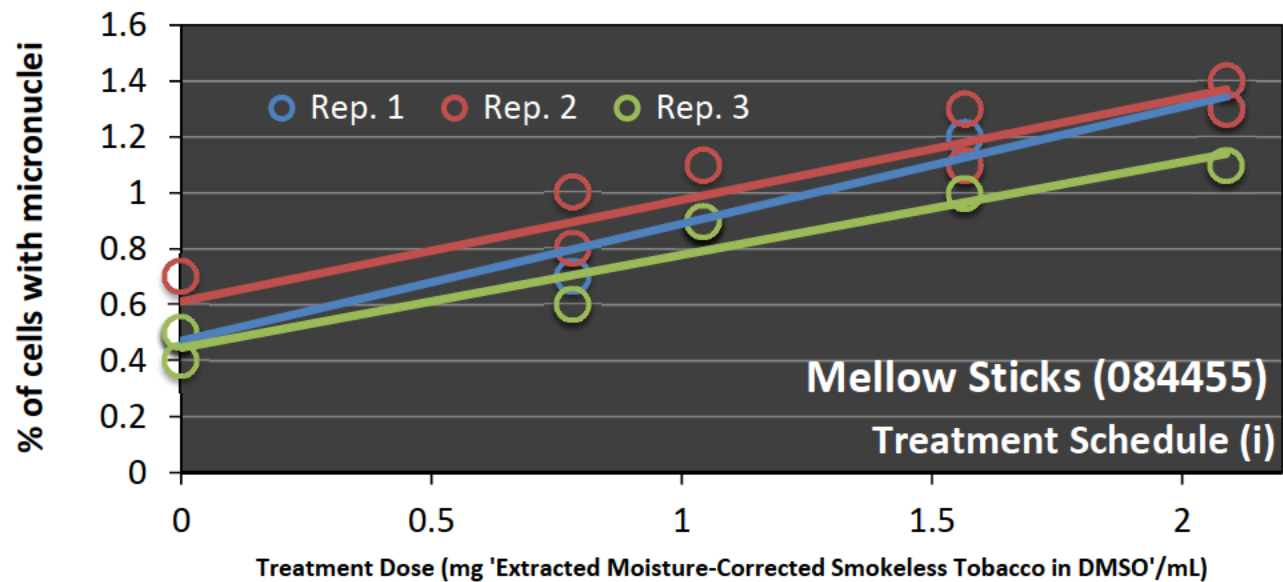
Schedule (i)

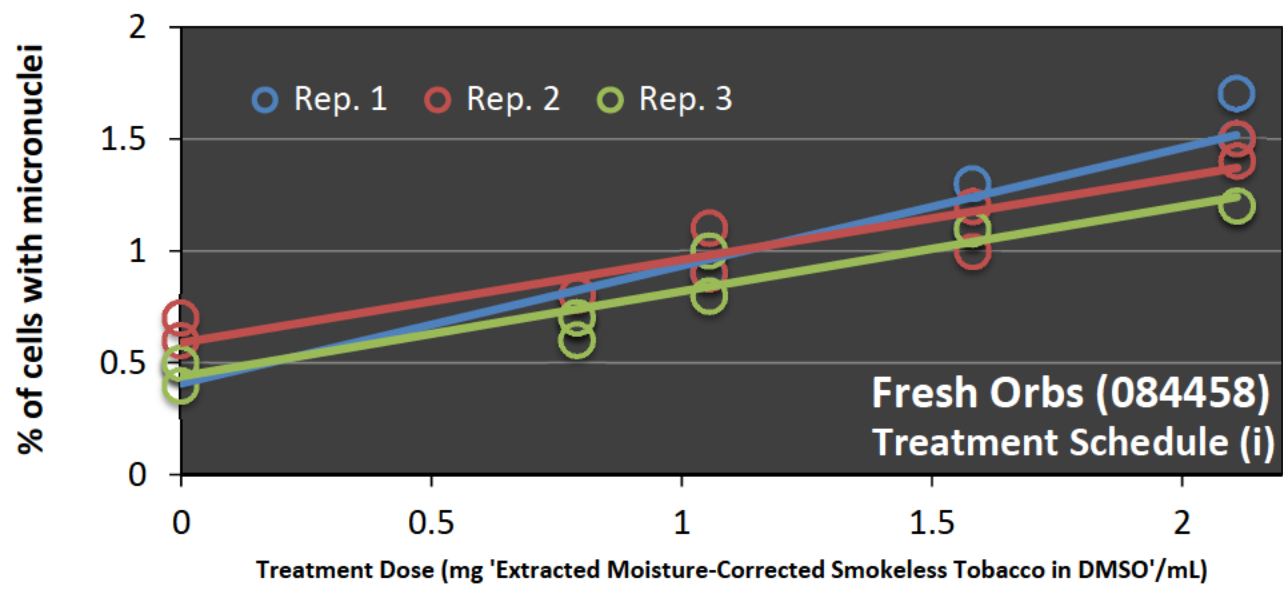
Sample Description	Sample ID	Mean Slope	Homogenous Groupings
Mellow Sticks	084455	0.371	X
Camel SNUS Frost	084394	0.384	X
Ariva Wintergreen	084457	0.401	X
Fresh Strips	084454	0.402	X
Fresh Orbs	084458	0.426	XX
2S3	084395	0.552	XX
Copenhagen Long Cut	084456	0.665	X

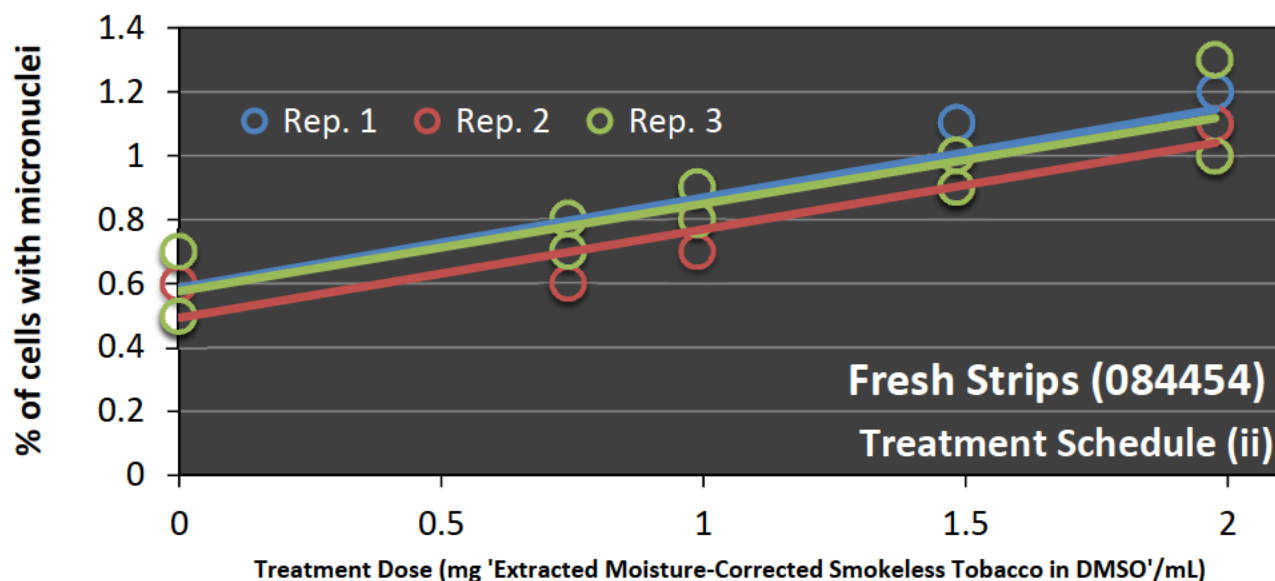
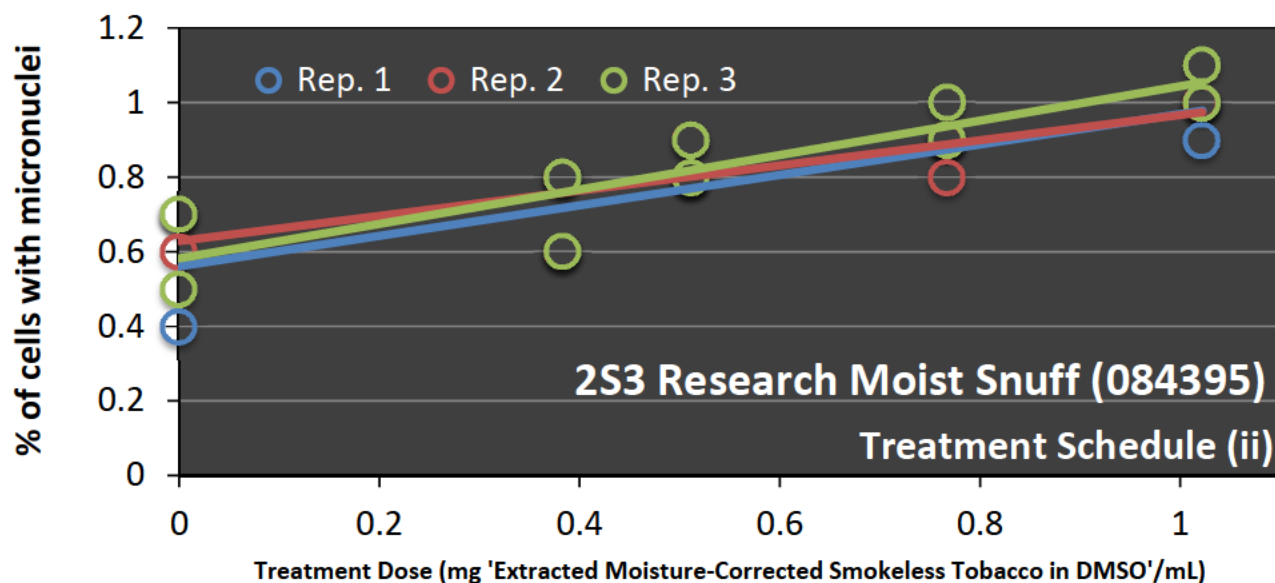
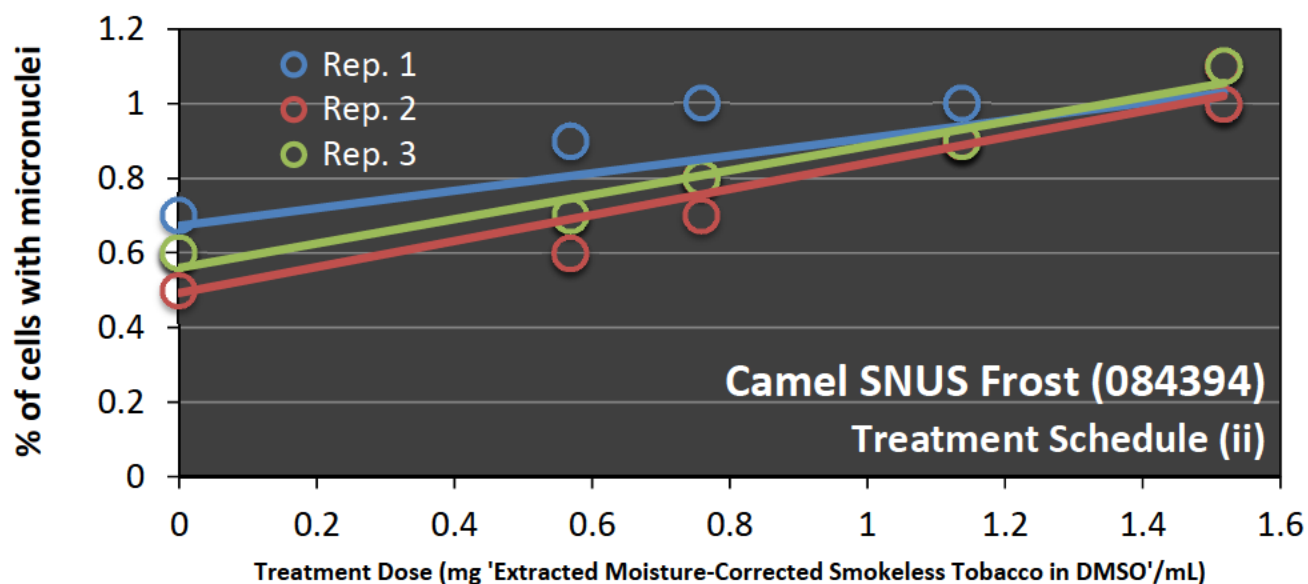
Schedule (ii)

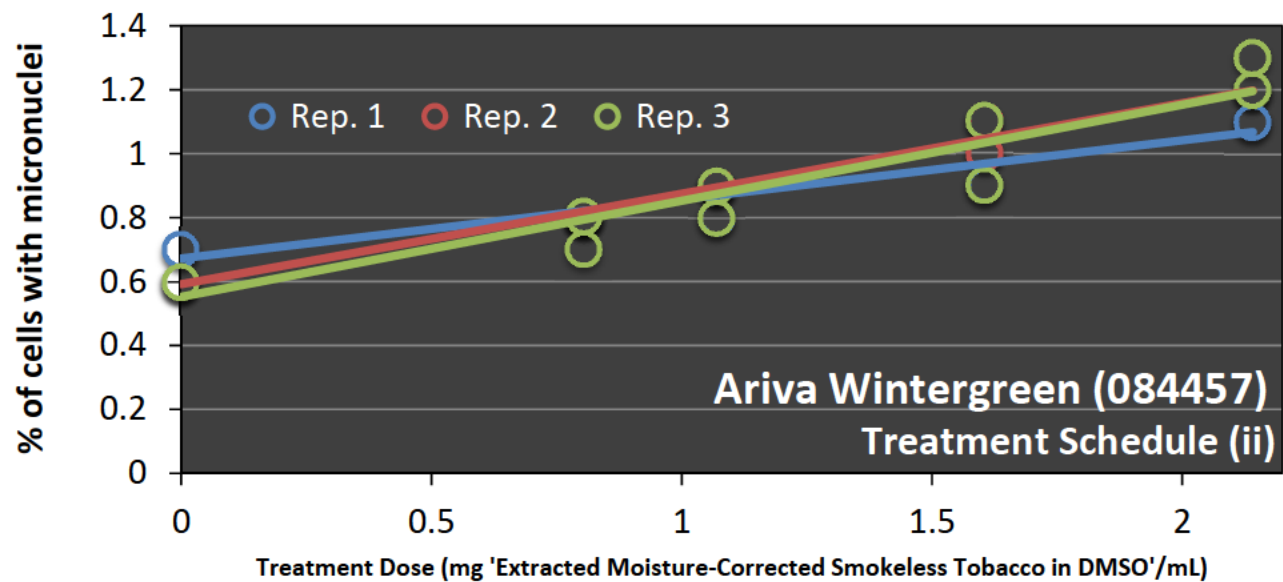
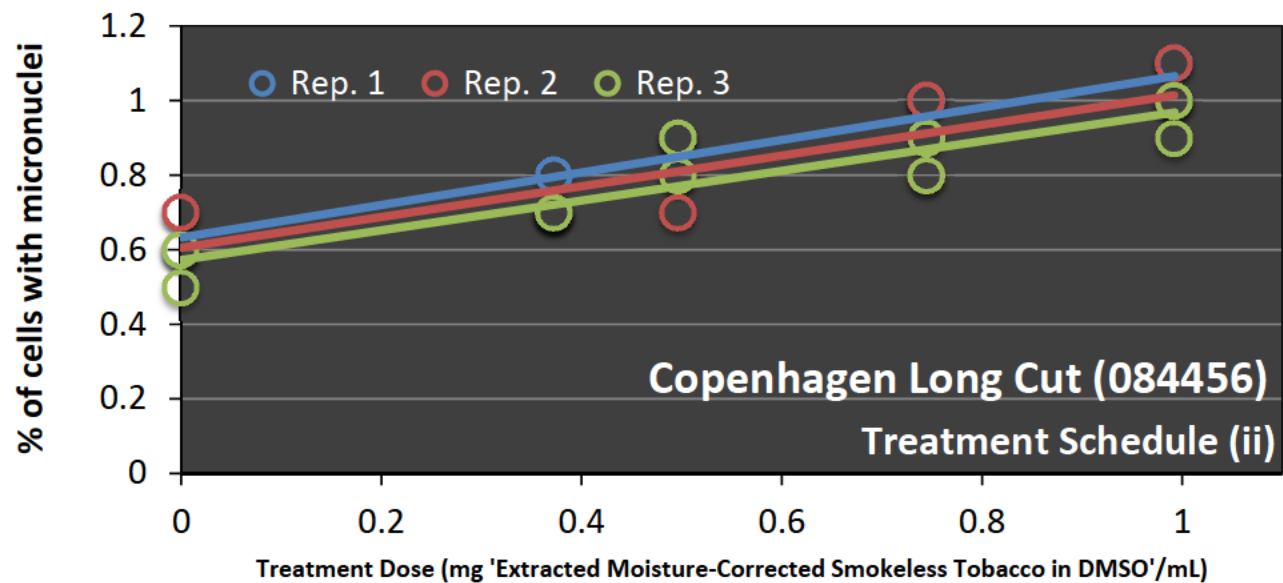
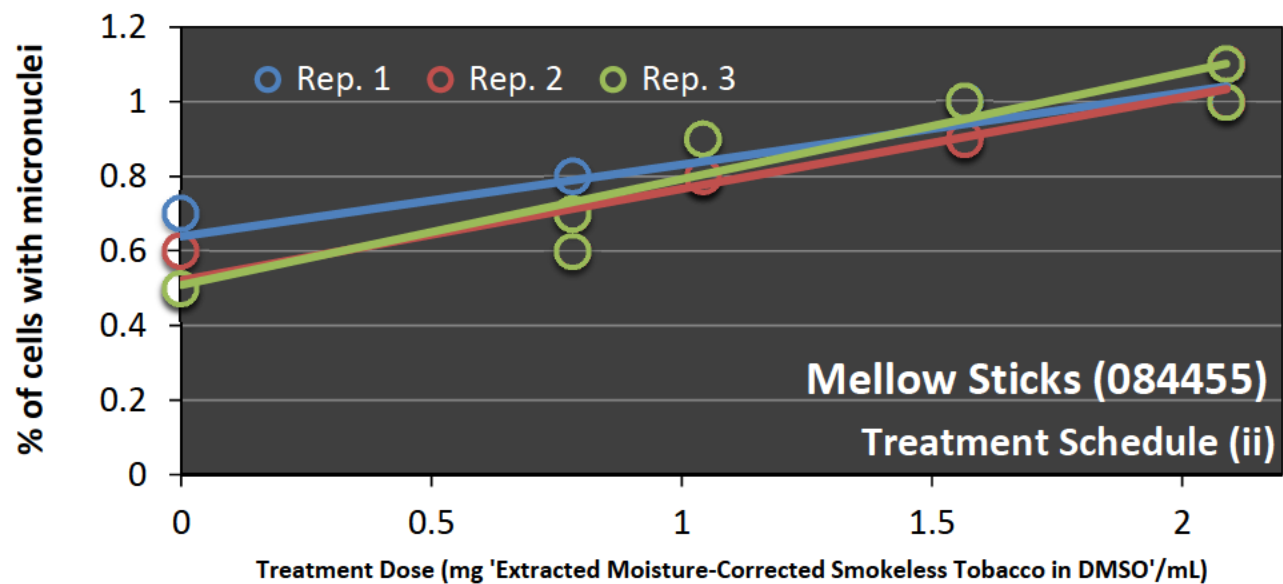
Sample Description	Sample ID	Mean Slope	Homogenous Groupings
Mellow Sticks	084455	0.241	X
Ariva Wintergreen	084457	0.256	X
Fresh Strips	084454	0.278	XX
Camel SNUS Frost	084394	0.303	XX
Fresh Orbs	084458	0.351	XX
2S3	084395	0.403	X
Copenhagen Long Cut	084456	0.416	X

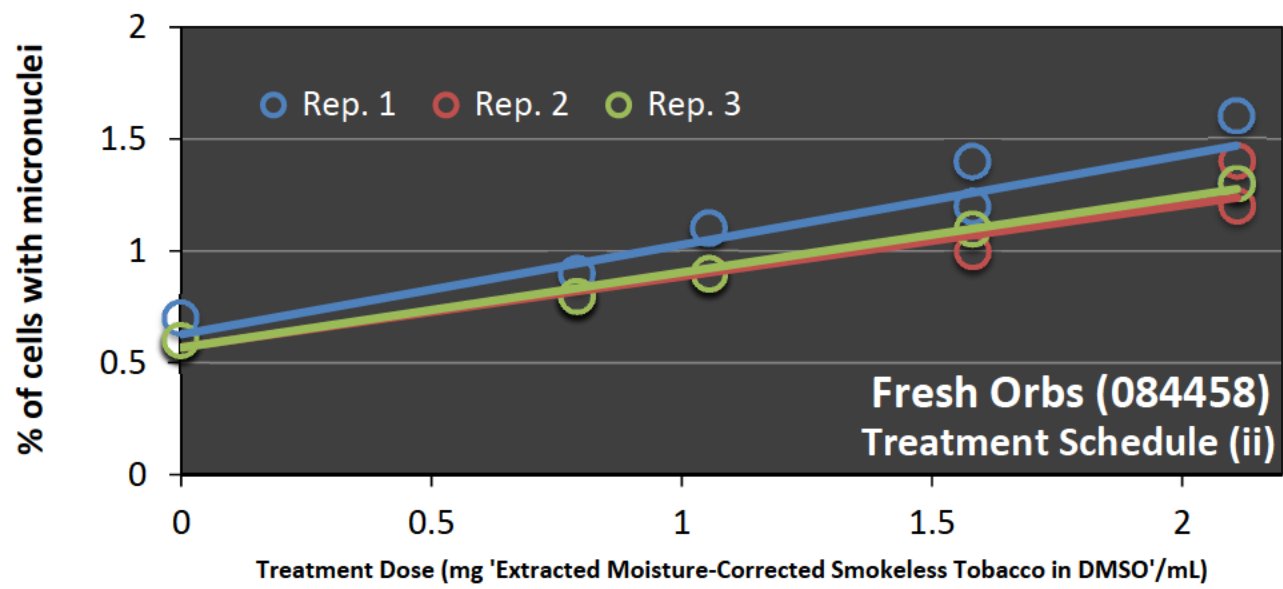


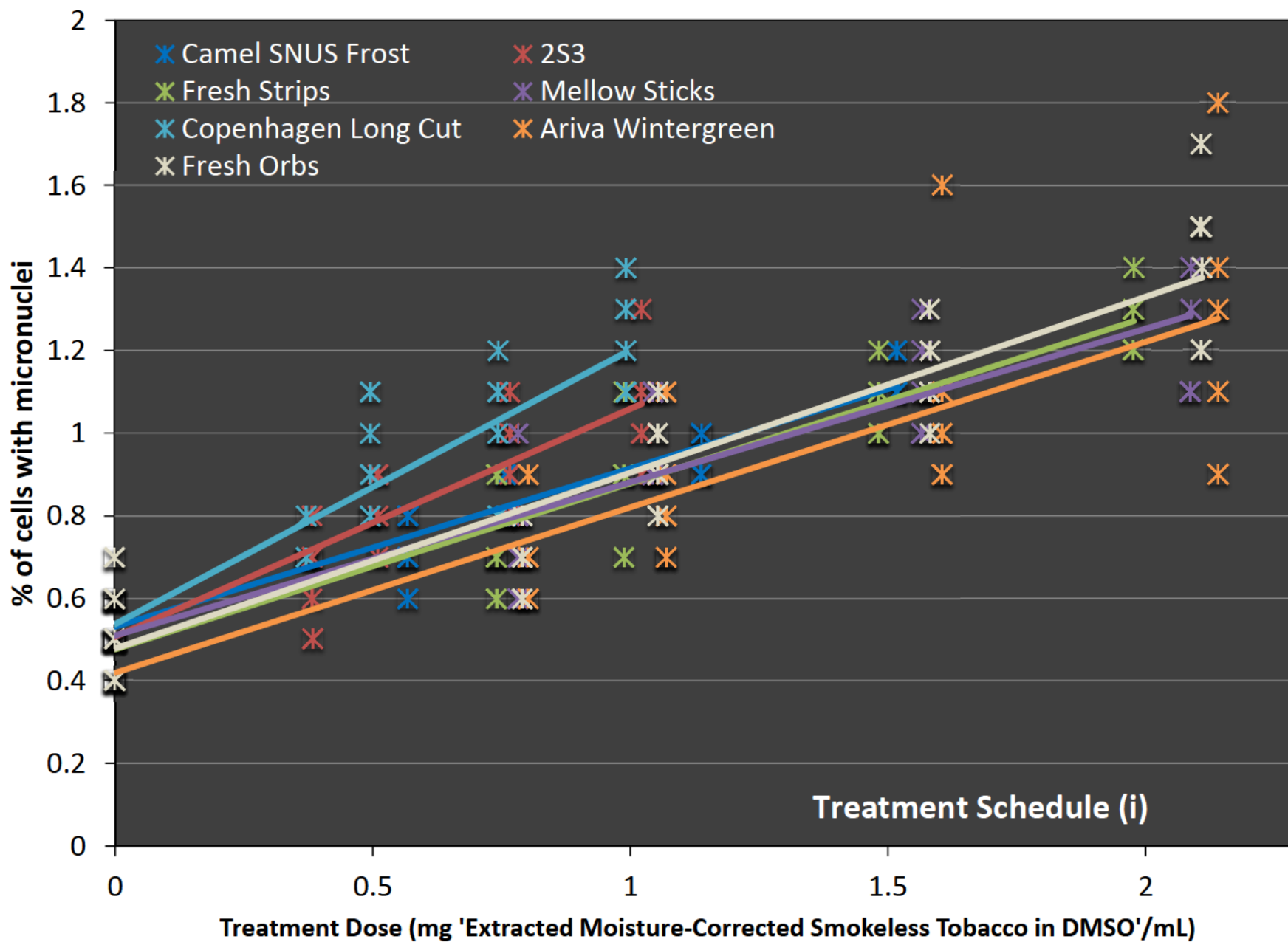


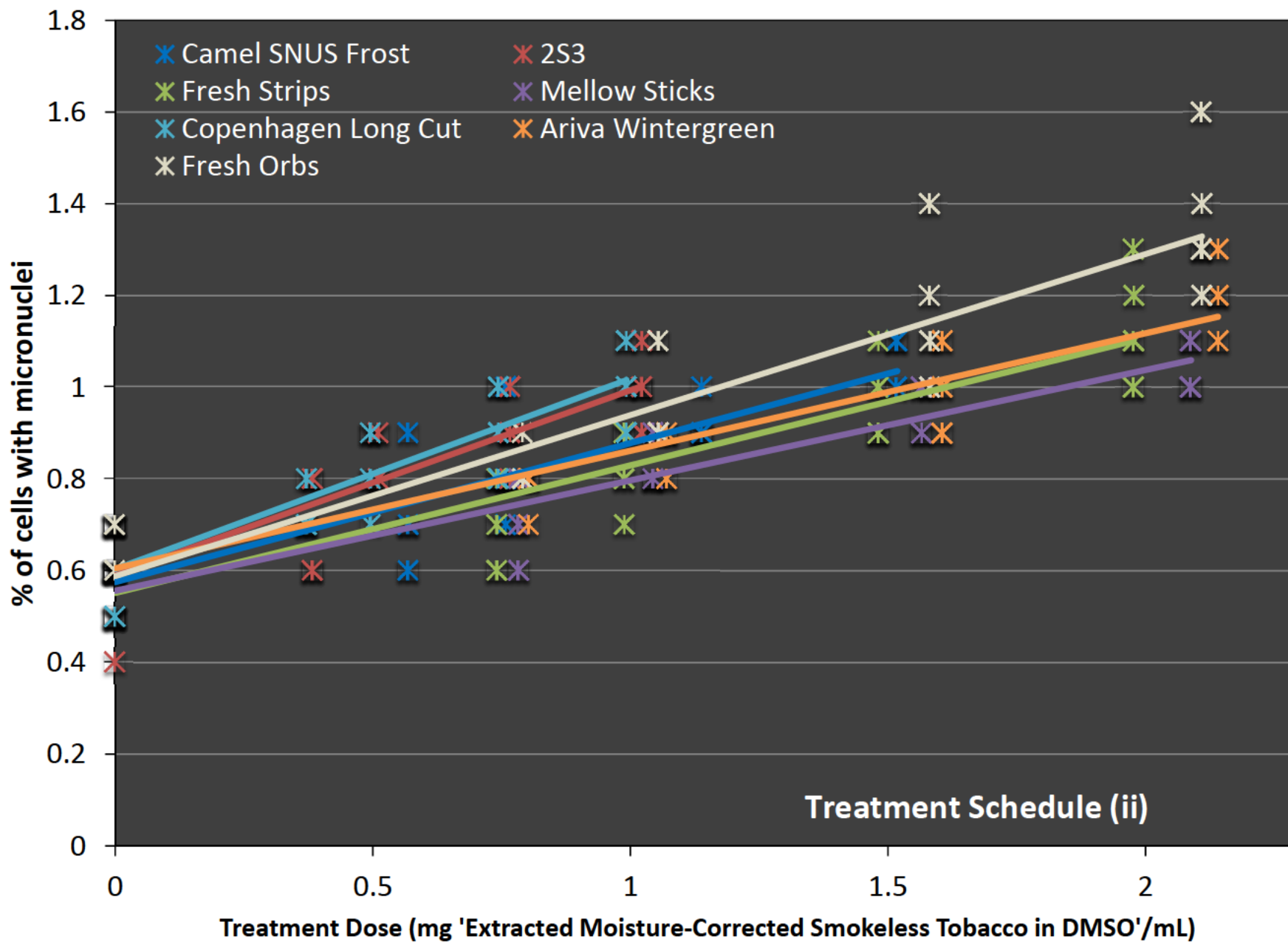












Test **Describe - Comparative**

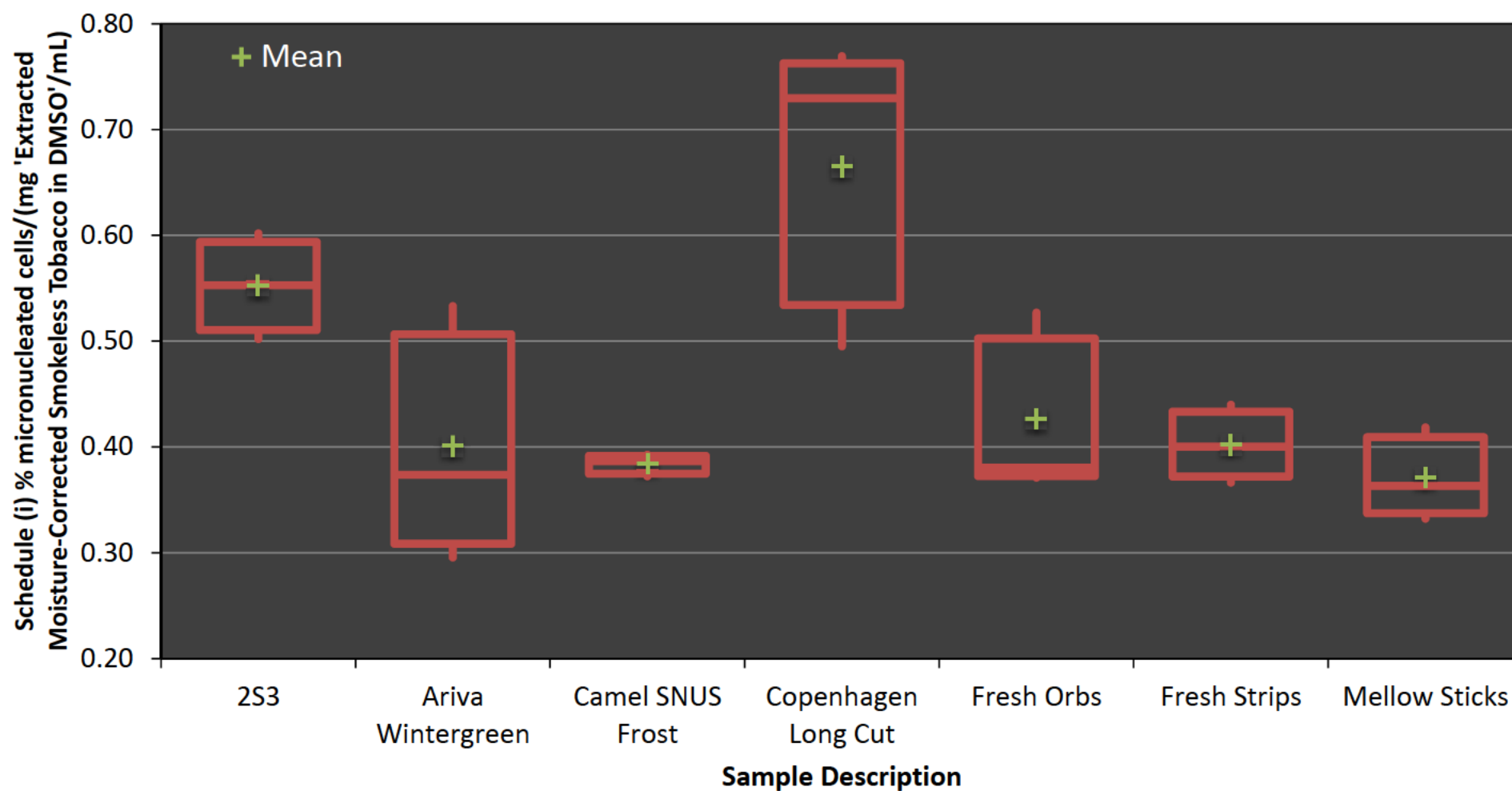
Performed by

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

